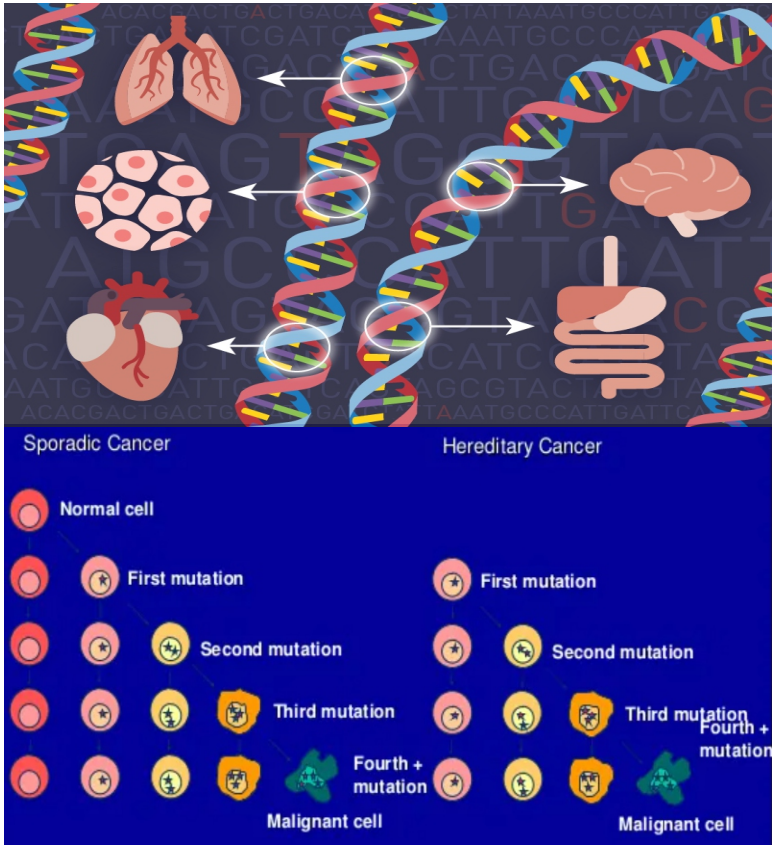
A Textbook of

Medical Genetics and Cancer Genetics



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Dr. V. Lakshmi Kalpana, M.Phil., Ph.D.
Dr. A. Anuradha, M.Phil., Ph.D.

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IP Innovative Publication Pvt. Ltd.
A-2, Gulab Bagh, Nawada, Uttam Nagar, New Delhi - 110059, India.
Ph: +91-11-61364114, 61364115
E-mail: info@ipinnovative.com
Web: www.ipinnovative.com

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Preface

In this generation of information overload, the present book put forth a comprehensive guidance about any application of genetics in relation to medical practice. With the specifications of the physical structure of DNA and technical advancements, majority of the diseases have found their roots in genes. Clinicians has taken a diversion from the symptomatic treatment to the root cause treatment of the diseases. This book encompasses the prevalence, symptoms, prognosis, diagnosis, treatment or management of various diseases emphasizing the genetic basis of the disease which helps the clinicians/students to get better insight and counsel the patients and their families appropriately. This knowledge elevates the standards for diagnosis, prediction and care, ultimately improving patient outcome for millions of people by leveraging genomic information.

Cancer prevalence is on the rise. It is also a fact that right now most of the cancer interventions do not rely on the knowledge derived from genetic studies on cancer. Researchers have learned that multiple gene mutations and their interactions with their environment further complicates understanding the role of genes in cancer. This book details development of cancer leading to the genetic changes in the cell, chromosomes in malignancies and sporadic versus familial cancers that assists in early detection, risk reduction, diagnostic, prognostic, and therapeutic aspects.

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Chapter 1

Scope of Medical Genetics

Introduction

Genetics became the integral part in the practice of clinical medicine. Medical genetics once chiefly restricted to relatively rare diseases seen only by a few specialists, is now becoming a central integrant of our understanding of most major diseases.

Medical genetics involves any application of genetics to medical practice. It encompass familial inheritance of the disease, the mapping of disease genes to specific locations on chromosomes, analyses of the molecular mechanisms through which genes cause disease, the diagnosis and the treatment of genetic disease. As a result of expeditious progress in molecular genetics, gene therapy and gene editing has recently been initiated. Genetic counselling, the communication of information regarding risks, prognosis, and treatment to patients and their families are other variables of Medical Genetics.

The inheritance of physical traits has been a subject of interest for thousands of years. **The ancient Hebrews and Greeks as well as later Medieval Scholars** described many genetic phenomena and proposed theories to account for them. Many of these theories were incorrect. **Gregor Mendel**, an Australian monk who is usually considered to be the "**Father"** of **Genetics**, advanced the field significantly by conducting a series of experiments upon living organisms **(Garden peas**). He then used this experimental information to formulate a series of fundamental principles of heredity.

Since the work of Mendel experiments of 1865 was published in a less common journal, his discoveries, which still form the foundation of genetics, received virtually no recognition for 35 years..Genetics as we know it today is largely the result of research done during this century. In **1900,** Mendel's principles were independently rediscovered by three different scientists working in three different countries which happens to be the same year of ABO blood groups discovered by

Landsteiner. In **1902, Archibald Garrod** described **Alkaptonuria** as the first **"Inborn Errors of Metabolism"**. In **1909, Johannsen** coined the term **gene** to denote the basic unit of heredity.

The next several decades were a period of notable experimental and theoretical work. **Drosophila and Neurospora** served as useful experimental systems to study the actions and interactions of genes. For example **H.J Muller** demonstrated the genetic consequences of ionizing radiation in the **Fruit Fly**. During this period much of the theoretical basis of population genetics was developed by three central figures, **Ronald Fisher, J.B.S Haldane** and **Sewall Wright**. In addition the modes of inheritance of several important genetic diseases including **Phenylketonuria, Sickle cell disease,Huntington disease, and Cystic fibrosis** were established. In **1944,Oswald Avery** showed that genes are composed of **Deoxyribo Nucleic Acid (DNA).**

Probably the most significant achievement of the **1950**'s was the specification of the physical structure of **DNA by James Watson and Francis Crick in 1953.** Their seminar paper which was only one page in length formed the basis for what is now known as molecular genetics (to study the structure and function of genes at the molecular level). Another significant accomplishment in this decade was the correct specification of the number of human chromosomes. Since the early **1920**s it had been thought that humans have 48 chromosomes in each cell. Only in **1956** was the correct number, **46,** finally determined by **Tjio and Levan**. The ability to count and identify chromosomes led to flurry of new findings in Cytogentics including the discovery in **1959 that Down syndrome** is caused by an extra copy of chromosome 21.

Technologic advancements since **1960** have brought about not able achievements at an ever increasing rate specially in the field of Molecular genetics. During the past decade more than **3000** genes have been mapped to specific chromosome locations. The **Human Genome Project** a large collaborative venture begun in **1991** hopes to provide a complete map of all human genes by the year **2005** (but it has completed in **2003)**. Important developments in computer technology will aid in decrypting the barrage of data being generated by this and related projects. In addition to mapping genes, molecular geneticists have pinpointed the molecular defects underlying a number of important genetic diseases. This research has contributed greatly to our understanding of the ways in which gene defects can cause diseases,opening the path to more effective treatment, potential cures and personalised medicine.

Types of Genetic Diseases

Approximately **50,000–1,00,000** different genes are estimated to present in a human body. Any changes in this genes, or in its combinations, can produce genetic disorders. These disorders are classified into several major groups:

Chromosome disorders, in which the whole chromosomes, or large segments of them, are missing, duplicated, or otherwise altered.

E.g.: Down syndrome and Turner syndrome.

Disorders in which single genes are altered (often termed "Mendelian" conditions or **single gene disorders**).

E.g.: Cystic fibrosis, Sickle cell disease and Haemophilia.

Multifactorial disorders, which are due to a combination of genetic as well as environmental causes.

E.g.: Many birth defects, such as cleft lip and/or cleft palate, adult disorders including heart disease and diabetes.

Mitochondrial disorders, alterations in the small cytoplasmic mitochondrial chromosomes, accounts for a small percentage of diseases.

The prevalence of single gene disorders made them receive the greatest amount of attention which are classified according to the way in which they are inherited in families (**Autosomal Dominant, Autosomal Recessive, and X-linked).**

Whereas some genetic disorders, particularly the single–gene conditions, are strongly determined by genes, many others are the result of multiple genetic and non genetic factors. We can therefore think of genetic diseases lying along a continuum with disorders such as Cystic fibrosis and Duchene muscular dystrophy situated at one end (strongly determined by genes) and conditions such as Measles situated at the other (strongly determined by environment). Many of the most prevalent disorders such as many birth defects and common diseases including Diabetes, Hypertension, Heart disease and Cancer, lie some where in the middle of the continuum. These diseases are the product of varying degrees of both genetic and environmental influences.

Table 1.1: Continuum of genetic diseases. Some diseases (e.g., cystic fibrosis) are strongly determined by genes whereas others (e.g., infectious disease) are strongly determined by environment.

Influenza Measles Infectious disease	Diabetes Heart diseases	Cystic fibrosis Haemophilia A
Environmental		**Genetic**

The most frequently occurred and genetically associated diseases of different parts of human body are discussed in detail in the further chapters.

❑

Chapter 2

Skin

Icthyosis

Icthyosis is a rare skin disorder which causes dry scaly skin, also known as **Fish Scale Disease**. The severity of dryness varies which categorises Icthyosis into different forms.

The process of the exfoliation of the skin may take several weeks and normally goes unnoticed. But in Icthyosis, the skin cells reproduce normally or much faster but ceases to shed from the skin like the normal process and sticks to the skin surface and remains as scales.

Icthyosis vulgaris occurs in two genetic types: **Autosomal Dominant, Autosomal Recessive** and **Sex** or **X-linked**. Most forms of Icthyosis are inherited though not all children of sufferers will inherit the Icthyosis gene. In case of the most common form of Icthyosis vulgaris, there is a 50% risk of passing the condition on to the children.

Icthyosis usually first appears in early childhood. It may remain throughout life although Icthyosis vulgaris usally disappears during adulthood, it may recur in old age. In rare cases Icthyosis is not an inherited disorder but is acquired by someone who has no family history of the condition. In such cases, it is usually linked with another medical problems such as kidney disease.

Symptoms

The symptoms common to all forms of Icthyosis is dry and rough with light grey – brown scaling which varies considerably in intensity. The scaling can become tight enough to restrict body movements and develop at skin cracks at creases and joints. Severity of scaling is more on the legs and may sometimes spread to the arms,hands,trunk and other areas. **X-linked Ichthyosis (XLI) or Steroid Sulfatase Deficiency**, and **X-linked Recessive Ichthyosis**) (from the ancient Greek 'Ichthys'

meaning 'Fish') is a skin condition caused by the hereditary deficiency of the Steroid Sulfatase (STS) enzyme that **affects 1 in 2000 to 1 in 6000 males**. XLI manifests with dry, scaly skin and is due to deletions or mutations in the **STS gene**. XLI can also occur in the context of larger deletions causing contiguous gene syndromes. Treatment is largely aimed at alleviating the skin symptoms.

In the **1960s**, Recessive X-linked Ichthyosis was distinguished clinically from other Ichthyosis. Scaling of the skin, is conspicuous largely on the neck, trunk, and lower extremities. The extensor surfaces are typically the most severely affected areas. The > 4 mm diameter scales adhere to the underlying skin and can be dark brown or grey in colour. Symptoms may lessen during the summers.

As the STS gene is located on the X-chromosome at band Xp22.3, the syndrome is an X-linked condition, and males and females show different modes of inheritance. The 23rd pair of chromosomes is typically termed the "sex chromosomes". Females with XX carry two copies and Males with XY carry one copy of STS gene. Also This gene partially escapes X-inactivation and females normally express higher amounts of the STS enzyme than males. XLI can occur through new deletions or mutations of the STS gene but is more commonly inherited from a carrier mother.

Genetic Counselling

Males with XLI will transmit the X chromosome harboring the STS deletion or mutation to each of his female offspring, who will therefore be an obligate carrier. However, all male offspring will be unaffected, since they receive their father's Y chromosome.

Female carriers of an STS deletion or mutation have a 50% chance with each pregnancy of transmitting it to an offspring. Thus, each male offspring has a 50% chance of being affected by XLI, while each female offspring has a 50% chance of being a carrier for this condition. Any individual that inherits the mother's normal copy of the STS gene will be unaffected and will have an extremely low chance of having a child affected with this condition.

Autosomal Recessive

Autosomal Recessive Congenital Ichthyosis **(ARCI)** is a heterogeneous group of disorders of keratinization characterized primarily by abnormal skin scaling all over the body. These disorders are limited to the skin, with approximately

two-thirds of patients presenting severe symptoms. The main skin phenotypes are **Lamellar Ichthyosis (LI) and Non bullous Congenital Ichthyosiform Erythroderma (NCIE),** although phenotypic overlap within the same patient or among patients from the same family can occur. Neither histopathologic findings nor ultrastructural features clearly distinguish between NCIE and LI.

Autosomal Recessive Congenital Ichthyosis **(ARCI)** is caused by mutation in the genes, encoding keratinocyte transglutaminase **(TGM1 190195**) on chromosome **14q11.2;** Arachidonate 12-Lipoxygenase **(ALOX12B)** gene on chromosome **17p13.1;** Arachidonate Lipoxygenase 3 **(ALOXE3)** gene on chromosome **17p13.1;** ATP-binding cassette **(ABCA12)** gene on chromosome **2q35;** Cytochrome P450 **(CYP4F22)** gene on chromosome **19p13;** Non-Imprinted In Prader-Willi/Angelman Syndrome**(NIPAL4)** gene on chromosome **5q33;** Lipase Family Member N **(LIPN)** gene on chromosome **10q23;** Ceramide Synthase 3(**CERS3)** gene on chromosome **15q26;** and patatin-like phospholipase**(PNPLA1)** gene on chromosome **6p21**. Of all the genes, at least one-third of **ARC**I cases are caused by mutations in TransGlutaMinase-1 **(TGM1)** gene.

Autosomal Dominant

Ichthyosis With Confetti (**IWC)** is an **Autosomal Dominant** congenital Ichthyosis, also known as Iichthyosis variegata or congenital reticular Ichthyosiform erythroderma. It manifests at birth with generalized Ichthyosiform erythroderma. IWC is a very rare genodermatosis, with a prevalence of <1/1,000,000 and only 40 cases reported worldwide. The most important associated clinical features include ear deformities, mammillae hypoplasia, palmoplantar keratoderma, hypertrichosis and ectropion. IWC is due to dominant negative mutations in the Keratin **(KRT10 and KRT1)** genes located on chromosome **17q21,** encoding for keratins 10 and keratin 1, respectively. Nevertheless, mutational analysis of KRT10 or KRT1 genes is at present the gold standard to confirm the diagnosis.

Most of reported IWC cases are sporadic, but familial cases with **Autosomal Dominant** mode of inheritance have been also described. Therefore, knowledge of the mutation is the only way to properly counsel the couples.

Diagnosis

XLI can be suspected based on clinical findings, although symptoms can take varying amounts of time to become evident, from a few hours after birth, upto a year in milder cases. The diagnosis is usually made by a Dermatologist, who also

typically formulates the treatment plan. Prenatal diagnosis is possible using either biochemical or molecular tests.

Treatment

No specific and satisfactory therapy is currently available for IWC. The only way of treatment is to minimise scaling by removing the excess, flaky scales, and keep the skin hydrated. A variety of topical treatments (mainly emollients and keratolytics) are widely prescribed for these symptoms and offer only temporary relief. Although at present there is no curative therapy for Ichthyosis, treatments have improved considerably over the years and the best therapy for each patient is always the result of both physician and patient efforts.

Psoriasis

Although the skin disease psoriasis was first recognized as a distinct disease as early as **1808**, its pathogenic mechanisms have eluded investigators for decades.

Psoriasis as distinct skin disease was recognised in early 1808, its pathogenic mechanisms have eluded investigators for decade. Molecular geneticists recently paid attention as it has fallen under the somewhat elusive descriptor '**complex disease'**. The development of localized lesions in response to skin trauma (Koebner reaction or Isomorphic response) was first described by **Koebner** in **1872** sand is a hallmark of psoriasis, a disease that derives its name from the Greek 'psora' meaning 'to itch'

This chronic, common, inheritable, non infectious skin disorder is characterized by Erythrometus (redness or inflammation of the skin) plates with thick dry large adherent silvery scales that are a result of excessive development of epithelial cells. The main abnormality of this is increased epidermal proliferation due to excessive division of cells in basal layers & a shorter cell cycled time.

Frequency

Prevalence varies with race and geography, being highest in the Northernmost regions of the Soviet Union and Norway (5–10% of individuals), of moderate prevalence in the UK, USA and Holland (2–3%) and of low prevalence among North American Indians, Latin American Indians, Mongoloids and Western Africans (0–0.3%). It may start at any place but it is not seen under 10 yrs & often between 15–40 years with an average onset of 27 years.

Symptoms

The course of the disease is unpredictable but usually chronic with excertations (an increase in the seriousness of the disease), permitting partial or complete disappearance of clinical characters of chronic diseases. Lesions, a wound, injury or pathological change in the body tissue may be any where on the body but more common on the external surfaces, hands, feet, bony prominences, scalp, ear, genitalia, perianal area. Although plaque forming psoriasis is most common, and affects 90% of patients, other forms include guttate, erythrodermic and palmar–plantar psoriasis. 5–10% of patients develop a co-existing, and sometimes debilitating, psoriatic arthritis.

Causes

The basic defect underlined the disease is not known. However there is a frequency of genetic predisposition in addition to other predisposing factors like drugs, stress and climate in susceptible individuals. A child with one affected parent has a 15% chance of developing the disease and this rises to 50% if both parents are affected. If non psoriatic patients have a child with psoriasis the risk for subsequent children is 10%. Prosiasis is probably heterogenous but some have considered inherited to be **Polygenic** and others **Autosomal Dominant** with **incomplete penetrance.**

The immune system has been strongly implicated in the pathogenesis of psoriasis since it resembles a T cell-mediated autoimmune disease.

Genetic Causes

In the last few years, molecular genetics analyses have permitted novel insights into psoriasis, a disease characterized by uncontrolled proliferation of keratinocytes and recruitment of T cells into the skin. The disease affects 1–2% of the Caucasian population and can occur in association with other inflammatory diseases such as Crohn's disease and in association with Human Immunodeficiency Virus **(HIV)** infection. Given that psoriasis has characteristics of an autoimmune disease, it is not surprising that HLA studies revealed an association with certain alleles, notably **HLA-Cw6.**

Despite this HLA component, psoriasis in some families is inherited as an **Autosomal Dominant** trait with high penetrance. Loci at chromosome **17q25** and **4q** have been identified following genome-wide linkage scans of large, multiply affected families. In the case of at least the susceptibility locus at 17q25, the development of psoriasis does not require the presence of HLA-Cw6. Sib-pair analyses have confirmed the association with HLA-Cw6, confirmed the existence of a locus at 17q25 and identified other possible susceptibility loci. Two dependent groups have reported a third region on chromosome 20p. Despite these findings, the extent of genetic heterogeneity and the role of environmental triggers and modifier genes is still not clear. The precise role of HLA also still needs to be defined.

The isolation of novel susceptibility genes will provide insights into the precise biochemical pathways that control this disease. Such pathways will also reveal additional candidate genes that can be tested for molecular alterations resulting in disease susceptibility.

Table 2.1: Summary of linked regions identified and replicated in independent studies

Region	Gene/locus	Map position	No. of families	Model
17q	D17S784	116.86	8	Dominant
17q	D17S802	106.80	115	Dominant
17q	D17S785	103.53	115	
17q	D17S928	126.46	23	
17q	D17S795	89.32	23	
6p	TNF-α	44.9	68	Recessive
6p	D6S273	44.96	68	Recessive
6p	HLA-C	44.7	68	Recessive
6p	TNF-β	44.9	115	Recessive
6p	HLA-C	44.7	101	
20p	D20S186	32.30	68	Recessive
20p	D20S851	24.70	115	Recessive

GH, GENEHUNTER; HRR, heliotype relative risk (Terwilliger, 1996 program ANALYZE. ftp://linkage.cpmc.columbia.edu). Map positions were obtained from the Marshfield genetic maps at http://www.marshmed.org/genetics.

Diagnosis

Psoriasis usually diagnosed by the medical history and examination of skin,scalp and nails. Rarely, skin biopsy is recommended to determine the exact type of psoriasis and to rule out other disorders.

Treatment

Tropical intra-lesional corticosteroids, U.V light, shampoos and creams. Tar solution baths, methotrexate and phosphor-chemo therapy.

Multiple Neurofibromatosis

Neurofibromatosis, a fibrous tumour of nerve tissue resulting from the abnormal proliferation of Schwann cells. Multiple growths of this type in the peripheral nervous system are often associated with extensive abnormalities in other tissue. It is also called as **Reckling Hausens Disease.**

Frequency

The disorder occurs in **1** of **2,500 to 3000** live births.This disease was first reported by Akenside (1768) a British physician. Friedrick and Recklinghausen described its gross and microscopic appearance in 1882. Today it is referred to as **Neurofibromatous** type I **(NFI)** and ranks as one of the most common neurologic disease. The disease is 100% penetrant with a highly variable onset of symptoms, from being present at birth to a diagnostic expression in middle age.This is a highly unpredictable as the parents gives no indication of how severe the disease will be in or between their children.

Symptoms

It is a congenital condition transmitted as an autosomal dominant trait characterized by numerous neurofibromas of the nerves and skin, by spots on the skin and in some cases by developmental anomalies of the muscles, bones and viscera. Neurofibromatosis may develop in the alimentary track, bladder, endocrine glands and cranial nerves. Sometimes it is associated with meningocele, spina bifida or epilepsy. Many large pedunculated soft tissue tumours may develop as exemplified by the famous case of the "**Elephant Man"** in nineteenth century, England. Bone changes may result is skeletal deformities especially curvature of the spine.

Neurofibromatosis Type 1 (NF1):

Of fifteen families studied there was no evidence of heterogeneity indicating that the majority of NFI cases in this study were the result of mutations at a single locus **(Barker et al., 1987).** At least half of the affected people studied have a negative family history indicating that these are cases of fresh mutations. **De novo mutations** cause upto **50%** of novel NF1 cases. The NF1 gene locus has a higher spontaneous mutation rate than do most gene loci. The fresh mutation rates for NFI has been calculated as high as **1 in 10,000** mutations per generations. This is one of the highest fresh mutation rates known in humans.

The NF1 gene is cytogenetically located on the long (q) arm of chromosome 17, at band 11.2 (**17q11.2).** Over 1000 pathogenic allelic variants of the gene have been identified. Of these variants, many are unique to a family. The NF1 gene product is a cytoplasmic protein called neurofibromin 1, which appears to have diverse functions in many different tissues. Mutations that have been observed in the NF1 gene include stop mutations, amino acid substitutions, insertions, deletions (partial or whole), and gross chromosomal rearrangements.

The NF1 phenotype is **highly penetrant** (ie, almost all individuals with an NF1 gene mutation have some phenotypic traits of the syndrome). A wide range of expression also exists among people diagnosed with NF1 (ie, there are varying degrees of clinical severity, with differences noted even within the same family).

Neurofibromatosis Type 2 (NF2):

A gene causing second type of Neurofibramatous called Bilateral Acoustic Neuro Fibromatosis or type II – NF II **(BANF)** has recently been located in the long arm of chromosome 22. This **Autosomal Dominant** disease is characterized by tumours affecting the central and peripheral nervous system. The hallmark of BANF is the bilateral occurrence of acoustic tumours that cause severe deafness and paralysis and other nervous disorders leading to premature death **(Seizinger, 1987).**

Neurofibromatosis type 2 (NF2), also called bilateral acoustic neurofibromatosis(BANF) or central neurofibromatosis, is an **Autosomal Dominant** genetic syndrome caused by a mutation in, or a deletion of, the NF2 gene. The NF2 gene codes for the cytoskeletal protein neurofibromin 2 and is cytogenetically located on the long (q) arm of chromosome 22, at band **12.2 (22q12.2).**

Individuals with NF2 have wide phenotypic expression. About 200 pathogenic allelic variants have been identified in patients with NF2; most of the altered gene products in this disease result from point mutations.

Only one copy of a mutated NF2 gene is required to affect an individual. As with NF1, descendents of an individual with NF2 have a 50% risk of inheriting the altered gene. A de novo mutation occurs in about 50% of individuals with NF2; somatic mosaicism is seen in 25-30% of these de novo cases.

Complete penetrance and **variable expression** characterize NF2. Tumour size, location, and number differ among affected individuals. Although these tumours are benign, their anatomic location and multiplicity cause significant morbidity and early mortality; the average life expectancy among persons with NF2 is 36 years.

Diagnosis

The Three important features in diagnosing NFI are:

1. **cafe–au–lait** (French for coffee with milk) spots. Darkened skin blotches are present in 99% of NF patients which vary in size from freckles to large knobs, several inches in diameter. They may be present at birth and may increase in number with age.
2. **Neurofibromas** (tumour made up of nerve cells and fibrous tissue) these tumours usually appear at puberty as knot like growths and increase in all adults in size and number.

   A patient may be covered with many thousands of fibromas as many as ten thousand neurofibromatosis of the skin have appeared on one person. The effect of the tumour growths depends on location. For eg, the benign tumours may appear in the brain spinal cord, nerve roots, or blood vesels causing blindness, deafness or high blood pressure. Approximately 1 in 2 children demonstrate learning disabilities and over 50% of preadolescents demonstrate scoliosis, a curvature of the spine.
3. **Lisch nodules** (small pigmented tumours in the iris of the eye) and these nodules are present in 94% of NFI patients at the age six or older. These too increase in size and number with age.

NF1 and NF2 are diagnosed clinically based on established diagnostic criteria. Cytogenetic and molecular testing is available to identify mutational changes in the NF1 and NF2 genes.

Cytogenetically, Fluorescent In-Situ Hybridization **(FISH)** is used to test for these diseases, including interphase FISH (for NF1 and NF2) and metaphase FISH (for NF1).

Sera and tissue analysis are used, although in prenatal diagnosis, chorionic villus tissue or amniotic fluid cells are tested.

The following are general categories of current genetic molecular testing available for NF1 and NF2:

1. Comprehensive gene analysis.
2. Targeted mutation detection.

3. Prenatal detection of a known mutations.
4. Comprehensive analysis in affected tissues.

Treatment

There is no cure for the disorder itself. Instead, people with neurofibromatosis are followed by a team of specialists to manage symptoms or complications.

Porphyrias

The term **Porphyria** is derived from the Greek, porphyra, meaning "purple pigment", a reference to the colour of the porphyrins. The Porphyrias are a group of **"Rare Diseases"** and a "**Metabolic Disorder"** in which chemical substances called **porphyrins accumulate**. The body requires porphyrins to produce **heme**, which carries **oxygen** in the **blood**; but, in the porphyrias, there is a deficiency (inherited or acquired) of the enzymes that transform the various porphyrins into others, leading to abnormally high levels of one or more of these substances. This manifests with either **neurological** complications or **skin problems** or occasionally both.

Porphyrias are classified in **two** ways, by **symptoms** and by **pathophysiology**. **Symptomatically, acute porphyrias** primarily cause brain and **nerve** involvement, often with severe abdominal pain, vomiting, neuropathy and mental disturbances. **Cutaneous Porphyrias** cause with **skin** manifestations often after exposure to sunlight, as porphyrins react with light. **Physiologically**, porphyrias are classified as hepatic or erythropoietic based on the sites of accumulation of heme precursors, either in the **liver** or **bone marrow** and **red blood cells.**

Frequency

It is rare though not absent, in most parts of the world, but seems to occur in **1%** of the **Afrikaner** population of South Africa. These people are descendents of Dutch and French settlers who arrived in Africa during the latter part of the seventeenth century. The prevalence of all types of Porphyria taken together has been estimated to be approximately **1 in 25,000** in the United States**.** The **worldwide** prevalence has been estimated to be somewhere between **1 in 500** to **1 in 50,000** people. The Porphyrias except for the Recessive Congenital Erythropoietic Porphyria, are genetic Dominant disorder (**Reily & Branner, 1982**). **Penetrance is reduced and expression** is highly variable. Some family members appear normal while others are severely affected.

Symptoms

The accumulation of haemoglobin in general produces light sensitivity nausea (urge to vomit), visual disturbances, headaches, convulsions and periods of incoherence (non stable).

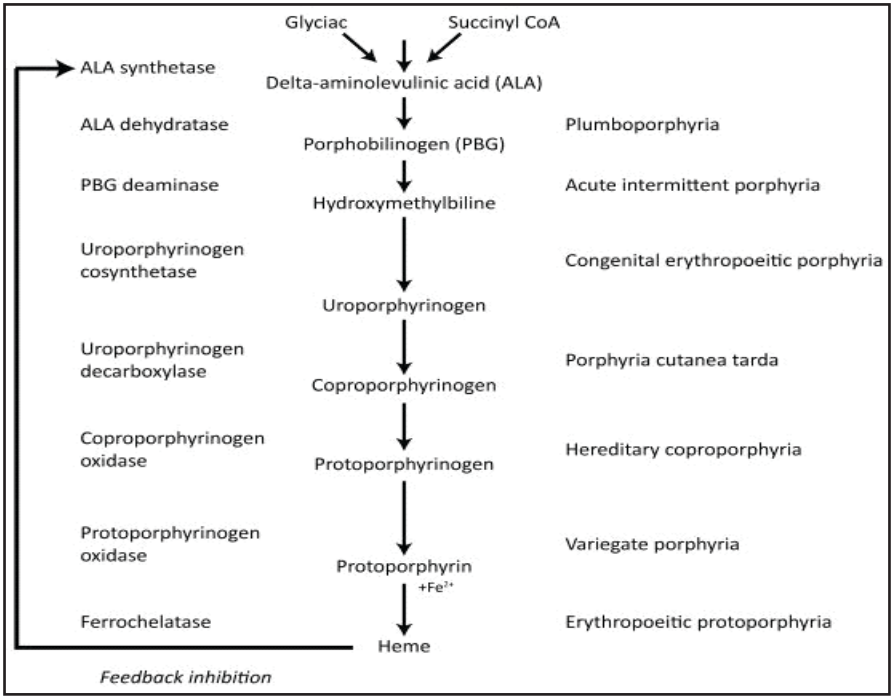
Causes

There are **6 types** of Porphyrias which are caused by 6 separate enzymatic blocks in the heme **biosynthetic pathway**. Each block results in the inability to metabolize used haemoglobin. **Five pathway** blocks are due to **Autosomal Dominant** conditions and one block is **Autosomal Recessive.**

The six pathway blocks are:

1. Acute Intermittent Porphyria
2. Congenital Erythropoietic Porphyria
3. Porphyria Cutanea Tarda
4. Hereditary Copro Porphyria
5. Variegate Porphyria
6. Erythropoeitic Proto Porphyria

Biosynthesis of Heme



Genetic Causes

Each form of Porphyria results from mutations in one of these genes: **ALAS, ALAD, HMBS, PBGD, UROS, UROD, CPOX, PPOX and FECH**. The genes related to Porphyria provide instructions for making the enzymes needed to produce Heme. Mutations in most of these genes reduce enzyme activity, which limits the amount of Heme the body can produce.

Table 2.2: Types of Porphyria, their patterns of inheritance, and the enzyme that is deficient in each.

Type	Inheritance	Deficient Enzyme	Gene	Gene Locus
ALA-Dehydratase Porphyria (ADP)	Autosomal Recessive	ALA-Dehydratase	ALAD	9q34
Acute Intermittent Porphyria (AIP)	Autosomal Dominant	Hydroxymethylbilane synthase (Porphobilinogen deaminase)	HMBS	11q23
Congenital Erythropoietic Porphyria (CEP)	Autosomal Recessive	Uroporphyrinogen III synthase	UROS	10q25-26
Porphyria Cutanea Tarda (PCT), familial form	Autosomal Dominant	Uroporphyrinogen decarboxylase	UROD	1p34
Hepatoerythropoietic Porphyria (HEP)	Autosomal Recessive	Uroporphyrinogen decarboxylase	UROD	1p34
Hereditary Coproporphyria (HCP)	Autosomal Dominant	Coproporphyrinogen oxidase	CPOX	3q12
Variegate Porphyria (VP)	Autosomal Dominant	Protoporphyrinogen oxidase	PPOX	1q22
Erythropoietic Protoporphyria (EPP)	Autosomal Recessive	Ferrochelatase	FECH	18q21
X-linked Protoporphyria (XLP)	X-linked	δ-Aminolevulinate synthase 2	ALAS2	Xp11.21

Acute Porphyrias

These are ALA (**Amino Levulinic Acid)** dehydratase (also known as **Porphobilinogen Synthase)** Porphyria, Acute Intermittent Porphyria,

Hereditary Coproporphyria and Variegate Porphyria. The Acute Porphyrias primarily affect the nervous system, resulting in episodic crisis known as acute attacks. The major symptoms of the acute attack is abdominal pain, often accompanied by vomiting, hypertension (elevated blood pressure) and tachycardia. The most severe episodes may develop neurological complications: typically a motor neuropathy (severe dysfunction of the peripheral nerves which innervate muscle), leading to muscle weakness and potentially to quadriplegia (paralysis of all four limbs), as well as central nervous system (brain and spinal cord) symptoms including seizures and coma.

Non-acute Porphyrias

Skin disease is encountered in those Porphyrias where excess porphyria accumulate in the skin. These are Congenital Erythropoietic Porphyria **(CEP),** X-linked Dominant Proto Porphyria **(XLDPP),** Porphyria Cutanea Tarda **(PCT)** and Erythropoietic Proto Porphyria **(EPP).** None of these are associated with acute attacks; their primary manifestation is with skin disease.

Diagnosis

Porphyria is diagnosed through biochemical analysis of blood, urine, and stool. In general, urine estimation of porphobilinogen **(PBG)** is the first step if acute Porphyria is suspected. As a result of feedback, the decreased production of heme leads to increased production of precursors, PBG being one of the first substances in the porphyrin synthesis pathway.

Further diagnostic tests of affected organs may be required, such as nerve conduction studies for Neuropathy or an Ultrasound of the liver. Basic biochemical tests may assist in identifying liver disease, hepatocellular carcinoma, and other organ problems.

Treatment

To date, there is no cure for any of the Porphyrias. Treatment and prevention depends on the type of Porphyria. Preventive measures, which include avoidance of **certain drugs and alcohol** in the Hepatic Porphyrias, and sun **exposure** in the Erythropoietic Porphyrias, are extremely important in those individuals who are identified as having an inherited Porphyria, even if they have never had symptoms.

Blooms Syndrome

Bloom Syndrome (often abbreviated as BS in literature), also known as Bloom–Torre–Machacek syndrome, is a rare **Autosomal Recessive Chromosomal Disorder** characterized by high frequency of chromosomal breaks and rearrangements in an effected persons chromosomes, short stature and predisposition to the development of cancer and genomic instability. BS is caused by mutations in the **BLM** gene leading to mutated DNA helicase protein formation. Cells from a person with Bloom syndrome exhibit a striking genomic instability that includes excessive crossovers between homologous chromosomes and sister chromatid exchanges **(SCEs).** The condition was discovered and first described by New York Dermatologist **Dr. David Bloom** in **1954**. In **1989, Nicotera *et al.,*** suggested that the major biochemical defect in persons with blooms syndrome is chronic over production of the superoxide radical anion.

Frequency

Bloom syndrome is an extremely rare disorder in most populations and the frequency of the disease has not been measured. However, the disorder is relatively more common amongst people of Central and Eastern European (Ashkenazi) Jewish background. Approximately **1 in 48,000 Ashkenazi Jews** are affected by Bloom syndrome, who account for about one-third of affected individuals worldwide, but reported in Japans and other countries.

In united states more than 120 case reports have been made. The frequency of parental consanguinity is much greater than in the general population. Male to female ratio is 1.3:1. The condition occurs in the first few months of life. Blooms syndrome patients who become pregnant are at high risk for premature delivery. IQ is normal, although mild deficiency has occurred in few affected persons.

Symptoms

Bloom syndrome is characterized by genome instability. The most prominent features include short stature and a rash on the face that develops early in life when exposed to the sun. The skin rash is erythematous, telangiectatic, infiltrated, and scaly, it can appear across the nose, on the cheeks and around the lips. As well as these areas, the rash will develop on any other sun-exposed areas including, the backs of the hands and neck. Other clinical features include a high-pitched voice; distinct facial features, including a long, narrow face, micrognathism, prominent

nose and ears; pigmentation changes of the skin including hypo-pigmented and hyper-pigmented areas, cafe-au-lait spots, and telangiectasias (dilated blood vessels), which can appear on the skin and eyes. Moderate immune deficiency, characterized by deficiency in certain immunoglobulin classes has also been related to BS, leading to recurrent pneumonia and ear infections. Bloom syndrome children are usually with a low birth weight. Hypogonadism is characterized by a failure to produce sperm, hence infertility in males, and premature cessation of menses (premature menopause), hence sub-fertility in females. However, several women with Bloom syndrome have had children. Cancer is the most common and serious complication of Bloom syndrome. Other complications of the disorder include chronic obstructive lung disease, diabetes, and learning disabilities. There is no evidence that mental retardation is more common in Bloom syndrome than in other people.

People with Bloom Syndrome also have a shortened life expectancy; the current average live span is approximately 27 years old. Bloom syndrome shares some features with Fanconi anaemia possibly because there is overlap in the function of the proteins mutated in this related disorder.

Genetic Causes

Bloom syndrome (**Congenital Telangiectatic Erythema**) is genetic with an **Autosomal Recessive** pattern of inheritance.

The syndrome is caused by a mutation in the gene designated BLM, traced to band **15q26.1.** The protein encoded by the normal gene has DNA helicase activity and function in the maintenance of genomic stability. Increased sister chromatid exchanges and chromosomal instability also occur, which is assumed to be responsible for the cancer predisposition. In **1989, Nicotera *et al.,*** suggested that the major biochemical defect in persons with Blooms syndrome is chronic over production of the superoxide radical anion. It is assumed that inefficient removal of peroxide might be responsible for the high rates of sister chromatid exchange and chromosomal damage in Bloom syndrome cells.

Among 63 chromosomes found in blooms syndrome Ashkenazi jewish patients 61 had the same 6bp deletion/7bp insertion at the nucleotide 2281 c DNA of the BLM gene (97%) and 2 had another mutation (c.2407-2408 dupT). More than 60 different BS causing mutation of BLM gene have been detected. Cytogenetic findings in a Bloom syndrome patient with acute myeloid leukaemia

of the French-American-British subtype M1 showed preferential occurrence of total or partial loss of chromosome 7.

Diagnosis

Bloom syndrome is diagnosed first by clinical features and then by using any of three tests - the presence of quadriradial (Qr, a four armed chromatid interchange) in cultured blood lymphocytes, and/or the elevated levels of Sister chromatid exchange in cells of any type, and/or the mutation in the BLM gene.

Prenatal screening: Chorionic villus sampling or amniocentesis are used.

Bloom syndrome has an autosomal recessive pattern of inheritance. Both parents must be carriers in order for a child to be affected. The carrier frequency in individuals of Eastern European Jewish (Ashkenazi Jewish) ancestry is about 1/100. If both parents are carriers, there is a 1 in 4, or 25%, chance with each pregnancy for an affected child. Genetic counseling and genetic testing is recommended for families who may be carriers of Bloom syndrome. For families in which carrier status is known, prenatal testing is available using cytogenetic or molecular methods. Molecular DNA testing for the mutation that is common in the Ashkenazi Jewish population is also available.

Treatment

No treatment and therefore medical intervention is primarily preventative.

Chapter 3

Skeletal System

Ankylosing Spondylitis

Ankylosing Spondylitis (**AS**, from Greek ankylos, crooked; spondylos, vertebra; -itis, inflammation), previously known as **Bekhterev's** disease and **Marie-Strümpell** disease, is a chronic inflammatory disease of the axial skeleton, with variable involvement of peripheral joints and nonarticular structures. As is one of the seronegative spondyloarthropathies and has a strong genetic predisposition. It mainly affects joints in the spine and the sacroiliac joint in the pelvis. In severe cases, complete fusion and rigidity of the spine can occur. "Bamboo spine" develops when the outer fibers of the fibrous ring of the Intervertebral discossify, which results in the formation of marginal syndesmophytes between adjoining vertebrae.

Frequency

Ankylosing spondylitis prevalence is between 0.1 and 0.2% of the general population. The disease is most prevalent in Northern European countries, and seen least in people of Afro-Caribbean descent. The ratio of male to female disease is 3:1, however many rheumatologists believe the number of women with AS is underdiagnosed, as most women tend to experience milder cases of the disease. The majority of people with AS, including 95% of white people with the disease, express the HLA-B27 antigen and high levels of immunoglobulin A (IgA) in the blood.

Although Ankylosing spondylitis can occur in more than one person in a family, it is not a purely genetic disease. Multiple genetic and environmental factors likely play a part in determining the risk of developing this disorder.

Symptoms

The symptoms of Ankylosing spondylitis often appear gradually, with peak onset being between 20 and 30 years of age. The initial symptoms are usually a chronic dull pain in the lower back or gluteal region combined with stiffness of

the lower back. Individuals often experience pain and stiffness that awakens them in the early morning hours. As the disease progresses, loss of spinal mobility and chest expansion, with limitation of anterior flexion, lateral flexion, and extension of the lumbar spine, is seen. Systemic features are common, with weight loss, fever, or fatigue often present. Pain is often severe at rest, but improves with physical activity. However, many experience inflammation and pain to varying degrees regardless of rest and movement. AS can occur in any part of the spine or the entire spine, often with pain referred to one or the other buttock or the back of the thigh from the sacroiliac joint. Arthritis in the hips and shoulders may also occur. When the condition presents before the age of 18, it is relatively likely to cause pain and swelling of large limb joints, particularly the knee. In prepubescent cases, pain and swelling may also manifest in the ankles and feet, where heel spurs may also develop. Less commonly ectasia of the sacral nerve root sheaths may occur.

About 40% of people with AS will also experience inflammation of the anterior chamber of the eye, causing eye pain, redness, floaters and sensitivity to light. Inflammation of the prostate occurs with increased frequency in men. Cardiovascular involvement may include inflammation of the aorta, aortic valve insufficiency or disturbances of the heart's electrical conduction system. Lung involvement is characterized by progressive fibrosis of the upper portion of the lung.

Genetic Causes

Ankylosing Spondylitis is a systemic rheumatic disease, meaning it affects the entire body. Approximately 90% of people with AS express the HLA-B27 genotype, meaning there is a strong genetic association. **HLA-B** gene is located on chromosome 6 **(6p21.3).** 1–2% of individuals with the HLA-B27 genotype contract the disease.

Tumour Necrosis Factor-alpha **(TNF-α)** and **IL-1** are also implicated in Ankylosing Spondylitis. Autoantibodies specific for AS have not been identified. Anti-Neutrophil Cytoplasmic Antibodies (ANCAs) are associated with AS, but do not correlate with disease severity. The TNF-α gene is located on the short arm of **chromosome 6** within the major histocompatibility complex. **IL-1** gene is located on chromosome2 **(2q14).**

Diagnosis

There is no direct test to diagnose AS. The **Schober's** test is a useful clinical measure of flexion of the lumbar spine performed during the physical examination.

Magnetic Resonance Imaging **(MRI),** and **X-ray** studies of the spine, which show characteristic spinal changes and inflammation of the sacroiliac joint, combined with a genetic marker blood test are the major diagnostic tools.

Blood Parameters

During acute inflammatory periods, people with AS may show an increase in the blood concentration of C-Reactive Protein (**CRP)** and an increase in the Erythrocyte Sedimentation Rate **(ESR**), but there are many with AS whose CRP and ESR rates do not increase, so normal CRP and ESR results do not always correspond with the amount of inflammation that is actually present. In other words, some people with AS have normal levels of CRP and ESR, despite experiencing a significant amount of inflammation in their bodies.

Treatment

There is no cure for AS, although symptoms and pain can be minimised with medications. A diet low in starches found in flour products and potatoes, and high in proteins and vegetables is proved to be beneficial for AS patients.

Physical Therapy

Though physical therapy remedies have been scarcely documented, some therapeutic exercises are used to help manage lower back, neck, knee, and shoulder pain.

Mortality

Mortality is increased in people with AS and circulatory disease is the most frequent cause of death. AS patients have an increased risk of 60% for cerebrovascular mortality, and an overall increased risk of 50% for vascular mortality.

Research

In **2007**, a collaborative effort by an international team of researchers in the United Kingdom, Australia and the United States led to the discovery of two genes that also contribute to the cause of AS: **ARTS-1** and **IL23R**. The findings were published in the November 2007 edition of Nature Genetics, a journal that emphasizes research on the genetic basis for common and complex diseases. Together with HLA-B27, these two genes account for roughly 70 percent of the overall incidence of the disease.

Rheumatoid Arthritis

Rheumatoid Arthritis (RA) is a long lasting autoimmune disorder that primarily affects joints. It typically results in warm, swollen, and painful joints. Pain and stiffness often worsen following rest.

The first recognized description of RA was made in **1800 by Dr. Augustin Jacob Landré-Beauvais (1772–1840) of Paris**. The term rheumatoid arthritis is based on the Greek for watery and inflamed joints. It is **Multifactorial** disorder.

Frequency

RA affects between 0.5 and 1% of adults in the developed world with between 5 and 50 per 100,000 people newly developing the condition each year. In 2010, it resulted in about 49,000 deaths globally. Onset is uncommon under the age of 15 and from then on the incidence rises with age until the age of 80. Women are affected three to five times as often as men.

The age at which the disease most commonly starts is in women between 40 and 50 years of age, and for men somewhat later.

Symptoms

The condition generally starts between the ages 20–50, although it can begin at any age. RA usually affect joints commonly become inflamed, painful swollen and later deformed, however it also affects other organs in more than 15–25% of individuals.

In addition there may be general symptoms such as weakness fatigue and loss of apetite. The disease is both chronic, irregular and can be severely disabling. The course of disease varies greatly from patient to patient. Some patients have mild short term symptoms but in most, the disease is progressive for life.

Causes

While the cause of rheumatoid arthritis is not clear, it is believed to involve a combination of genetic and environmental factors.

RA is a chronic autoimmune disorder, the causes of which are not completely understood. It is a systemic (whole body) disorder principally affecting synovial tissues.

Half of the risk for RA is believed to be genetic. It is strongly associated with the inherited tissue type Major Histo Compatibility Complex **(MHC)**

antigen HLA-DRB1, and the genes PTPN22 and PADI4—hence family history is an important risk factor. Inheriting the PTPN22 gene has been shown to double a person's susceptibility to RA. PADI4 has been identified as a major risk factor in people of Asian descent, but not in those of European descent.

Smoking is the most significant non-genetic risk with RA being upto three times more common in smokers than non-smokers, particularly in men, heavy smokers, and those who are rheumatoid factor positive. Modest alcohol consumption may be protective.

Genetic Causes

Studies have confirmed a potential association between RA and two Herpes virus infections: Epstein-Barr Virus **(EBV)** and Human Herpes Virus 6 **(HHV-6).**

Vitamin D deficiency is more common in people with rheumatoid arthritis than in the general population. The **VDR gene** is located on chromosome 12 **(12q13.11).**

TNF-α plays a major role in the pathogenesis of RA. **TNF-α** gene is located on chromosome 6 **(6p21.3**).

Although TNF appears to be the dominant, other cytokines (chemical mediators) are likely to be involved in inflammation in RA. Blockade of TNF does not benefit all persons or all tissues (lung disease and nodules may get worse). Blockade of IL-1, IL-15 and IL-6 also have beneficial effects. The location of **IL-1** gene is **2q14**, gene **IL-6** is **7q21** and gene **IL-15** is **7q31**.

Diagnosis

X-rays of the hands and feet are generally performed in people with a many joints affected. Other medical imaging techniques such as Magnetic Resonance Imaging **(MRI)** and Ultrasound are also used in RA. There have been technical advances in Ultrasonography.

When RA is clinically suspected, testing done for the presence of Rheumatoid Factor **(RF**, a non-specific antibody), Anti-Citrullinated Protein Antibodies (**ACPAs),** Cyclic Citrullinated Peptide **(Anti-CCP)** test and the Anti-MCV assay (Antibodies against Mutated Citrullinated Vimentin). Recently a serological Point-Of-Care Test **(POCT)** for the early detection of RA has been developed.

Also, several other blood tests are usually done to allow for other causes of Arthritis, such as lupus erythematosus. The Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein, full blood count, kidney function, liver enzymes and other immunological tests (e.g., Anti Nuclear Antibody/ANA) are all performed at this stage.

Prevention

There is no known prevention for the condition other than being cautious with the risk factors.

Treatment

There is no cure for RA, but treatment can relieve symptoms and slows down the progress of the disease. Disease-modifying treatment has the best results when it is started early and aggressively. The treatment targets to minimize symptoms such as pain and swelling, to prevent bone deformity (for example, bone erosions visible in X-rays), and to maintain day-to-day functioning.

Regular exercise is recommended as both safe and useful to maintain muscles strength and overall physical function. It is uncertain if specific dietary measures have an effect. Physical activity is beneficial for persons with Rheumatoid arthritis complaining of fatigue. Occupational therapy has a positive role to play in improving functional ability of persons with rheumatoid arthritis.

Mortality: RA reduces lifespan on average from three to twelve years.

Osteogenesis Imperfecta

Osteogenesis Imperfect (OI), also known as Brittle bone disease or Lobstein syndrome, is a congenital bone disorder characterized by brittle bones that are prone to fracture. People with OI are born with defective connective tissue, or without the ability to make it, usually because of a deficiency of type I collagen. Eight types of OI can be distinguished. Most cases are caused by mutations in the **COL1A1** and **COL1A2** genes.

Classification of the eight different types of OI, type I is the most common, though the symptoms vary from person to person.

Type	Description	Gene	OMIM	Mode of inheritance
I	mild	Null COL1A1allele	166240 (IA), 166200 (IB)	autosomal dominant, 60% de novo
II	severe and usually lethal in the perinatal period	COL1A1, COL1A2,	166210 (IIA), 610854 (IIB)	autosomal dominant, ~100% de novo
III	considered progressive and deforming	COL1A1, COL1A2	259420	autosomal dominant, ~100% de novo
IV	deforming, but with normal sclerae most of the time	COL1A1, COL1A2	166220	autosomal dominant, 60% de novo
V	shares the same clinical features of IV, but has unique histologic findings (“mesh-like”)	IFITM5	610967	autosomal dominant
VI	shares the same clinical features of IV, but has unique histologic findings (“fish scale”)	SERPINF1	610968	autosomal recessive
VII	associated with cartilage associated protein	CRTAP	610682	autosomal recessive]
VIII	severe to lethal, associated with the protein leprecan	LEPRE1	610915	autosomal recessive

Frequency

The OI effects an estimated 6 to 7 per 1,00,000 people worldwide. In the United States, the incidence of Osteogenesis Imperfecta is estimated to be one per 20,000 live births. An estimated 20,000 to 50,000 people are affected by OI in the United States.

Frequency is approximately the same across groups, but for unknown reasons, the Shona and Ndebele of Zimbabwe seem to have a higher proportion of Type III to Type I than other groups. However, a similar pattern was found in segments of the Nigerian and South African populations. In these varied cases, the total number of OIs of all four types was roughly the same as any other ethnicity.

Symptoms

Osteogenesis Imperfecta congenital is the most severe form and may be apparent at birth. Multiple fractures are present in the newborn which have occurred in utero and is usually severely deformed because of imperfect formation and mineralization of bone. Most infants die shortly after birth, although a few survive as deformed dwarfs with normal mental development if no head trauma (injury) has occurred.

Osteogenesis Imperfecta tarda,usually a milder form and late onset. Though mild symptoms are visible when the child begins to walk, they become less severe with age and the tendency to fracture and often disappears after puberty. Other manifestations of the condition include blue sclera, translucent skin, hyper extensibility of ligaments, hypoplasia of the teeth, recurrent epistaxis (bleeding from nose caused by irritation of nose), excess diaphoresis(secretion of sweat), mild hyperpyrexia and a tendency to bruise(Injury that does not break the skin) easily and to develop otosclerosis (irregular osscification in the bony labryrinth of inner ear). There is a broad expressivity of the disease so that the number and extent of pathologic features may range from minimal to severe involvement.

Genetic Causes

As a genetic disorder, OI has historically been viewed as an autosomal dominant disorder of type I collagen. Most cases have been caused by mutations in the genes **COL1A1(17q21.33), COL1A2(17q22.1), IFITM5(11p15.5), SERPINF1(17p13.3), CRTAP(3p22.3)** and **LEPRE1(1p34.2).** In the past several years, there has been the identification of **Autosomal Recessive** forms. Most

people with OI receive it from a parent but in **35%** of cases it is an individual **("de novo"** or **"sporadic**") mutation.

Other Genes

A family with Recessive Osteogenesis Imperfecta has been reported to have a mutation in the **TMEM38B** gene on **chromosome 9**. This gene encodes TRIC-B, a component of TRIC, a mono valent cation-specific channel involved in calcium release from intracellular stores. It is extremely likely that there are other genes associated with this disease that have yet to be reported.

Diagnosis

There is no definitive test for OI. The diagnosis is usually suggested by the occurrence of bone fractures with little trauma and the presence of other clinical features. Skin biopsy can be performed to determine the structure and quantity of type I collagen. DNA testing can confirm the diagnosis, however it cannot exclude it, because not all mutations causing OI are known and/or tested for. OI type II is often diagnosed by Ultrasound during pregnancy, where already multiple fractures and other characteristic features may be present. Relative to control, OI cortical bone shows increased porosity, canal diameter, and connectivity in Micro-computed Tomography.

Treatment

There is no cure for OI. Treatment is aimed at increasing overall bone strength to prevent fracture and maintain mobility. Bisphosphonates can increase bone mass, and reduce bone pain and fracture. In severe cases, bones are surgically corrected, and rods are placed inside the bones, particularly to enable infants to learn to walk. Bone infections are treated as and when they occur with the appropriate antibiotics and antiseptics.

❑

Chapter 4

Muscle

Muscular Dystrophies

Muscular Dystrophies are a group of genetically transmitted diseases characterizied by progressive atrophy degenerate, decay of symmetric groups of skeletal muscles with out evidence of involvement or degeneration of neural tissue. In all forms of muscular dystrophy there is an insidious (slight) loss of strength with increasing disability and deformity, although each type differs in the groups of muscles affected, the age of onset, the rate of progression and the mode of genetic inheritance, the basic cause is unknown but appears to be an inborn error of metabolism-serum creatine phosphokinase is increased in affected individuals and acts as a diagnostic aid, especially in asymptomatic children in families in risk.

The main types of the disease are Pseudohypertrophic, Duchenne Muscular Dystrophy **(DMD),** limb gridle muscular dystrophy and facioscapulohumeral muscular dystrophy, rarer forms include Becker's Muscular Dystrophy **(BMD**), distal muscular dystrophy, ocular myopathy and Myotonic Muscular Dystrophy **(MMD).** DMD is a common disorder. The isolation of the gene affected in this **X-linked** disorder and the charatcterisation of its protein (named dystrophin because of its association with DMD) has given insight into every aspect of the disease. **(Worton** & **Gillard, 1991).**

Duchenne Muscular Dystrophy (DMD)

Duchenne Muscular Dystrophy **(DMD)** is a recessive X-linked form of muscular dystrophy, which results in muscle degeneration and premature death. Dystrophin, a protein within muscle tissue that provides structural stability to the Dystro Glycan Complex (DGC) of the cell membrane. DMD is due to the mutation in the gene dystrophin located on the human X chromosome.

Frequency

Affecting around 1 in 3,600 boys. DMD is inherited in an X-linked recessive pattern. Females will typically be carriers for the disease while males will be affected. While both sexes can carry the mutation, females are rarely affected.

The average life expectancy for individuals afflicted with DMD is around 25.

Symptoms

Symptoms usually appear in boys between the ages of 2 and 3 and may be visible in early infancy. The main symptom of DMD, a progressive neuromuscular disorder, is muscle weakness associated with muscle wasting with the voluntary muscles being first affected, especially those of the hips, pelvic area, thighs, shoulders, and calves. Muscle weakness also occurs later, in the arms, neck, and other areas. Calves are often enlarged.

Other physical symptoms are:

1. Awkward manner of walking, stepping, or running.
2. Frequent falls.
3. Fatigue.
4. Difficulty with motor skills (running, hopping, jumping).
5. Progressive difficulty walking.
6. Muscle fiber deformities.
7. Pseudohypertrophy (enlarging of tongue and calf muscles).
8. Higher risk of neurobehavioral disorders.
9. Eventual loss of ability to walk (usually by the age of 12).
10. Skeletal deformities (including scoliosis in some cases).
11. Trouble getting up from lying or sitting position.

Genetic Causes

Duchenne Muscular Dystrophy (DMD) is caused by a mutation of the dystrophin gene at locus **Xp21.2**, located on the short arm of the X chromosome. Dystrophin is responsible for connecting the cytoskeleton of each muscle fiber to the underlying basal lamina (extracellular matrix), through a protein complex containing many subunits.

More than 1,000 mutations in the DMD gene have been identified in people with the Duchenne and Becker forms of muscular dystrophy. These conditions occur almost exclusively in males and are characterized by progressive muscle weakness and wasting (atrophy). Most of the mutations that cause these conditions delete part of the DMD gene. Other mutations abnormally duplicate part of the gene or change a small number of DNA building blocks (nucleotides) in the gene.

Diagnosis

1. Muscle biopsy.
2. Electromyography.
3. Genetic pedigree.
4. Genetic counselling is advised for people with a family history of the disorder. Duchenne Muscular Dystrophy can be detected with about 95% accuracy by genetic studies performed during pregnancy.
5. DNA test: The muscle-specific isoform of the dystrophin gene is composed of 79 exons, and DNA testing and analysis can usually identify the specific type of mutation of the exon or exons that are affected.

Treatment

1. There is no cure for DMD.
2. Treatment is generally aimed at controlling the onset of symptoms to maximize the quality of life.
3. Physical therapists are concerned with enabling patients to reach their maximum physical potential.

Becker's Muscular Dystrophy (BMD)

Becker Muscular Dystrophy (BMD) is an X-linked recessive inherited disorder characterized by slowly progressive muscle weakness of the legs and pelvis. It is a type of dystrophinopathy. This is caused by mutations in the dystrophin gene, which encodes the protein dystrophin. Becker Muscular Dystrophy is related to Duchenne muscular dystrophy in that both result from a Mutation in the Dystrophin gene.

Frequency

Becker Muscular Dystrophy occurs in approximately 1.5–6 in 100,000 male births, making it much less common than Duchenne Muscular Dystrophy. Symptoms usually appear in men at about ages 8–25, but may sometimes begin later.

Symptoms

1. Muscle weakness, slowly progressive difficulty walking.
2. Severe upper extremity muscle weakness.
3. Toe-walking .
4. Use of Gower's Maneuver to get up from floor.
5. Difficulty breathing.
6. Skeletal deformities, chest and back (scoliosis).
7. Pseudohypertrophy of calf muscles.
8. Muscle cramps.
9. Heart muscle problems.
10. Elevated creatine kinase levels in blood.

Possible complications associated with MD are:

1. Cardiac arrhythmias.
2. Mental impairment (less common in BMD than it is in DMD).
3. Pulmonary failure.
4. Pneumonia.

Genetic Causes

The disorder is inherited with an **X-linked recessive** inheritance pattern. The gene is located on the X chromosome. Since women have two X chromosomes, if one X chromosome has the non-working gene, the second X chromosome will have a working copy of the gene to compensate, because of this ability to compensate, women rarely develop symptoms. All dystrophinopathies are inherited in an X-linked Recessive manner. The risk to the siblings of an affected individual depends upon the carrier status of the mother. Carrier females have a 50% chance of passing the DMD mutation in each pregnancy. Sons who inherit the mutation will be affected; daughters who inherit the mutation will be carriers. Men who have Becker Muscular Dystrophy can have children, and all their daughters are carriers, but none of the sons will inherit their father's mutation.

Diagnosis

1. Muscle biopsy.
2. Creatine kinase test.
3. Electromyography (shows that weakness is caused by destruction of muscle tissue rather than by damage to nerves).
4. Genetic testing.
5. Genetic counseling may be advisable when potential carriers or patients want to have children. Sons of a man with Becker Muscular Dystrophy do not develop the disorder, but daughters will be carriers (and some carriers can experience some symptoms of Muscular Dystrophy), the daughters› sons may develop the disorder.

Treatment

There is no known cure for Becker Muscular Dystrophy yet. Treatment is to control the symptoms and to maximize the quality of life which can be measured by specific questionnaires. Activity is encouraged. Inactivity (such as bed rest) or sitting down for too long can worsen the muscle disease. Physical therapy may be helpful to maintain muscle strength. Orthopedic appliances such as braces and wheelchairs may improve mobility and self-care.

Myotonia

Congenital Myotonia (also Myotonia Congenita) (Myo- from Greek; muscle, and Tonus from Latin; tension), is a Genetic, neuromuscular channelopathy that affects skeletal muscles (muscles used for movement). The disease was first described by Danish/German physician **Julius Thomsen in 1876**, who himself suffered from the disease. The hallmark of the disease is the failure of initiated contraction to terminate, often referred to as delayed relaxation of the muscles (myotonia) and rigidity.

Frequency

In Northern Scandinavia, the prevalence of Myotonia Congenita has been estimated at 1:10,000.

Myotonia Congenita is estimated to affect 1 in 1,000,000 people worldwide.

Inheritance

Two types of Myotonia Congenita exist; **Autosomal Dominant Myotonia Congenita** also called Thomsens disease (OMIM 160800), after Julius Thomsen, and **Recessive Generalized Myotonia** (RGM) or **Becker Myotonia** (OMIM 255700), after the German professor Peter Emil Becker, who discovered the recessive subtype of patients suffering from Myotonia Congenita. The term congenital, congenital disorder, strictly applies only to Thomsens disease, as the onset of Becker Myotonia may be delayed upto the age of 4–6 years. In Myotonia Congenita, the term reflects that the disease is genetically present from birth, while the onset may be delayed.

The two forms of Myotonia Congenita have different patterns of inheritance. **Thomsen disease** is inherited in an **Autosomal Dominant** pattern, Becker disease is inherited in an Autosomal Recessive pattern.

Symptoms

Symptoms include delayed relaxation of the muscles after voluntary contraction (Myotonia), and may also include stiffness, hypertrophy (enlargement), transient weakness in some mutations, and cramping.

Early symptoms in a child may include:

1. Difficulty swallowing.
2. Gagging.
3. Stiff movements that improve when they are repeated.
4. Frequent falling.
5. Difficulties opening eyelids after strenuous contraction or crying.

Possible complications may include:

1. Aspiration pneumonia (caused by swallowing difficulties).
2. Frequent choking or gagging in infants (also caused by swallowing difficulties).
3. Abdominal muscle weakness.
4. Chronic joint problems.
5. Injury due to falls.

Causes

Myotonia Congenita is caused by a problem in the part of the muscle cells that are needed for muscles to relax. Abnormal repeated electrical signals occur in the muscles, causing a stiffness called Myotonia.

Genetics Causes

Myotonia Congenita is caused by a genetic change (mutation). It is passed down from either one or both parents to their children (inherited). Chloride channel protein, skeletal muscle (CLCN1) is a protein that in humans is encoded by the **CLCN1 gene**, located on chromosome 7 (**7q35).**

Myotonia Congenita is caused in humans by loss of function mutations in the gene CLCN1. CLCN1 is the gene encoding the protein CLCN1, that forms the ClC-1 chloride channel, critical for the normal function of skeletal muscle cells.

More than 80 mutations in the CLCN1 gene have been identified in people with Myotonia Congenita. Most of these mutations cause the Autosomal Recessive form of the disorder, which is known as Becker disease. CLCN1 mutations also cause the Autosomal Dominant form of Myotonia Congenita, which is known as Thomsen disease.

Because several CLCN1 mutations can cause either Becker disease or Thomsen disease, doctors usually rely on characteristic signs and symptoms to distinguish the two forms of Myotonia Congenita.

Diagnosis

1. Electromyography (EMG, a test of the electrical activity of the muscles).
2. Genetic testing.
3. Muscle biopsy.

Treatment

Some cases of Myotonia Congenita do not require treatment, or it is determined that the risks of the medication outweigh the benefits. If necessary, however, symptoms of the disorder may be relieved with quinine, phenytoin, carbamazepine, mexiletine andother anticonvulsant drugs. Physical therapy and other rehabilitative measures may also be used to help muscle function. Genetic counselling is available.

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Chapter 5

Eye

Glaucoma

The word "Glaucoma" comes from the Greek, "opacity of the crystalline lens". **Glaucoma** is a group of eye diseases with multi-factorial etiology which result in damage to the optic nerve and vision loss. A major risk factor is increased pressure in the eye. The disorders can be roughly divided into two main categories: "**open-angle**" and "**closed-angle**" (or "**angle closure**") Glaucoma. Open-angle chronic Glaucoma is painless, tends to develop slowly over time and often has no symptoms until the disease has progressed significantly. Closed angle Glaucoma is usually chronic and asymptomatic but can present all of a sudden as well. Glaucoma may be inherited in different ways, either **Autosomal Dominant (AD) or Autosomal Recessive (AR).**

Frequency

As of 2010, there were 44.7 million people in the world with open angle Glaucoma. The same year, there were 2.8 million people in the United States with open angle Glaucoma. By 2020, the prevalence is projected to increase to 58.6 million worldwide and 3.4 million in the United States.

Internationally, Glaucoma is the second-leading cause of blindness, after cataract. Glaucoma is also the leading cause of blindness in African Americans, who have higher rates of primary open angle Glaucoma. Bilateral vision loss can negatively affect mobility and interfere with driving.

Symptoms

Sudden eye pain, blurred vision, mid-dilated pupil, redness, nausea and vomiting results from a sudden spike in intraocular pressure from iridotrabecular contact. Glaucoma can permanently damage vision in the affected eye, first by decreasing peripheral vision (reducing the visual field), and then potentially leading to blindness if left untreated.

Causes

Of the several causes for Glaucoma, ocular hypertension (increased pressure within the eye) is the most important risk factor in most Glaucoma's, but in some populations, only 50% of people with primary open-angle Glaucoma actually have elevated ocular pressure.

Open-angle Glaucoma accounts for 90% of Glaucoma cases in the United States. Closed-angle Glaucoma accounts for less than 10% of Glaucoma cases in the United States, but as many as half of Glaucoma cases in other nations (particularly Asian countries).

Dietary

There is no clear evidence to show that Glaucoma is the result of vitamin deficiencies and hence oral vitamin supplementation is not a recommended treatment for Glaucoma. The patients may develop intraocular pressure with caffeine intake unlike for normal individuals

Ethnicity and Sex

Many people of East Asian descent are amenable to developing angle closure Glaucoma due to shallower anterior chamber depths.

Genetic Causes

Positive family history is a risk factor for glaucoma. The relative risk of having Primary Open-Angle Glaucoma (**POAG**) is increased about two- to four-fold for individuals who have a sibling with Glaucoma. Glaucoma, particularly primary open-angle Glaucoma, is associated with mutations in several genes including **MYOC** (Cytogenetic Location: **1q23-q24**), **ASB10** (Cytogenetic Location: **7q36.**1), **WDR36** (Cytogenetic Location: **5q22.1**), **NTF4** (Cytogenetic Location: **19q13.3**), and **TBK1**(Cytogenetic Location: **12q14.1**, although most cases of Glaucoma do not involve these genetic mutations. Normal-tension Glaucoma, which comprises one-third of POAG, is also associated with genetic mutations including **OPA1**(CytogeneticLocation: **3q28**) and **OPTN** (Cytogenetic Location: **10p13**) genes.

Various rare congenital/genetic eye malformations are associated with Glaucoma. Occasionally, failure of the normal third-trimester gestational atrophy of the hyaloids canal and the tunica vasculosa lentis is associated with other

anomalies. Angle closure-induced ocular hypertension and glaucomatous optic neuropathy may also occur with these anomalies.

Diagnosis

1. Measuring intraocular pressure (Tonometry)
2. Testing for optic nerve damage (Aptholomoscopy)
3. Checking for areas of vision loss (Visual field test)
4. Measuring corneal thickness (Pachymetry)
5. Inspecting the drainage angle (Gonioscopy)
6. Imaging technology

Treatment

Glaucoma has been called the "**silent thief of sight**" because the loss of vision often occurs gradually over a long period of time, and symptoms only occur when the disease is quite advanced. Once lost, vision cannot normally be recovered, so treatment is aimed at preventing further loss. The modern goals of Glaucoma management are to avoid glaucomatous damage and nerve damage, and preserve visual field and total quality of life for patients, with minimal side effects. This requires appropriate diagnostic techniques and follow-up examinations, and judicious selection of treatments for the individual patient. Although intraocular pressure is only one of the major risk factors for Glaucoma, lowering it via various pharmaceuticals and/or surgical techniques is currently the main stay of Glaucoma treatment.

Research

Scientists track eye movements in glaucoma patients to check vision impairment while driving.

Rho kinase inhibitors, such as ripasudil, work by inhibition of the actin cytoskeleton, resulting in the morphological changes in the trabecular meshwork and increased aqueous outflow. More compounds in this class are being investigated in phase 2 and phase 3 trials.

Cataract

A **Cataract** is a clouding of the lens in the eye leading to a decrease in vision. It can affect one or both eyes. Often it develops slowly. Symptoms may include faded colours, blurry vision, and halos around light, trouble with bright lights, and trouble seeing at night. This may result in trouble driving, reading, or recognizing faces. Poor vision may also result in an increased risk of falling and depression. Cataracts are the cause of half of blindness and 33% of visual impairment worldwide.

Approximately 30% of cases of Congenital Cataract are hereditary. The majority of the isolated forms being inherited as an **Autosomal Dominant** gene although **Autosomal Recessive** and **X-linked** forms are also known.

Frequency

About 20 million people globally are blind due to Cataracts. It is the cause of about 5% of blindness in the United States and nearly 60% of blindness in parts of Africa and South America. Blindness from Cataracts occurs in about 10 to 40 per 100,000 children in the developing world and 1–4 per 100,000 children in the developed world. Cataracts become more common with age. About half the people in the United States have had Cataracts by the age of 80.

Symptoms

Symptoms vary depending on the type of Cataract, though considerable overlap occurs. People with nuclear sclerotic or brunescent Cataracts often notice a reduction of vision. Those with posterior subcapsular Cataracts usually complain of glares their major symptom.

The severity of Cataract formation, assuming no other eye disease is present, is judged primarily by a visual acuity test. The appropriateness of surgery depends on a patient›s particular functional and visual needs and other risk factors, all of which may vary widely.

Cataracts are most commonly due to aging, but may also occur due to trauma, radiation exposure, congenital, or occur following eye surgery for other problems.

Causes

Risk factors include diabetes, smoking tobacco, prolonged exposure to sunlight, and alcohol. Either clumps of protein or yellow-brown pigment may be deposited in the lens reducing the transmission of light to the retina at the back of the eye.

Genetic Causes

Genes that control the mechanisms in protection and maintenance of the eye lens play a key role in development of cataract. Childhood cataract or early life cataracts are occasionally be due to a particular syndromes such as 1q21.1 deletion syndrome, cri-du-chat syndrome, Down syndrome, Patau syndrome, Edward syndrome, and Turner syndrome.

In the case of Neurofibromatosis type 2, juvenile Cataract on one or both sides may be noted. Examples of single-gene disorder include Alport's syndrome, Conradi›s syndrome, Myotonic dystrophy, and Oculocerebrorenal syndrome or Lowe syndrome.

Diagnosis: Eye examination.

Treatment

Prevention includes wearing sunglasses and not smoking. Early on the symptoms may be improved with eyeglasses. If this does not help, surgery to remove the cloudy lens and replace it with an artificial lens is the only effective treatment. Surgery is only needed if the Cataracts are causing problems. Surgery generally results in an improved quality of life. Cataract surgery is not easily available in many countries, especially for women.

Prevention

Although no means of preventing Cataracts has been scientifically proven, wearing ultraviolet-protecting sunglasses may slow the development.

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Chapter 6

Jaws

Cleft Lip and Palate

Cleft Lip (**CL**) and Cleft Palate(**CP**), also known as Oro Facial Cleft (**OFC**) and cleft lip and palate, is a group of conditions that includes Cleft lip, Cleft palate, and both together (**CLP**). A Cleft lip contains an opening in the upper lip that may extend into the nose. The opening may be on one side, both sides, or in the middle. A Cleft palate is when the roof of the mouth contains an opening into the nose. These disorders can result in feeding problems, speech problems, hearing problems, and frequent ear infections. Less than half the time the condition is associated with other disorders.

Frequency

Cleft lip and palate occurs in about 1–2 per 1000 births in the developed world.

Different ethnic groups show different rates for Cleft lip with or without Cleft palate and Cleft palate alone. The highest prevalence rates for (CL ± P) are reported for Native Americans and Asians. Africans have the lowest prevalence rates.

Native Americans: 3.74/1000

Japanese: 0.82/1000 to 3.36/1000

Chinese: 1.45/1000 to 4.04/1000

Caucasians: 1.43/1000 to 1.86/1000

Latin Americans: 1.04/1000

Africans: 0.18/1000 to 1.67/1000

CL and CP are a type of birth defect (congenital).CL is about twice as common in males as females, while CP without CL is more common in females. The inheritance is **Sex linked and Autosomal**. Harelip and Cleft palate are developmental abnormalities with a great genetic basis. Penetrance is incomplete

and expressivity varies from very slight external clefts to very severe clefts and even the hard palate.

Penetrance and expressivity as consequences of development events in gene action are interrelated. Many genes with a low degree of penetrance express themselves weakly and high penetrance and strong expresivity often together. Harelip and Cleft palate will be cited as examples of these conditions.

Symptoms

If the Cleft does not affect the palate structure of the mouth it is referred to as Cleft lip. Cleft lip is formed in the top of the lip as either a small gap or an indentation in the lip (partial or incomplete cleft) or it continues into the nose (complete cleft). Lip cleft can occur as a one sided (unilateral) or two sided (bilateral). It is due to the failure of fusion of the maxillary and medial nasal processes (formation of the primary palate).

Clefts can also affect other parts of the face, such as the eyes, ears, nose, cheeks, and forehead.

Causes

Great majority are in the **Multi factorial** group as they are highly susceptible to environmental and genetic factors, rationalising the high incidence of facial malformations.

The cause in most cases is unknown. Risk factors include smoking during pregnancy, diabetes, an older mother, obesity, and certain medications such as some used to treat seizures.

Genetic Causes

Genetic factors contributing to Cleft lip and Cleft palate formation have been identified for some syndromic cases, but knowledge about genetic factors that contribute to the more common isolated cases of Cleft lip/palate is still patchy.

Many Clefts run in families, even though in some cases there does not seem to be an identifiable syndrome present, possibly because of the current incomplete genetic understanding of mid facial development. A number of genes are involved including Cleft lip and palate trans membrane protein 1 and GAD1, one of the glutamate de-carboxylases. Many genes are known to play a role in

craniofacial development and are being studied through the face base initiative for their part in clefting. These genes are **AXIN2, BMP4(14q22); FGFR1,FGFR2, FOXE1, IRF6, MAFB, MMP3, MSX1(4P16.1); MSX2** (Msh homeobox 2); **MSX3, PAX7, PDGFC, PTCH1, SATB2, SOX9, SUMO1(2q32.2-q33)** (Small ubiquitin-related modifier; 1)**TBX22, TCOF** (Treacle protein); **TFAP2A, VAX1, TP63(3q27); ARHGAP29, NOG, NTN1, WNT** genes.

Diagnosis

Traditionally, the diagnosis is made at the time of birth by physical examination. Recent advances in prenatal diagnosis have allowed obstetricians to diagnose facial Clefts in utero. They can often be diagnosed during an ultrasound done during pregnancy.

Treatment

Cleft lip and palate is very treatable; however, the kind of treatment depends on the type and severity of the cleft.

A Cleft lip or palate can be successfully treated with surgery. This is often done in the first few months of life for Cleft lip and before eighteen months for Cleft palate. Speech therapy and dental care may also be needed. With appropriate treatment outcomes are good.

Mortality

It caused about 4,000 deaths globally in 2010 down from 8,400 in 1990.

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Chapter 7

Ears

Deafness

A person is considered to be deaf if they cannot hear the same range of sounds as a person with normal hearing ability. People that cannot hear any sounds are also deaf. People who are partially deaf may hear some sounds and may hear words. People who can hear and understand words are hard of hearing.

Hearing loss, also known as hearing impairment, or anacusis, is a partial or total inability to hear. An affected person may be described as hard of hearing. A deaf person has little to no hearing. Hearing loss may occur in one or both ears. In children hearing problems can affect the ability to learn language and in adults it can cause work related difficulties. In some people, particularly older people, hearing loss can result in loneliness. Hearing loss can be temporary or permanent.

Frequency

Globally hearing loss affects about 10% of the population to some degree. It caused moderate to severe disability in 124.2 million people as of 2004 (107.9 million of whom are in low and middle income countries). Of these 65 million acquired the condition during childhood. At birth ~3 per 1000 in developed countries and more than 6 per 1000 in developing countries have hearing problems.

Hearing loss increases with age. In those between 20 and 35, rates of hearing loss are 3% while in those 44–55, it is 11% and in those 65–85, it is 43%.

Incidence of hearing loss more in males than females and in older than younger persons.

Symptoms

1. Difficulty using the telephone.
2. Loss of directionality of sound.
3. Difficulty understanding speech, especially women and children.

4. Difficulty in speech discrimination against background noise (cocktail party effect).
5. Sounds or speech becoming dull, muffled or attenuated.
6. Need for increased volume on television, radio, music and other audio sources.

Hearing loss is sensory, but may have accompanying physiological symptoms:

1. Pain or pressure in the ears.
2. Punctured eardrum.
3. Effusion in the middle ear.
4. Otitis externa, inflammation or infection of the ear canal or eardrum.
5. Eustachian tube dysfunction or inflammation.

Causes

Age: People will lose their hearing as they get older.

Exposure to noise: A noisy environment may affect the hearing of people and cause people to become deaf.

Genetic conditions: There can be a family history of deafness. If the mother and/or father are deaf, their child will have a strong chance of being deaf.

Diseases: Certain diseases may cause deafness.

Drugs: Certain drugs may affect hearing.

Chemicals: Certain chemicals can damage the ear.

Genetic Causes

Hearing loss can be inherited. Around 75–80% of all these cases are inherited by **Recessive genes**, 20–25% are inherited by **Dominant genes**, 1–2% are inherited by **X-linked** patterns, and fewer than 1% are inherited by **Mitochondrial inheritance.**

Deafness can be of two forms i.e., syndromic and non-syndromic. Any serious medical problems can result in syndromic form and accounts for 30% and Non syndromic deafness is seen in individuals without any medical history and accounts for 70%, and represents the majority of hereditary hearing loss.

The Dominantly inherited deafness loci are conventionally designated with a suffix ‘A’, i.e., **DFNA**, the recessive with suffix ‘B’, i.e., **DFNB**, to a number, indicating the order of their discovery and **DFN for X-linked inheritance.**

Already around 80 chromosomal locations harbouring genes involved in non-syndromic hearing loss have been reported, with mapping of approximately half the genes in these loci. The protein products of these genes range from transcriptional factors **(POU3F4, EYA4, TFCP2L3),** motor molecules (myosin 2, 6, 7 and 15), ion channel, transporter (pendrin**, KCNQ4**), integral membrane protein (**TMC1, TMIE**), adhesion molecules (Catherine and protocadherin), gap junction proteins (connexins 26, 30, 31 and 43), extracellular protein and many other novel molecules.

Identification of genes and mutation analysis in families segregating Recessive and Dominant inheritance has revealed unique behaviour of several mutant alleles. It has been documentated that a gene expressing **Recessive** inheritance in some families was implicated in other families segregating **Autosomal Dominant** inheritance. The gene located in the **DFNB7/11** interval on **chromosome 9**, encoding a transmembrane protein **TMC1** is example of one such gene that was identified in several Recessive families from India and Pakistan, as well as in an American large kindred segregating Dominant inheritance.

Other deafness genes segregating non-syndromic/syndromic **Autosomal Recessive** inheritance, contributed to 15% of genetic cause of deafness in India. In order of precedence, the genes associated with deafness in Indian families that were identified in the study were (1) Myo7A, segregating with UshlB, in the **DFNB2** interval on chromosome **11q13.5** (2) **Myo 15 (DFNB3**) on chromosome **17p11.2** (3) **SLC26A4** (**DFNB4**) on **7q31**, also cause of Pendred syndrome, 16 (4) **TMC1** gene (**DFNB7/11**)on chromosome **9q13.6** (5) **OTOF** located in **DFNB9** interval on chromosome **2p22-23** (6) **Cadherin 23(DFNB12**) on chromosome **I0q21-q22** segregating with UshlD 7**) Harmonin (DFNB18**) on **11p14-15**.1 also causing UshlC, 8) **Protocadherin 15 (DFNB23**) underlying UshlF syndrome.

Diagnosis

Diagnosis of a hearing loss is usually conducted by a general practitioner Medical Doctor, Otolaryngologist, certified and Licensed Audiologist, School or Industrial Audiometrist, or other Audiology Technician.

Prevention

It is estimated that half of cases of hearing loss are preventable. A number of preventative strategies are effective including: immunization against rubella to

prevent congenital rubella syndrome, immunization against H. influenza and S. pneumonia to reduce cases of otitis media, and avoiding or protecting against excessive noise exposure.

Treatment

Treatment depends on the specific cause if known as well as the extent, type and configuration of the hearing loss. Most hearing loss, that resulting from age and noise, is progressive and irreversible, and there are currently no approved or recommended treatments; management is by hearing aid. A few specific kinds of hearing loss are amenable to surgical treatment. In other cases, treatment is addressed to underlying pathologies, but any hearing loss incurred may be permanent.

There are a number of devices that can improve hearing in those who are hearing impaired or deaf or allow people with these conditions to manage better in their lives.

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Chapter 8

Alimentary System

Pyloric Stenosis

Pyloric Stenosis or Pyloro Stenosis is narrowing (stenosis) of the opening from the stomach to the first part of the small known as the duodenum, due to enlargement (hypertrophy) of the muscle surrounding this opening (the pylorus, meaning "gate"), which spasms (involuntary contraction of muscle) when the stomach empties. This condition causes severe projectile non-bilious vomiting. It most often occurs in the first few months of life, when it may thus be more specifically labeled as infantile hypertrophic Pyloric Stenosis. The thickened pylorus is felt classically as an olive-shaped mass in the middle upper part or right upper quadrant of the infant›s abdomen. In Pyloric Stenosis, it is uncertain whether there is a true congenital anatomic narrowing or whether there is merely a functional hypertrophy of the Pyloric sphincter muscle. This condition typically develops in male babies in the first 2–6 weeks of life.

Pyloric Stenosis also occurs in adults, where the cause is usually a narrowed pylorus due to scarring from chronic peptic ulceration. This is a different condition from the infantile form.

Frequency

It is commonly associated with people of Scandinavian ancestry. Pyloric Stenosis is more common in Caucasians than Hispanics, Blacks, or Asians. The incidence is 2.4 per 1000 live births in Caucasians, 1.8 in Hispanics, 0.7 in Blacks, 0.6 in Asians and 1–5 per 1000 in Brittan. It is also less common amongst children of mixed race parents.

Symptoms

Babies with this condition usually present any time in the first weeks to months of life with progressively worsening vomiting.

Some infants present with poor feeding and weight loss but others demonstrate normal weight gain. Dehydration may occur which causes a baby to cry without having tears and to produce less wet or dirty diapers due to not urinating for hours or for a few days. Constant hunger, belching (sendout wind from stomach to mouth) and colic (severe abdominal pain) are other possible signs that the baby is unable to eat properly.

Causes

Pyloric Stenosis seems to be **Multifactorial**, with some genetic and some environmental components. Males are more commonly affected than females, with first born males affected about four times as often, and there is a genetic predisposition for the disease. Rarely, infantile Pyloric Stenosis can occur as an **Autosomal Dominant** condition.

Infantile Hypertrophic Pyloric Stenosis (**IHPS**), characterized by enlarged pyloric musculature and gastric-outlet obstruction, is associated with altered expression of neuronal Nitric Oxide Synthase (**nNOS**).**Chang et al.,1996** suggested that NoS is a susceptible locus for Pyloric Stenosis.

Multiple susceptible loci have been implicated in **IHPS** on chromosome **12q**; **IHPS 2(610260)** on chromosome **16p12-p13**; **IHPS 3(612017)** on chromosome **11q14-q22; IHPS 4(300711)** on chromosome **Xq23; IHPS 5(612525)** on chromosome **16q24.**

Diagnosis

Previous history and physical examination, often supplemented by Radiographic Imaging studies are the sources to diagnose the disease. Pyloric Stenosis should be suspected in any young infant with severe vomiting. On physical exam, palpation (examine medically by touch) of the abdomen may reveal a mass in the epigastrium. Most cases of Pyloric Stenosis are diagnosed/confirmed with ultrasound, if available, showing the thickened pylorus.

Treatment

Infantile Pyloric Stenosis is typically managed with surgery; very few cases are mild enough to be treated medically. Intravenous and oral atropine may be used to treat Ploric Stenosis. It might be an alternative to surgery in children who have contraindications for anaesthesia or surgery, or in children whose parents do not want surgery.

Cirrhosis of Liver

Cirrhosis is a condition in which the liver slowly deteriorates and is unable to function normally due to chronic, or long lasting, injury. Scar tissue replaces healthy liver tissue and partially blocks the flow of blood through the liver.

Frequency

Cirrhosis resulted in 1.2 million deaths in 2013, up from 0.8 million deaths in 1990. Of these, alcohol caused 384,000, hepatitis C caused 358,000, and hepatitis B caused 317,000. In the United States, more men die of Cirrhosis than women. The first known description of the condition is by Hippocrates in the 5th century BCE. It is a **Multi factorial** inheritance disease.

Symptoms

Many people with cirrhosis have no symptoms in the early stages of the disease. However, as the disease progresses, a person may experience the following symptoms:

Fatigue, or feeling tired.

Causes

Chronic hepatitis: Hepatitis C is due to a viral infection that causes inflammation, or swelling, and damage to the liver.

Alcohol related liver disease: Alcoholism is the second most common cause of cirrhosis in the United States.

Non Alcoholic Steato Hepatitis (NASH): Now ranks as the third most common cause of cirrhosis in the United States.

Chronic Hepatitis B: Hepatitis B, like hepatitis C, is due to a viral infection that causes inflammation and damage to the liver.

Less Common Causes of Cirrhosis

Autoimmune Hepatitis

1. In this form of Hepatitis, the body's immune system attacks liver cells and causes inflammation, damage, and eventually Cirrhosis.
2. Diseases that damage, destroy, or block the bile ducts.
3. Inherited diseases that affect the liver.

4. Rare viral infections of the liver**.** Hepatitis D, or Hepatitis Delta, and Hepatitis E are two rare viral infections of the liver.

Genetic Causes

Researchers discovered that variants of two genes, interleukin **12A (IL12A) (Location:3q25.33**) and interleukin **12RB2 (IL12RB2**)(**Location:1p31.3-p31.2**) were strongly associated with Primary Biliary Cirrhosis. These two genes constitute a pathway of the immune system. Potential therapeutic manipulation of this pathway provides new possibilities for more effective treatments of these patients, says **Dr. Lazaridis.**

Researchers also confirmed that the Human Leukocyte Antigen (**HLA**) region of the genome is linked to primary biliary Cirrhosis, an association which had been identified in previous research. "Although both the **HLA region** and the **IL12** pathway are equally involved with susceptibility to primary biliary Cirrhosis, **HLA** is very complicated to dissect genetically, with multiple pathways," says **Dr. Lazaridis**. "It will be difficult to modulate with the intention to treat, while **IL12** is a single pathway and thus more amenable to treatment."

Diagnosis

Medical and family history.	Imaging tests.
Physical exam.	Liver biopsy.
Blood test.	

Treatment

Treatment for Cirrhosis depends on the cause of the disease and whether complications are present. In the early stages of Cirrhosis, the goals of treatment are to slow the progression of tissue scarring in the liver and prevent complications. As Cirrhosis progresses, a person may need additional treatments and hospitalization to manage complications.

Treatment may include the following:

1. Avoiding Alcohol and Illegal Substances.
2. Preventing problems with medications.
3. Viral Hepatitis vaccination and screening.
4. Treating Causes, Symptoms and complications of Cirrhosis.

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Chapter 9

Respiratory System

Cystic Fibrosis

Cystic Fibrosis (**CF**), also known as mucoviscidosis, is a genetic disorder which mainly affects the lungs besides the pancreas, liver, kidneys, and intestine.

CF is inherited in an **Autosomal Recessive** manner. It is caused by the presence of mutations in both copies of the gene for the Cystic Fibrosis Transmembrane conductance Regulator (CFTR) protein.

Frequency

Although technically a rare disease, Cystic Fibrosis is ranked as one of the most widespread life-shortening genetic diseases. It is most common among nations in the Western world. An exception is Finland, where only 1 in 80 people carry a CF mutation. The World Health Organisation states that "In the European Union, 1 in 2000–3000 newborns is found to be affected by CF".In the United States, 1 in 3,500 children are born with CF. In 1997, about 1 in 3,300 Caucasian children in the United States was born with cystic fibrosis. In contrast, only 1 in 15,000 African American children suffered from Cystic Fibrosis, and in Asian Americans the rate was even lower at 1 in 32,000.

Symptoms

The main symptoms of Cystic Fibrosis are salty-tasting skin, poor growth, and poor weight gain despite normal food intake, accumulation of thick, sticky mucus, frequent chest infections, and coughing or shortness of breath. Males can be infertile due to congenital absence of the vas deferens. Symptoms of CF can be recognized in infancy and early childhood.

Causes

CF is caused by a mutation in the gene Cystic Fibrosis Transmembrane conductance Regulator (CFTR). The most common mutation, ΔF508, is a deletion (Δ signifying deletion) of three nucleotides. That results in a loss of the amino acid phenylalanine (F) at the 508th position on the protein. This mutation accounts for two-thirds (66–70%) of CF cases worldwide and 90% of cases in the United States; however, there are over 1500 other mutations that can produce CF. Although most people have two working copies (alleles) of the CFTR gene, only one is needed to prevent cystic fibrosis. CF develops when neither allele can produce a functional CFTR protein. Thus, CF is considered an **Autosomal Recessive** disease.

The **CFTR gene**, found at the **q31.2** locus of chromosome **7**, is 230,000 base pairs long, and creates a protein that is 1,480 amino acids long. More specifically the location is between base pair 117,120,016 to 117, 308, 718 on the long arm of chromosome **7**, region 3, band 1, and sub-band 2, represented as **7q31.2**. Structurally, **CFTR** is a type of gene known as an **ABC gene**. The product of this gene (**CFTR**) is a chloride ion channel important in creating sweat, digestive juices and mucus.

Diagnosis

CFTR is involved in production of sweat, digestive fluids, and mucus. When CFTR is not functional, secretions which are usually thin instead become thick. The condition is diagnosed by a sweat test and genetic testing. Screening of infants at birth takes place in some areas of the world.

Treatment

While there are no cure for Cystic Fibrosis, there are several treatment methods. The management of Cystic Fibrosis has improved significantly over the past 70 years. While infants born with Cystic Fibrosis 70 years ago would have been unlikely to live beyond their first year, infants today are likely to live well into adulthood. Recent advances in the treatment of Cystic Fibrosis have meant that an individual with Cystic Fibrosis can live a fuller life less encumbered by their condition. The cornerstones of management are proactive treatment of airway infection, and encouragement of good nutrition and an active lifestyle. Pulmonary rehabilitation as a management of Cystic Fibrosis continues throughout a person›s life, and is aimed at maximizing organ function, and therefore quality of life.

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Chapter 10

Cardio Vascular System

Congenital Heart Disease

Congenital Heart Defect (**CHD**), also known as a Congenital heart Anomaly or Congenital Heart Disease, is a problem in the structure of the heart that is present at birth.

Classic studies including the Baltimore-Washington Infant Study have found that CHD is **Multifactorial**, due to both genetic predisposition and environmental influences. Sequencing of the human genome and advances in molecular techniques has led to increasing evidence implicating a stronger role for genetic factors.

Frequency

Heart defects are the most common birth defect. In 2013 they were present in 34.3 million people Globally. They affect between 4 and 75 per 1,000 live births depending upon how they are diagnosed. About 6–19 per 1,000 cause a moderate to severe degree of problems. Congenital Heart Defects are the leading cause of birth defect-related deaths. In 2013 they resulted in 323,000 deaths down from 366,000 deaths in 1990.

Symptoms

Symptoms are related to type and severity of the heart defect. Symptoms frequently present early in life, but it is possible for some CHDs to go undetected throughout life. Some children have no signs while others may exhibit shortness of breath, cyanosis, fainting, heart murmur, under-development of limbs and muscles, poor feeding or growth, or respiratory infections. Congenital Heart Defects cause abnormal heart structure resulting in production of certain sounds called heart murmur. These can sometimes be detected by auscultation; however, not all heart murmurs are caused by Congenital Heart Defects.

Causes

Either genetic or environmental, but is usually a combination of both.

Certain cases may be due to infections during pregnancy such as rubella, use of certain medications or drugs such as alcohol or tobacco, parents being closely related, or poor nutritional status or obesity in the mother. Having a parent with a congenital heart defect is also a risk factor. A number of genetic conditions are associated with heart defects including Down syndrome, Turner syndrome, and Marfan syndrome.

Genetic Causes

Most of the known causes of Congenital Heart Disease are sporadic genetic changes, either focal mutations or deletion or addition of segments of DNA. Large chromosomal abnormalities such as **trisomies 21, 13, and 18** cause about 5–8% of cases of CHD, with **trisomy 21** being the most common genetic cause. Small chromosomal abnormalities also frequently lead to Congenital Heart Disease, and examples include micro deletion of the long arm of chromosome **22** (22q11, **DiGeorge syndrome**), the long arm of chromosome **1** (1q21), the short arm of chromosome **8** (8p23) and many other, less recurrent regions of the genome, as shown by high resolution genome-wide screening (Array comparative genomic hybridization).

A number of genes have been associated with cardiac manifestations. Mutations of a heart muscle protein, α-myosin heavy chain (**MYH6)** are associated with atrial septal defects. Several proteins that interact with **MYH6** (gene location: **14q11.2-q13**) are also associated with cardiac defects. The transcription factor **GATA4**(gene location: **8p23.1-p22**) forms a complex with the **TBX5** (gene location**: 12q24.1**)which interacts with **MYH6.** Another factor, the home box (developmental) gene, **NKX2-5**(gene location: **5q34**) also interacts with **MYH6**. Mutations of all these proteins are associated with both atrial and ventricular septal defects. Another T-box gene, **TBX1**(gene location: **22q11.2)** involved in defects of the cardiac out flow track.

Diagnosis

Many Congenital Heart Defects can be diagnosed prenatally by Fetal Echocardiography. This is a test which can be done during the second trimester of pregnancy, when the woman is about 18–24 weeks pregnant. It can be an Abdominal Ultrasound or Transvaginal Ultrasound.

Treatment

Sometimes CHD improves without treatment. Other defects are so small that they do not require any treatment. Most of the time CHD is serious and requires surgery and/or medications.

Hypertension

Hypertension (**HTN or HT**), also known as high blood pressure or Arterial Hypertension, is a chronic medical condition in which the blood pressure in the arteries is persistently elevated. Hypertension is a complex **Multifactorial** disorder with genetic, environmental and demographic factors contributing to its prevalence.

Hypertension is classified as either **Primary** (essential Hypertension or **Secondary** Hypertension. About 90–95% of cases are categorized as Primary Hypertension, defined as high blood pressure with no obvious underlying cause. The remaining 5–10% of cases are categorized as Secondary Hypertension, defined as Hypertension due to an identifiable cause, such as chronic kidney disease, narrowing of the aorta or kidney arteries, or an endocrine disorder such as excess aldosterone, cortisol.

Frequency

As of 2000, nearly one billion people or ~26% of the adult population of the world had Hypertension. It was common in both developed (333 million) and undeveloped (639 million) countries. However, rates vary markedly in different regions with rates as low as 3.4% (men) and 6.8% (women) in rural India and as high as 68.9% (men) and 72.5% (women) in Poland. In Europe Hypertension occurs in about 30–45% of people as of 2013.

Symptoms

Hypertension is rarely accompanied by any symptoms, and its identification is usually through screening, or when seeking healthcare for an unrelated problem. Some with high blood pressure report headaches (particularly at the back of the head and in the morning), as well as lightheadedness, vertigo, tinnitus (buzzing or hissing in the ears), altered vision or fainting episodes. These symptoms, however, might be related to associated anxiety rather than the high blood pressure itself.

Causes

Primary Hypertension

Hypertension results from a complex interaction of genes and environmental factors. Numerous common genetic variants with small effects on blood pressure have been identified as well as some rare genetic variants with large effects on

blood pressure, but the genetic basis of Hypertension is still poorly understood.

Blood pressure rises with aging and the risk of becoming hypertensive in later life is considerable. Several environmental factors influence blood pressure. High salt intake raises the blood pressure in salt sensitive individuals; lack of exercise, obesity, stress, and depression can play a role in individual cases.

Secondary Hypertension

Secondary Hypertension results from an identifiable cause. Kidney disease is the most common secondary cause of Hypertension. Hypertension can also be caused by endocrine conditions.

Genetic Causes

Linkage was obtained between Hypertension and Markers near a gene that is highly similar in DNA sequence to a human gene that encodes the Angiotension Converting Enzyme **(ACE).**

More than 50 genes have been examined in association studies with hypertension, and the number is constantly growing. One of these genes is the Angio Tension Gen **(AGT)** gene, studied extensively by **Kim *et al***. They showed that increasing the number of AGT increases the blood pressure and hence this may cause Hypertension. Twins have been included in studies measuring ambulatory blood pressure.

Therefore, it is not biased by previous hypotheses of molecular pathogenesis. GWS (Genome Wide Scanes) studies identified linkage to different chromosomal regions. For example, **Krushkal *et al***.,1999 identified four regions of the genome; viz. **2q22.1– 2p21, 5q33.3–5q34, 6q23.1–6q24.1, 15q25.1– 15q26.1**, linked to **SBP**. **Sharma *et al***., 2012 identified a sibling-pair linkage to Hypertension at a locus on chromosome **11q**.

Diagnosis

Hypertension is diagnosed on the basis of a persistently high blood pressure. Traditionally, the National Institute of Clinical Excellence recommends three separate sphygmomanometer measurements at one monthly interval. The American Heart Association recommends at least three measurements on at least two separate health care visits.

Treatment

Dietary and lifestyle changes can improve blood pressure control and decrease the risk of health complications, although treatment with medication is still often necessary in people for whom lifestyle changes are not enough or not effective. The treatment of moderately high arterial blood pressure (defined as >160/100 mmHg) with medications is associated with an improved life expectancy.

Coronary Heart Disease

Coronary Heart Disease (**CHD**) is a complex disease that is affected by environmental as well as genetic factors. It is **Multifactorial** inheritance. Research is ongoing that probes the relationship of human genetic variation to disease, potentially leading to better diagnosis and therapy. Variation in factors such as low-density lipoprotein cholesterol, Sapolipoprotein E, high-density lipoprotein cholesterol, apo lipoprotein A-UCIIVA-IV, lipoprotein lipase, cholesterol ester transfer protein, lipoprotein (a), and homocysteine may affect CHD risk via genetic or environmental mechanisms or their interactions.

Frequency

There are 7.3 million deaths and 58 million Disability Adjusted Life Years (DALYS) lost due to CHD worldwide.

Symptoms

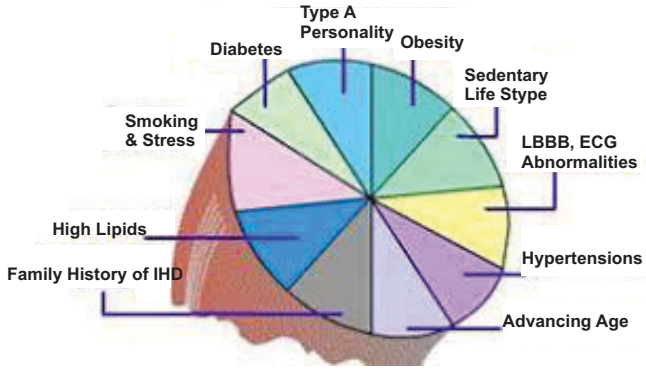
Symptoms may be very noticeable, but sometimes the disease may not show any symptoms. This is especially true in the early stages of heart disease. Chest pain or discomfort(angina) is the most common symptom. Other symptoms include shortness of breath and fatigue with activity(exertion) and weakness.

Causes

Coronary Heart Disease (CHD) is the leading cause of death in the United States for men and women. Coronary Heart Disease is caused by the buildup of plaque in the arteries of the heart. This may also be called hardening of the arteries. Fatty material and other substances form a plaque build-up on the walls of coronary arteries. The coronary arteries bring blood and oxygen to the heart. This buildup causes the arteries to get narrow. As a result, blood flow to the back to top.

Risk factors for Coronary Heart Disease

Age (older than 45 for men and 55), Hypertension, Hyperlipidemia, Cigarette smoking, Lack of exercise, Type 2 diabetes, Genetics.



Genetic Causes

CHD is a complex disease, comprising both genetic and environmental factors. In a complex genetic disorder, many genes acting in combination determine the predisposition. Disease susceptibility is influenced by environmental factors, and disease occurrence is determined by genetic and environmental interactions. In fact, genetic and environmental interactions largely determine who actually gets the disease. Genes can affect lipoproteins, blood pressure, obesity, clotting, the immune system, or the blood vessel wall, but environmental factors such as diet, cigarette smoking, physical inactivity, and stress also play a role in CHD susceptibility.

Location of the genes contributing to CHD

Apolipo protein **(ApoE) (Gene location: 19q13.2)**

Angiotensin1- converting enzyme **(ACE) (Gene location: 17q 23)**

Endothelial nitrc oxide synthase **(eNOS) (Gene location: 7q35)**

Methylene tetra hydro folate reductase **(MTHFR Gene location: 1q36.3)**

Table 10.1: Mendelian disorders influencing CHD risk factors

Type	Disease (gene)	Characteristics
Increased LDL-C	FH(LDLR)	Dominant, CHD
	Familial-defective apo B- 100	Dominant, CHD
Decreased HDL-C	Apo A-I defect	Recessive, CHD
	Tangierdisease (ABC I)	Recessive, CHD
Diabetes (type 2)	MODY I to IV (TFs, glucokinase)	Dominant, early-onset type 2 Diabetes Mellitus
Hypertension	GRH (1 I -P-OH-AS) glucokinase)	Dominant, HBP, stroke
	Liddle's syndrome (Na Ch)	Dominant, HBP, alkalosis

Abbreviations: CHD =coronary heart disease, LDL-C = low-density lipoprotein cholesterol, Apo = apolipoprotein, HDL-C = high-density lipoprotein cholester

Diagnosis

1. Coronary angiography - an invasive test that evaluates the heart arteries under X-ray.
2. Echocardiogram stress test.
3. Electrocardiogram (ECG).
4. Electron Beam Computed Tomography (EBCT) to look for calcium in the lining of the arteries - the more calcium, the higher your chance for CHD.
5. Exercise stress test.
6. Heart CT scan.
7. Nuclear stress test .

Treatment

Medicines are used to treat blood pressure, diabetes, or high cholesterol levels. The doctor's directions help to prevent coronary artery disease from getting worse.

Goals for treating these conditions in people who have coronary artery disease:

1. Blood pressure less than or equal to 140/90 (even lower for patients with diabetes, kidney disease, or heart failure).
2. HbA1c levels if you have diabetes at a level recommended by your doctor.
3. LDL cholesterol level less than or equal to 100 mg/dL (even lower for some patients).

Procedures and surgeries used to treat CHD include:

1. Angioplasty and Stent placement, called Percutaneous Coronary Interventions (PCIs).
2. Coronary Artery Bypass Surgery.
3. Minimally Invasive Heart Surgery .

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Chapter 11

Central Nervous System

Neural Tube Defects

Neural Tube Defects **(NTDs)** are a group of conditions in which an opening in the spinal cord or brain remains from early in human development. In the 3rd week of pregnancy called gastrulation, specialized cells on the dorsal side of the embryo begin to change shape and form of the neural tube. When the neural tube does not close completely, an NTD develops. NTD's are of **Multifactorial** inheritance.

Specific types include, Spina bifida affects the spine; Anencephaly results in little to no brain, NTDs are one of the most common birth defects, affecting over 300,000 births each year worldwide.

Causes

Folate deficiency: Folate (vitamin B9 and vitamin B12) are very important in reducing the occurrences of NTDs. Folate is required for the production and maintenance of new cells, for DNA synthesis and RNA synthesis. Folate is needed to carry one carbon groups for methylation and nucleic acid synthesis. It has been hypothesized that the early human embryo may be particularly vulnerable to folate deficiency due to differences of the functional enzymes in this pathway during embryogenesis combined with high demand for post translational methylations of the cytoskeleton in neural cells during neural tube closure. Failure of post-translational methylation of the cytoskeleton, required for differentiation has been implicated in neural tube defects. Vitamin B_{12} is also an important receptor in the folate biopathway such that studies have shown deficiency in vitamin B_{12} contributes to risk of NTDs as well. Importantly, a deficiency of folate itself does not cause neural tube defects. The association seen between reduced neural tube defects and folic acid supplementation is due to a gene-environment interaction such as venerability caused by the C677T Methylenetetrahydrofolate reductase **(MTHFR)** variant.

Spina Bifida

Spina Bifida (Latin: "split spine") is a birth defect where there is incomplete closing of the backbone and membranes around the spinal cord.

Frequency

About 5% of people have spina bifida occulta. Rates of various forms of Spin bifida vary significantly by country and falls between the range of 0.1–5 per 1000 births. In developed countries, it occurs in about 0.4 per 1000 births, in USA- about 0.7 per 1000 births, and in India, about 1.9 per 1000 births. Part of this difference is believed to be due to race - with Caucasians at higher risk - and partly due to environmental factors. NDTs are of **Multifactorial** inheritance.

Symptoms

Physical signs of spina bifida may include:

1. Leg weakness, paralysis and back pain.
2. Orthopedic abnormalities (i.e., club foot, hip dislocation, scoliosis).
3. Bladder and bowel control problems, including incontinence, urinary tract infections, and poor kidney function.
4. Pressure sores and skin irritations.
5. Abnormal eye movement.

The spinal cord lesion or the scarring due to surgery may result in a tethered spinal cord. In some individuals, this causes significant traction and stress on the spinal cord and can lead to a worsening of associated paralysis.

Causes

Spina bifida is believed to be due to a combination of genetic and environmental factors. After having one child with the condition or if a parent has the condition there is a 4% chance the next child will also be affected. Deficiency of folic acid during pregnancy also plays a significant role. Other risk factors include certain anti seizure medications, obesity, and poorly controlled diabetes.

Genetic Causes

Certain mutations in the gene **VANGL1,** a cell polarity protein and the gene is located on chromosome **1 (1p13.1)**, are implicated as a risk factor for spina bifida which was proved in some families with a history of spina bifida.

Diagnosis

Open spina bifida can usually be detected during pregnancy by fetal ultrasound. Increased levels of Maternal Serum Alpha Feto Protein **(MSAFP)** should be followed up by two tests - an Ultrasound of the fetal spine and Amniocentesis of the mother's amniotic fluid (to test for alpha-fetoprotein and acetylcholinesterase).

Prevention

There is neither a single cause of spina bifida nor any known way to prevent it entirely. However, dietary supplementation with folic acid has been shown to be helpful in reducing the incidence of spina bifida. Sources of folic acid include whole grains, fortified breakfast cereals, dried beans, leaf vegetables and fruits.

Genetic Counselling

Genetic counselling and further genetic testing, such as amniocentesis, may be offered during the pregnancy, as some neural tube defects are associated with genetic disorders such as trisomy 18. Ultrasound screening for spina bifida is partly responsible for the decline in new cases, because many pregnancies are terminated out of fear that a newborn might have a poor future quality of life. With modern medical care, the quality of life of patients has greatly improved.

Treatment

There is no known cure for nerve damage caused by spina bifida. Standard treatment is surgery after delivery. This surgery aims to prevent further damage of the nervous tissue and to prevent infections. Pediatric neurosurgeons operate to close the opening on the back. The spinal cord and its nerve roots are put back inside the spine and covered with meninges. In addition, a shunt may be surgically installed to provide a continuous drain for the excess cerebrospinal fluid produced in the brain, as happens with hydrocephalus. Shunts most commonly drain into the abdomen or chest wall.

Anencephaly

Anencephaly is the absence of a major portion of the brain, skull, and scalp that occurs during embryonic development. It is a cephalic disorder that results from a neural tube defect that occurs when the rostral (head) end of the neural tube fails to close, usually between the 23rd and 26th day following conception. Strictly speaking, the Greek term translates as "no in-head" (that is, totally lacking the inside part of the head, i.e., the brain), but it is accepted that children born with this disorder usually only lack a telencephalon, the largest part of the brain consisting mainly of the cerebral hemispheres, including the neo-cortex, which is responsible for cognition. The remaining structure is usually covered only by a thin layer of membrane— skin, bone, meninges, etc. are all lacking. With very few exceptions, infants with this disorder do not survive longer than a few hours or possibly days after their birth.

Frequency

In the United States, anencephaly occurs in about 1 out of every 10,000 births. Rates may be higher among black Africans with rates in Nigeria estimated at 3 per 10,000 in 1990, while rates in Ghana estimated at 8 per 10,000 in 1992. Rates in China are estimated at 5 per 10,000.

Research has suggested that, overall, female babies are more likely to be affected by the disorder. NDTs are of **Multifactorial** inheritance.

Symptoms

The National Institute of Neurological Disorders and Stroke (NINDS) describe the presentation of this condition as follows: "A baby born with Anencephaly is usually blind, deaf, unaware of its surroundings and unable to feel pain. Although some individuals with Anencephaly may be born with a main brain stem, the lack of a functioning cerebrum permanently rules out the possibility of ever gaining awareness of their surroundings. Reflex actions such as breathing and responses to sound or touch may occur".

Causes

The cause of Anencephaly is disputed.

Folic acid has been shown to be important in neural tube formation since at least **1995**, and as a subtype of neural tube defect, folic acid may play a role in

Anencephaly. Studies have shown that the addition of folic acid to the diet of women of child bearing age may significantly reduce, although not eliminate, the incidence of neural tube defects.

It is known that people on certain anticonvulsants or insulin-dependent diabetes have a higher risk of having a child with a neural tube defect. High exposure to toxins such as lead, chromium, mercury, and nickel are also held responsible for Anencephaly and other physical and mental deformities.

Genetic Causes

Genetics research has been found Cartilage Homeoprotein **(CART1)** is selectively expressed in chondrocytes (cartilage cells) is the cause of anencephaly.The CART1 gene to chromosome **12q21.3–q22** has been mapped. Also, it has been found that mice homozygous for deficiency in the Cart1 gene manifested acrania and meroanencephaly, and prenatal treatment with folic acid will suppress acrania and meroanencephaly in the Cart1-deficient mutants.

Genetic Counselling

Studies show that a woman who has had one child with a neural tube defect such as Anencephaly has about a 3% risk of having another child with a neural tube defect, as opposed to the background rate of 0.1% occurrence in the population at large. Genetic counselling is usually offered to women at a higher risk of having a child with a neural tube defect to discuss available testing.

Diagnosis

Anencephaly can often be diagnosed before birth through an ultrasound examination. The maternal serum alpha-fetoprotein (AFP screening) and detailed fetal ultrasound can be useful for screening for neural tube defects such as Spina bifida or Anencephaly.

Treatment

There is no cure or standard treatment for Anencephaly and the prognosis for patients is death. Most Anencephalic foetuses do not survive birth, accounting for 55% of non-aborted cases. If the infant is not stillborn, then he or she will usually die within a few hours or days after birth from cardiorespiratory arrest.

Hereditary Spastic Paraplegia

Hereditary Spastic Paraplegia (**HSP**), also known as Hereditary Spastic Paraparesis, Familial Spastic Paraplegias, French Settlement Disease, or Strumpell-Lorrain disease, is a group of inherited diseases whose main feature is progressive stiffness and contraction (spasticity) in the lower limbs, as a result of damage to or dysfunction of the nerves.

Symptoms of HSP may begin at any age, from infancy to older than 60 years. If symptoms begin during the teenage years or later, then spastic gait disturbance usually progresses insidiously over many years.

Frequency

Worldwide, the prevalence of all hereditary spastic paraplegias combined is estimated to be 2–6 in 100,000 people. A Norwegian study of more than 2.5 million people published in March 2009 has found an HSP prevalence rate of 7.4/100,000 of population, a higher rate, but in the same range as previous studies. No differences in rate relating to gender were found, and average age at onset was 24 years. In the United States, Hereditary Spastic Paraplegia is listed as a "rare disease" by the Office of Rare Diseases (ORD) of the National Institutes of Health which means that the disorder affects less than 200,000 people in the US population.

Symptoms

The condition sometimes also affects the optic nerve and retina of the eye, causes cataracts, ataxia (lack of muscle coordination),epilepsy, cognitive impairment, peripheral neuropathy, and deafness.

Symptoms depend on the type of HSP inherited. The main feature of the disease is progressive spasticity in the lower limbs, due to pyramidal tract dysfunction. This also results in brisk reflexes, extensor plantar reflexes, muscle weakness, and variable bladder disturbances. Furthermore, among the core symptoms of HSP are also included abnormal gait and difficulty in walking, decreased vibratory sense at the ankles, and paresthesia. Initial symptoms are typically difficulty with balance, stubbing the toe or stumbling.

Causes

HSP is caused by defects in the mechanisms that transport proteins and other substances through the cell. Long nerves are affected because they have to transport

cellular material through long distances, and are particularly sensitive to defects of cellular transport. This neuronal degeneration is thought to be caused by mutations at specific genes. Genetic mapping has identified at least 52 different **HSP** loci, designated **SPG** (Spastic Paraplegia) 1 through 52 in order of their discovery.

The Gene Location

Genotype	Gene Function	Inheritance	Age of Onset	Gene Location
SPG1	Glycoprotein	X linked Recessive	Early	Xq28
SPG2	Transmembrane protein	X linked Recessive	Variable	Xq22.2
SPG3A	Membrane anchored GTPase	Autosomal Dominant	Early	14q22.1
SPG4	AAA ATPase	Autosomal Dominant	Variable	2p22.3
SPG5	Cytochrome P45	Autosomal Recessive	Variable	8q12.3
SPG13	Heat shock protein	Autosomal Dominant	Variable	2q33.1

Diagnosis

Initial diagnosis of HSPs relies upon family history, the presence or absence of additional signs and the exclusion of other nongenetic causes of spasticity, the latter being particularly important in sporadic cases. Cerebral and Spinal MRI is an important procedure performed in order to rule out other frequent neurological conditions, such as multiple sclerosis, but also to detect associated abnormalities such as Cerebellar or corpus callosum atrophy as well as white matter abnormalities.

Ultimate confirmation of HSP diagnosis can only be provided by carrying out genetic tests targeted towards known genetic mutations.

Treatment

No specific treatment is known that would prevent, slow, or reverse HSP. Available therapies mainly consist of symptomatic medical management and promoting physical and emotional well being. Therapeutics offered to HSP patients include.

Physical Therapy used to restore and maintain the ability to move; to reduce muscle tone; to maintain or improve range of motion and mobility; to increase strength and coordination; to prevent complications, such as frozen joints, contractures, or bedsores.

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Chapter 12

Kidney and Urinogenetal Tract

Cystinosis

Cystinosis is a lysosomal storage disease characterized by the abnormal accumulation of the amino acid cystine. Cystinosis was the first documented genetic disease belonging to the group of lysosomal-transport-defect disorders. It is a rare **Autosomal Recessive** disorder resulting from accumulation of free cystine in lysosomes, eventually leading to intracellular crystal formation throughout the body. Cystinosis is the most common cause of Fanconi syndrome in the pediatric age group.

Frequency

Cystinosis affects approximately 1 in 100,000 to 200,000 new bornes. And there are only around 2,000 known individuals with Cystinosis in the wolrd. The incidence is higher in the province of Brittany, France, where the disorder affects 1 in 26,000 individuals.

Symptoms

There are three distinct types of Cystinosis each with slightly different symptoms: Nephropathic Cystinosis, Intermediate Cystinosis, and Non-nephropathic or Ocular Cystinosis.

Infants affected by **Nephropathic Cystinosis** initially exhibit poor growth and particular kidney problems (sometimes called Renal Fanconi syndrome). The loss of nutrients not only impairs growth, but may result in soft, bowed bones (hypophosphatemic rickets), especially in the legs. The nutrient imbalances in the body lead to polyuria (increased urination), thirst, dehydration, and abnormally acidic blood (acidosis). Ultimately kidney failure by age 6 years in the nephropathic form.

The symptoms of **Intermediate Cystinosis** are the same as Nephropathic Cystinosis, but they occur at a later age. Intermediate Cystinosis typically begins to affect individuals around age twelve to fifteen.

People with **Non-nephropathic** or Ocular Cystinosis do not usually experience growth impairment or kidney malfunction. The only symptom is photophobia due to cystine crystals in the cornea. The disease is attributed to deficiency in transport and metabolism of amino acids.

Causes

Cystinuria is a cause of persistent kidney stones. It is a disease involving the defective transepithelial transport of cystine and dibasic amino acids in the kidney and intestine, and is one of many causes of kidney stones. If not treated properly, the disease could cause serious damage to the kidneys and surrounding organs, and in some rare cases death.

Genetic Causes

Cystinosis is caused by mutations in the **CTNS** gene that code for Cystinosin, the lysosomal membrane-specific transporter for cystine, located on **chromosome 17.**

All forms of Cystinosis are **Autosomal Recessive**, which means that the trait is located on an Autosomal gene, and an individual who inherits two copies of the gene- one from both parents- will have the disorder. There is a 25% risk of having a child with the disorder, when both parents are carrier of an Autosomal Recessive trait.

Diagnosis

Definitive diagnosis and treatment monitoring are most often performed through measurement of white blood cell cystine level using **Tandem Mass Spectrometry**.

Treatment

Cystinosis is usually treated with **cysteamine**, which is prescribed to decrease intralysosomal cystine accumulation.

Polycystic Kidney Disease

Polycystic Kidney Disease (**PKD or PCKD**), also known as polycystic kidney syndrome) is a genetic disorder in which abnormal cysts develop and grow in the kidneys. Cystic disorders can express themselves at any point, infancy, childhood, or adulthood. The disease occurs in humans and some other animals. PKD is characterized by the presence of multiple cysts (hence, "polycystic") typically in both kidneys; however, 17% of cases initially present with observable disease in one kidney, with most cases progressing to bilateral disease in adulthood.

The two major forms of Polycystic Kidney Disease are distinguished by the usual age of onset and their pattern of inheritance. The **Autosomal Dominant** form (sometimes called **ADPKD**) has symptoms that typically begin in adulthood, although cysts in the kidney are often present from childhood. Autosomal Dominant Polycystic Kidney Disease can be further divided into type 1 and type 2, depending on which gene is mutated. The **Autosomal Recessive** form of polycystic kidney disease (sometimes called **ARPKD)** is much rarer and is often lethal early in life. The symptoms of this condition are usually apparent at birth or in early infancy.

Frequency

Polycystic Kidney Disease is one of the most common disorders caused by mutations in a single gene. It affects about 500,000 people in the United States. The Autosomal Dominant form of the disease is much more common than the Autosomal Recessive form. Autosomal Dominant Polycystic Kidney Disease affects 1 in 500–1,000 people, while the Autosomal Recessive type occurs in an estimated 1 in 20,000–40,000 people.

Symptoms

Symptoms include high blood pressure, headaches, abdominal pain, blood in the urine, and excessive urination. Other symptoms include pain in the back, headaches and cyst formation (renal and other organs).

Causes

Polycystic Kidney Disease is a general term for the two types of PKD, each having their own pathology and causes. The two types of PKD are Autosomal Dominant Polycystic Kidney Disease (**ADPKD)** and Autosomal Recessive Polycystic Kidney Disease(**ARPKD**), which differ in their mode of genetic inheritance.

Genetic Causes

Autosomal Dominant

Autosomal Dominant Polycystic Kidney Disease (**ADPKD**) is the most common of all the inherited cystic kidney diseases with an incidence of 1:500 live births. Studies show that 10% of End Stage Kidney Disease (**ESKD**) patients being treated with dialysis in Europe and the US were initially diagnosed and treated for ADPKD.

There are three genetic mutations in the PKD1, PKD2, and PKD3 gene with similar phenotypical presentations. Mutations in the **PKD1**(gene location : **16 p13.3**) and **PKD2**(gene location:**4q21**) cause Polycystic Kidney Disease. Mutations in either the PKD1 or PKD2 gene can cause Autosomal Dominant Polycystic Kidney Disease. These genes provide instructions for making proteins whose functions are not fully understood. Researchers believe that they are involved in transmitting chemical signals from outside the cell to the cell's nucleus. The two proteins work together to promote normal kidney development, organization, and function. Mutations in the PKD1 or PKD2 genes lead to the formation of thousands of cysts, which disrupt the normal functions of the kidneys and other organs. People with mutations in the PKD2 gene, particularly women, typically have a less severe form of the disease than people with PKD1 mutations. The symptoms, including a decline in kidney function, tend to appear later in adulthood in people with a PKD2 mutation.

Autosomal Recessive

Autosomal Recessive Polycystic Kidney Disease (**ARPKD**) (OMIM #263200) is the lesser common of the two types of PKD, with an incidence of 1:20,000 live births and is typically identified in the first few weeks after birth. Unfortunately, the kidneys are often underdeveloped resulting in a 30% death rate in newborns with ARPKD.

Mutations in the **PKHD1** gene cause Autosomal Recessive Polycystic Kidney Disease. This gene provides instructions for making a protein whose exact function is unknown; however, the protein likely transmits chemical signals from outside the cell to the cell nucleus. Researchers have not determined how mutations in the **PKHD1** gene lead to the formation of numerous cysts characteristic of Polycystic Kidney Disease.

Although Polycystic Kidney Disease is usually a genetic disorder, a small percentage of cases are not caused by gene mutations. These nonhereditary cases

are called Acquired Polycystic Kidney Disease. This form of the disorder occurs most often in people who have been treated for several years with hemodialysis (a procedure that filters the blood in people with kidney failure).

Prognosis

ADPKD individuals might have a normal life; conversely, ADPKD can cause kidney dysfunction and can lead to kidney failure by the age of 40–60. ADPKD1 and ADPKD2 are very different, in that ADPKD2 is much milder. Currently, there are no therapies proven effective to prevent the progression Polycystic Kidney Disease (Autosomal Dominant).

Diagnosis

Imaging tests used to diagnose PKD include:

1. Abdominal Ultrasound: the most useful, non-invasive study using sound waves to look for cysts.
2. Abdominal CT scan: can detect smaller cysts in the kidney; uses X-rays to build a cross-section of your abdomen.
3. Abdominal MRI scan: uses strong magnets to image your body to visualize kidney structure and look for cysts.
4. Abdominal Ultrasound: uses sound waves to see inside your body.
5. Intra Venous Pyelogram (IVP): uses a dye to make your blood vessels show up more clearly on an X-ray.

Treatment

Obviously, if and when the disease progresses enough in a given case, the Nephrologists or other practitioner and the patient will have to decide what form of renal replacement therapy will be used to treat end-stage kidney disease (kidney failure, typically stage 4 or 5 of chronic kidney disease). That will either be some form of dialysis, which can be done at least two different ways at varying frequencies and durations (whether it is done at home or in the clinic depends on the method used and the patient's stability and training) and eventually, if they are eligible because of the nature and severity of their condition and if a suitable match can be found, unilateral or bilateral kidney transplantation.

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Chapter 13

Reproductive System

Polycystic Ovary Syndrome or Disease (PCOD/PCOS)

Polycystic ovary syndrome (PCOS) is a syndrome involving defects in primary cellular control mechanisms that result in the expression of chronic anovulation and hyperandrogenism. Polycystic ovary syndrome (PCOS) is a common gynecological endocrine disorder; the precise cause of it remains elusive. Polycystic ovary syndrome has been proven to be a familial condition. Although the role of genetic factors in PCOS is strongly supported, the genes that are involved in the etiology of the syndrome have not been fully investigated until now, as well as the environmental contribution in their expression. Some genes have shown altered expression suggesting that the genetic abnormality in PCOS affects signal transduction pathways controlling steroidogenesis, steroid hormones action, gonadotrophin action and regulation, insulin action and secretion, energy homeostasis, chronic inflammation and others.

The prevalence of PCOS was estimated in different populations:

1. Caucasian and black races - nearly 4.0% in both races.
2. Greek women - 6.8%.
3. Spanish Caucasians - 6.8%.
4. Chinese women - 5.6%.
5. Indian females - 9.13%.

The prevalence of PCOS is significantly higher in the South Asian population, especially in Pakistan, as compared to Caucasians.

PCOS is a condition in which the ovaries produce an abnormal amount of androgens, male sex hormones that are usually present in women in small amounts. The name polycystic ovary syndrome describes the numerous small cysts (fluid-filled sacs) that form in the ovaries. But cysts development cannot be the only consideration for PCOS in women.

Ovulation occurs when a mature egg is released from an ovary which will be fertilized by a male sperm (if available) or sent out of the body during your period.

Due to the hormonal imbalance, ovulation ceases leading to the development of many small cysts in ovaries. These cysts make hormones called androgens. Women with PCOS often have high levels of androgens causing more problems with a woman's menstrual cycle. And it can cause many of the symptoms of PCOS.

Women with PCOS are more likely to develop certain serious health problems. These include type 2 diabetes, high blood pressure, problems with the heart and blood vessels, and uterine cancer. Women with PCOS often have problems with their ability to get pregnant (fertility).

Symptoms

The symptoms of PCOS may include:

1. Missed periods, irregular periods, or very light periods
2. Ovaries that are large or have many cysts
3. Excess body hair, including the chest, stomach, and back (hirsutism)
4. Weight gain, especially around the belly (abdomen)
5. Acne or oily skin
6. Male-pattern baldness or thinning hair
7. Infertility
8. Small pieces of excess skin on the neck or armpits (skin tags)
9. Dark or thick skin patches on the back of the neck, in the armpits, and under the breasts

Genetics of PCOS

The genetic basis of PCOS was first reported by Cooper and colleagues in 1968. Studies on PCOS reported multiple relatives and siblings in families with autosomal dominant inheritance. The prevalence of PCOS in the first-degree relative of the proband that was found in nearly 55–60% in several small families supported the hypothesis of autosomal dominant inheritance of PCOS. Later on, monogenic causes of hirsutism and oligomenorrhea in PCOS women and male-pattern baldness were identified.

Twin studies in small cohorts of mono- and dizygotic twin pairs suggested that PCOS is neither an autosomal dominant nor a monogenic disease; rather, it is an X-linked polygenic disorder. Moreover, twin studies estimated 72% variance in risk of PCOS to be genetic in basis, highlighting the genetic involvement.

Many studies have been conducted in multiple families to find the causative gene/mutation, but no true penetrance of a single gene mutation has been reported until now. All genes/mutations reported in familial aggregation show low penetrance associated with other covariant, hormonal or environmental factors to cause disease. Conclusively, PCOS is a polygenic and multifactorial syndromic disorder.

The possible genes involved in the causation of PCOS are:

In Ovarian and Adrenal Steroidogenesis

CYP11a: The gene CYP11a encodes an enzyme that is required in an intermediary step of cholesterol conversion to progesterone.

CYP21: A less-active enzyme due to variation leads to ineffective anabolism of steroidogenesis, which further causes PCOS

CYP17: The conversion of pregnenolone and progesterone into 17-hydroxypregnenolone and 17-hydroxyprogesterone is catalyzed by an enzyme (P450c17α) that is encoded by CYP17

CYP19: Lower activity of aromatase activity is reported in both obese and lean women with PCOS.

In Steroid Hormone Effects

Androgen Receptor Gene: Mutations and structural disruption of the gene are reported to cause PCOS.

Sex Hormone-Binding Globulin Gene: The protein product of **SHBG** controls the level of sex hormones in the body by binding to androgens, predominantly with estrogens and testosterone.

In Gonadotropin Action and Regulation

Lutein Hormone (LH) and Its Receptor Gene: Both LH level and distorted function of LH are frequently reported as a cause of PCOS. These abnormalities cause annulations, thus producing PCOS.

AMH: The gene encodes a protein that is involved in infertility.

Follicular Stimulating Hormone Receptor (FSHR): The gene encodes a protein G-coupled receptor, which is required for gonad development.

In Insulin Action and Secretion

The Insulin Gene: Insulin also plays a significant role in the production of androgen by receptors present on theca cells.

Insulin Receptor Substrate Proteins: Insulin binds with its receptor. Activation of the receptor is autophosphorylated by the binding of insulin.

Calpain10 Gene, Fat Mass Obesity (**FTO**), **SRD5A2 and SRD5A1 and** PCOS1 are some the amenable genes to develop PCOS.

Diagnosis

Medical history, symptoms and physical exam(a pelvic exam) checks the health of reproductive organs, both inside and outside body.

Some of the symptoms of PCOS are like those caused by other health problems,

Ultrasound is used to look at the size of the ovaries, the thickness of the lining of the uterus (endometrium). and for any cysts.

Blood tests. To check for high levels of androgens,other hormones,blood glucose levels,cholesterol and triglyceride levels.

Treatment

Treatment for PCOS is often done with medication. This can't cure PCOS, but it helps reduce symptoms and prevent some health problems.

A change in diet and activity. A healthy diet and more physical activity can help lose weight and reduce symptoms.

Medications to cause ovulation. the ovaries to release eggs normally.

Birth control pills. These help to control menstrual cycles, lower androgen levels, and reduce acne.

Diabetes medication. This is often used to lower insulin resistance in PCOS. It may also help reduce androgen levels, slow hair growth, and help ovulate more regularly.

A change in diet and activity. A healthy diet and more physical activity can help lose weight and reduce your symptoms.

Medications to treat other symptoms. Some medications can help reduce hair growth or acne.

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Chapter 14

Endocrine System

Congenital Hypothyroidism

Cretinism or Congenital Hypothyroidism (**CH**) or is a condition of thyroid hormone deficiency present at birth. Approximately 1 in 4000 newborn infants has a severe deficiency of thyroid function, while even more have mild or partial degrees.

Cretinism is a condition of severely stunted physical and mental growth due to untreated congenital deficiency of thyroid hormones (Congenital Hypothyroidism) usually due to maternal Hypothyroidism. Many inherited cases are **Autosomal Recessive.**

Frequency

Neonatal thyroid screening programs from all over the world have revealed that Congenital Hypothyroidism (CH) occurs with an incidence of 1:3000 to 1:4000. The differences in CH incidence are more likely due to iodine deficiency thyroid disorders or to the type of screening method than to ethnic affiliation. CH is caused by an absent or defective thyroid gland classified into agenesis (22–42%), ectopy (35–42%) and gland in place defects (24–36%). It is also found to be of increased association with female gender and gestational age > 40 weeks.

Symptoms

Infants born with Congenital Hypothyroidism may show no effects, or may display mild effects that often go unrecognized as a problem: excessive sleeping, reduced interest in nursing, poor muscle tone, low or hoarse cry, infrequent bowel movements, exaggerated jaundice, and low body temperature. Other Symptoms may include thickened skin, enlarged tongue (macroglossia), or a protruding abdomen.

In adults, cretinism results in mental deterioration, swelling of the skin, loss of water and hair. Bone maturation and puberty are severely delayed. Ovulation is impeded, and infertility is common.

Neurological impairment may be mild, with reduced muscle tone and coordination, or so severe that the person cannot stand or walk. Cognitive impairment may also range from mild to so severe that the person is nonverbal and dependent on others for basic care.

Causes

Congenital Hypothyroidism can be endemic, genetic, or sporadic. If untreated, it results in mild to severe impairment of both physical and mental growth and development.

Genetic Causes

Mutations in the **DUOX2** (Cytogenetic Location: **15q15.3**); **PAX8** (Cytogenetic Location: **2q13**); **SLC5A5** (Cytogenetic Location: **19p13.11**); **TG** (Cytogenetic Location: **8q24)**; **TPO** (Cytogenetic Location: **2p25**); **TSHB**(Cytogenetic Location: **1p13**) and **TSHR** (Cytogenetic Location: **14q31**) genes cause Congenital Hypothyroidism.

Gene mutations cause the loss of thyroid function in one of two ways. Mutations in the PAX8 gene and some mutations in the TSHR gene prevent or disrupt the normal development of the thyroid gland before birth. Mutations in the **DUOX2, SLC5A5, TG, TPO**, and **TSHB** genes prevent or reduce the production of thyroid hormones, even though the thyroid gland is present.

Mutations in other genes that have not been well characterized may also cause Congenital Hypothyroidism.

Most cases of Congenital Hypothyroidism are sporadic, which means they occur in people with no history of the disorder in their family.

An estimated 15–20% of cases are inherited. Many inherited cases are Autosomal Recessive, which means both copies of the gene in each cell have mutations. Most often, the parents of an individual with an **Autosomal Recessive** condition each carry one copy of the mutated gene, but do not show symptoms of the condition.

Some inherited cases (those with a mutation in the PAX8 gene or certain TSHR gene mutations) have an Autosomal Dominant pattern of inheritance, which means one copy of the altered gene in each cell is sufficient to cause the disorder.

Diagnosis

In the developed world, nearly all cases of Congenital Hypothyroidism are detected by the newborn screening program. These are based on measurement of TSH or thyroxin (T_4) on the second or third day of life (Heel prick).

Treatment

The goal of newborn screening programs is to detect and start treatment within the first 1–2 weeks of life. Treatment consists of a daily dose of thyroxin, available as a small tablet. The generic name is levothyroxine, and several brands are available.

As the child grows up, these levels are checked regularly to maintain the right dose. The dose increases as the child grows.

Goiter

A **Goiter** (from the Latin gutteria, struma) is a swelling of the neck or larynx resulting from enlargement of the thyroid gland (thyromegaly), associated with a thyroid gland that is not functioning properly.

Worldwide, over 90.54% cases of Goiter are caused by iodine deficiency. Goiter presents an **Autosomal Dominant** pattern of inheritance.

Frequency

The incidence of Goiter, diffuse and nodular, is very much dependent on the status of iodine intake of the population. In areas of iodine deficiency, Goiter prevalence may be very high and especially in Goiters of longstanding, multinodularity develops frequently. The incidence of multinodular Goiter in areas with sufficient iodine intake has been documented in several reports. In a comprehensive population survey of 2,749 persons in Northern England, **Tunb ridge *et al.,*** found obvious Goiters in 5.9% with a female/male ratio of 13:1. Single and multiple thyroid nodules were found in 0.8% of men and 5.3% of women, with an increased frequency in women over 45 years of age. Routine autopsy surveys and the use of sensitive imaging techniques produce a much higher incidence. In three reports nodularity was found in 30% to 50% of subjects in autopsy studies, and in 16% to 67% in prospective studies of randomly selected subjects on Ultrasound.

In Framingham, the prevalence of Multinodular Goiter as found in a population study of 5234 persons over 60 years was 1%. Results from Singapore show a prevalence of 2.8%. In an evaluation in 2,829 subjects, living in Southwestern Utah and Nevada (USA, between 31 and 38 years) of age, 23% had non-toxic Goiter, including 18 single nodules, 3 cysts, 38 colloid goiters and 7 without a histological diagnosis. No mention was made of Multinodular Goiters, although some might have been present in the colloid and unidentified group. In general, in iodine sufficient countries the prevalence of Multinodular Goiter is not higher than 4%. In countries with previous deficiency that was corrected by universal salt iodination, elderly subjects may have an incidence of, approximatively, 10% of nodular and Multinodular Goiter, attributed to lack of nutritional iodine in early adult life.

Symptoms

1. Often family history of benign thyroid disease.
2. Slowly growing anterior neck mass.
3. Uni or multinodularity on examination.
4. Enlargement during pregnancy.
5. Cosmetic complaints.
6. Asymmetry, tracheal deviation, and/or compression.
7. Rarely upper airway obstruction, dyspnea, cough, and dysphagia.
8. Sudden transient pain or enlargement secondary to hemorrhage.
9. Gradually developing hyperthyroidism.
10. Superior vena cava obstruction syndrome (rare).
11. Recurrent nerve palsy (rare).
12. Horner´s syndrome (rare).

Causes

Primary Factors

1. Functional heterogeneity of normal follicular cells, most probably due to genetic and acquisition of new inheritable qualities by replicating epithelial cells. Gender (women) is an important factor.
2. Subsequent functional and structural abnormalities in growing Goiters.

Secondary Factors

1. Elevated TSH (induced by iodine deficiency, natural goitrogens, inborn errors of thyroid hormone synthesis).
2. Smoking, stress, certain drugs.
3. Thyroid-stimulating factors (IGF-1 and others).
4. Endogenous factor (gender).

Genetic Causes

In contrast to Sporadic Goiters, caused by spontaneous Recessive genomic variation, most cases of Familial Goiter present an **Autosomal Dominant** pattern

of inheritance, indicating predominant genetic defects. Gene-gene interactions or various polygenic mechanisms (i.e., synergistic effects of several variants or polymorphisms) could increase the complexity of the pathogenesis of nontoxic Goiter and offer an explanation for its genetic heterogeneity. A strong genetic predisposition is indicated by family and twin studies. Thus, children of parents with Goiter have a significantly higher risk of developing Goiter compared with children of nongoitrous parents. The high incidence in females and the higher concordance in monozygotic than in dizygotic twins also suggested a genetic predisposition. Moreover, there is preliminary evidence of a positive family history for thyroid diseases in those who have postoperative relapse of goiter, which can occur from months to years after surgery.

Defects in genes that play an important role in thyroid physiology and thyroid hormone synthesis could predispose to the development of Goiter, especially in case of borderline or over iodine deficiency. Such defects could lead to dyshormonogenesis as an immediate response, thereby indirectly explaining the nodular transformation of the thyroid as late consequences of dyshormonogenesis, as a form of maladaptation. The genes that encode the proteins involved in thyroid hormone synthesis, such as the thyroglobulin-gene (**TG-gene**) (location:**8q24**); the thyroid peroxidase-gene (**TPO-gene**) (location:**2p25)**; the sodium – iodide – symporter-gene (**SLC5A5**) (location:**19p13.11**); the Pendred syndrome-gene (**SLC26A4**) (Location: **7q31**); the TSH receptor-gene (**TSH-R-gene**)(location:**3p24.2**); the iodotyrosine deiodinase (**DEHAL 1)** and the thyroid oxidase gene (**DUOX2**) (Location: **15q15.3**)are convincing candidate genes in familial euthyroid goiter. Originally, several mutations in these genes were identified in patients with Congenital Hypothyroidism. However, in cases of less severe.

Diagnosis

TSH normal or decreased, normal free T4, and free T3, Serum Tg usually elevated Thyroid auto antibodies (TPO and Tg) usually negative Scintigraphy with solitary or multiple hot and/or cold areas. Ultrasound finding of solitary or multiple nodules with varying echogenicity (no homogeneity) Computed Tomography and MR imaging demonstrating solitary or multiple nodules with varying echogenicity. Lung function testing may demonstrate impaired inspiratory capacity.

Treatment of Multinodular Goiter

In the past iodine supplementation seems to be an adequate approach because goiter development is associated with mild iodine deficiency in many countries worldwide. The effect of iodine once a Multinodular Goiter has developed a limited value in reducting the MNG. A major problem of iodine supplementation is the risk for inducing subclinical/clinical Hyperthyroidism. Therefore aside from a few European countries iodine is no longer used alone or associated with L-T4 to treat thyroid enlargement.

This leaves in essence three modalities of therapy:

1. L-T4 suppressive therapy.
2. Radioiodine (^{131}I) alone or preceded by rhTSH.
3. Surgery.

Diabetes Mellitus

The etiology of **Diabetes** is complex and not fully understood. Nevertheless, progress is being made in understanding the genetic basis of this disorder, which is a leading cause of blindness, heart diseases, kidney failure. An important advance has been the recognition that diabetes is actually a heterogenous group of disorders, all characterized by elevated blood sugar. It is a complex disorder of carbohydrates, fat and protein metabolism that is primarily a result of a relative or complex lack of insulin secretion by the beta cells of the pancreas or of defect of the insulin receptors. The disease often familial but may be acquired.

The various forms of Diabetes have been organized into a series of categories developed by the national diabetes data group of the national institute of health.

Frequency

As of 2014, an estimated 387 million people have Diabetes worldwide.

Type I Diabetes (insulin – dependent) and type II Diabetes (Non insulin type dependent), both clusters in families, with clustering observed for Type II diabetes. Type I has an earlier average age of onset, is HLA associated and is an auto immune disease. TYPE II is not an auto immune disease and is more likely to be seen in obese individuals, some cases of "Maturity Onset Diabetes of the Young"(**MODY**), a subset of Type II Diabetes, are caused by mutation of glucokinase gene.

Type I Diabetes

This is previously called as juvenile – onset diabetes, brittle diabetes or ketosis - prone diabetes. It is Insulin Dependent Diabetes Milletus **(IDDM)** subclass. This form of Diabetes, which is characterized by T – cell infiltration of the pancreas and destruction of the insulin – producing β cells usually presents before age 40. Patients with Type I Diabetes, must receive insulin to survive.

Siblings of individuals with Type I Diabetes face a substantial elevation in risk; approximately 6% as opposed to a risk of about 0.3–0.5% in the general population. Although sexes are affected in almost equal proportions, there is slight excess in males. Recurrence risk for offspring vary substantial with the sex of the parent. The risk of offspring of diabetic mothers is only 1–3% while it is 4–6% for the offspring of diabetic fathers (Note that is inconsistent with the sex – specific threshold model for **Multifactorial** traits). Twin studies show that the empirical

risks for identical twins of type I diabetes patients range from 30–50%. The fact that type I diabetes is not 100% concordant among identical twins indicates that genetic factors are not solely responsible for disorder. There are good evidence that viral infections, for e.g., contribute to the causation of type I diabetes in at least some individuals.

The insulin gene itself, which is located on the short arm of chromosome **11,** is another logical candidate for Type I Diabetes susceptibility, polymorphisms in and around the insulin gene have been studied extensively and alleles of some of these polymorphisms are associated with susceptibility of Type I Diabetes.

Type II Diabetes

Type II Diabetes accounts for 80–90% all diabetes cases in the United States. A number of features distinguish it from Type I Diabetes. Unlike Type I Diabetes there is always some endogenous insulin production in person with Type II Diabetes and it can often be treated successfully with dietary modification and/or oral drugs. Type II Diabetes patients also suffer from insulin resistance (i.e. their bodies have difficulty in using the insulin they produce). The disease typically occurs among people over age 40 and in contract To Type I Diabetes, is seen more commonly among the obese. Neither HLA associations nor auto antibodies are seen commonly in this form of diabetes. Monozygotic twin's concordance rates are substantially higher than in Type I Diabetes, often exceeding 90%. The empirical recurrence risks for 1st degree relatives of Type Ii Diabetes cases are higher than those for type I generally ranging from 10–15%.

Despite the apparently high degree of genetic involvement in Type II Diabetes, specific genes for this disorder have not yet been identified. The insulin and insulin receptor genes have both been studied, but it appears unlikely that defects in either gene are responsible for a substantial portion of disease genes.

The two most important risk factors for Type II Diabetes are positive family history and obesity. The later increases insulin resistance.

A small proportion of Type II Diabetes cases manifest the disease early in life, typically before 25 years of age. This subset termed Maturity Onset Diabetes of the Young (**MODY)** can be inherited as an **Autosomal Dominant** trait. Studies MODY pedigrees have shown that some cases of the disease are caused by mutations in the glucokinase gene.

Table 14.1: A comparison of the major features of type I and type II diabetes

Features	Type I Diabetes	Type II Diabetes
Age of onset	usually < 40 years	usually > 40 years
Insulin production	None	Partial
Insulin resistance	No	Yes
Autoimmunity	Yes	No
Obesity	Not common	Common
MZ twin concordance	0.90	0.55
Sibling recurrence risk	1– 6%	10– 15%

Those with **Gestational Diabetes Mellitus (GDM),** usually identified as **type III** are in a separate subclass composed of women who developed glucose intolerance in association with pregnancy.

Type IV also identified as other types of diabetes includes patients whose diabetes is associated with a pancreatic disease, hormonal changes, and adverse effects of drugs or genetic or other anomalies.

V class, the **Impaired Glucose Tolerance (IGT)** group, includes persons whose plasma glucose levels are abnormal although not sufficiently beyond the normal range to be diagnosed as diabetic.

Symptoms

The classic symptoms of untreated Diabetes are weight loss, Polyuria (increased urination), Polydipsia (increased thirst), and Polyphagia (increased hunger).

The onset of diabetes is sudden in children and usually insidious in non insulin dependent diabetes (Type II). Characteristically the course in progressive and symptoms includes polyuria (increased urination), polydipsia (increased thirst), weight loss, polyphagia (increased hunger), hyperglycemia (greater amount of glucose in blood) and glycosuria (abnormal presence of sugar). The eyes, kidneys, nervous system, skin and circulatory system may be affected, infections are common and arthrosclerosis (presence of cholesterol and lipids on the inner wall of large and medium sized arteries) often develops.

Causes

T2D is believed to be a **Multifactorial** disease, i.e., it is influenced by both genetic and environmental factors. People with a family history of the disease are at higher risk of developing it themselves since they share genetic background and likely share similar environments. It has been estimated that 30%- 70% of T2D risk can be attributed to genetics, with multiple genes involved and different combinations of genes playing roles in different subsets of individuals. It is not yet known how many genes are involved or how much control each exerts over the development of the disease, but recent research has identified a number of promising candidates.

Genetic Causes

Type-1 Diabetes is associated with vitamin D receptor gene (cytogenetic location: **12q) (VDR)** polymorphisms like FokI, Bsm1, Apa1, and Taq1.

Genes associated with developing Type 2 Diabetes, include **TCF7L2** (cytogenetic location: **10q25.3**); **PPARG** (cytogenetic location: **3p25); FTO** (cytogenetic location:**16q12.2**); **KCNJ11** (cytogenetic location:**11p151.1**); **NOTCH1** (cytogenetic location: **9q34.3**); **WFS1**(cytogenetic location: **4p24.11**) and **SLC30A8** (cytogenetic location: **4p16.1**), there is also a mutation to the Islet Amyloid Polypeptide gene that results in an earlier onset, more severe, form of Diabetes.

Diagnosis

In childhood and in the type I advanced stage of the disease, when no endogenous insulin is being secreted, ketoacidosis (accumulation of ketones in the body) is a constant danger. The diagnosing is confirmed by glucose tolerance tests, history and urinalysis.

Treatment

The goal of treatment is to maintain the insulin glucose homostasis. Mild early or late onset of the disease may be controlled by diet alone. In more severe diabetes insulin is administered to keep blood glucose levels below the point where ketoacidosis is likely. Good control of diabetes may decrease the severity of the symptoms and the progression of the disease. The kind and amount of insulin given varies with the person's condition. Stress of any kind may require an adjustment in the dosage.

Diabetic patients need extensive teaching and emotional support. The person is taught the need for continued medical supervision and dietary restriction, how to test the urine for sugar and interpret the result.

Certain safety precautions are emphasized; the patient should avoid infection, carry a supply of glucose at all times, wear a medical alert tag and use sterile technique giving self medication.

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Chapter 15

Cancer Genetics

Characteristics of Cancer Cells

Introduction

Cancer is one of the most common and severe problems of clinical medicine. It accounts for more than 20% of all deaths. Cancer is not a single disease but rather a name applied to a great variety of malignant tumours that are formed by the some basic process of uncontrolled growth. Cell proliferation results is a mass (Neoplasm or Tumour) that invade neighbouring tissue (hence the name cancer meaning crab) and may also metastasize to more distant sites. The growth is autonomous, increasingly malignant and if untreated, invariably fatal.

These are 3 main forms:

1. Carcinomas, which originate in epithelial tissue
2. Sarcomas, in which the tumour has arisen is mesenchymal tissue
3. Lymphoid malignancies, such as leukaemia's and lymphomas.

Unlike normal cells injured by infectious diseases, cancerous cells are quite healthy by the usual standards so much so that they interfere with the well being of neighbouring tissue. A mass of cells that multiplies when it should not is called a tumour or neoplasm. A benign tumour remains localized in the place of origin often separated from the surrounding cells by a layer of connective tissue. Although compact and slow growing, benign tumours may eventually contain billions of cells, become quite large, and cause damage by pressing against vital organs. They do not, however, spread to other sites or recur following surgical removal. In benign tumour cells, the chromosomal make up is usually completely normal.

The cells of a malignant tumour, a cancer, however have the following characteristics:

1. They do not respond to the mechanisms that normally restrict cell numbers to those required for growth or replacement. Like the growth of benign tumours, the proliferation of cancer cells may be slow, but it continues unabated.
2. Cancer cells become disorganized and may revert to a more primitive form, losing their specialized structures and functions. Pathologists look for these characteristic changes under the microscope to distinguish benign from malignant tumours.
3. Cancer cells are invasive, damaging adjacent tissues and often producing internal bleeding. They may also be shed from the primary site and Circulate through the blood and lymph to other locations in the body, where they initiate secondary cancers. The spreading to different sites called metastasis, poses a severe problem in treatment. Deaths of cancer patients often result from the destruction of vital organs at secondary sites or from overwhelming infections due to general debilitation and damage to the immune system.
4. Tumour cells pass through stages as they go from relatively benign to highly malignant. This process of tumour progression may follow the order of characteristics given in the preceding list, i.e., cells first divide without control, then become disordered and less distinctive, and then invade surrounding tissue and metastatize. These steps may be accompanied by increasing chromosomal aneuploidy or by changes in genes that code for proteins that regulate growth and division. It is possible that everybody has some of the early mutational changes is some of our body cells that could progress to cancer cells.

Cancer cells have a distinctive to appearance:

The cells of malignant tumours usually have a distinctive appearance that can be recognized by microscopic examination. Although no single morphological trait is sufficient of distinguishing a cancer cell from a normal cell, some frequently encountered structural features are quite useful in diagnosing the presence of a malignancy. Prominent among these features is a tendency of malignant cells to undergo anaplasia, a process involving the loss of cell differentiation and the disruption of the proper orientation of cells to one another.

Cancer cells also tend to exhibit large, irregularly shaped nuclei, prominent nucleoli and cell surface covered with microvillus and lamellipodia. The number of cells is elevated and abnormal mitosis and multinucleated giant cells are also encountered.

The nucleus is often enlarged (presumbly in relation to an increased chromosome complement) and the outline is irregular: the nuclear membrane shows deep infoldings (or)bleb formation, and cytoplasmic inclusions may be found within the nucleus. Conversely, parts of the nucleus may be cut off from the next, to form separate masses of chromatin surrounded by their own nuclear membrane; this could be one of the mechanisms by which the chromosome complement is altered following cell division.

There are also cytoplasmic abnormalities seen with the electron microscope. The mitochondria are often structurally abnormal. Endoplasmic reticulum and Golgi apparatus are usually poorly developed, but the number of free ribosomes is increased, as it is in developing embryo.

The changes in the nuclear membrane are of particular interest in view of the chromosomes appear to play in organizing its formation and the relationship which the ends of chromosomes probably have to it. It is Possible to speculate that the role of the Philadelphia chromosome in chronic myeloid leukaemia may be related to the function of a deleted end vis-à-vis the nuclear membrane. The chromosome concerned is such a small are that the deletion does not cause cell death; but it may cause a fetal interference with the proper formation and functioning of the nuclear membrane.

Cancer cells exhibit chromosomal abnormalities:

It has been known years that cancer cells exhibit genetic alterations that are often reflected in abnormalities in chromosome numbers and appearance. A classical example is the Philadelphia chromosome, an abnormally shaped chromosome that is produced by translocation of a piece of chromosome 9. The Philadelphia chromosomes occur in nearly 90% of individuals suffering from chronic granulocytic leukaemia.

Cancer cells almost always have abnormal karyotypes. These induce translocations, iso chromosomes, deletions, inversions, monosomies and extra chromosomes-the latter sometimes far beyond the diploid number. Specific chromosomal aberrations are sometimes associated with particular cancers.

Cancer cells produced tumours when injected into laboratory animals:

Perhaps the most distinctive features of cancer cells is their ability to produce tumours when an injected into an appropriate organism.

Cancer cells grow to high densities in culture:

Normal cells typically exhibit a limited life span when grown in culture. Human fibroblast, for example, multiplies for about 50-60 generations and then deteriorates and dies. Malignant cells, on the other hand, behave as if they are immortal. Human Hela cells, which were obtained from a uterine carcinoma in 1953, have divided more than 10,000 times in culture without signs of deterioration. When normal cells are placed in culture, they divide until the surface of the culture vessel is covered by a single layer of cells. When this monolayer stage is reached, cell movement and cell division usually cease. Malignant cells instead of stopping at the monolayer stage continue to divide and pile up on top of each other, forming multilayered aggregates.

Cancer cell growth is Anchorage – Independent:

Most normal cells do not grow well when they are suspended in a liquid medium or a semisolid material such as soft agar. But when provided with an appropriate surface, spread out and commence growth. This type of growth is said to be anchorage-dependent. In contrast to the behaviour of normal cells, most cancer cells grow well when they were suspended in a liquid or semisolid medium. Cancer cell growth is therefore characterized as being anchorage-independent.

Cancer cells lack normal cell cycle control:

When normal cells are exposed to suboptimal growth conditions such as inadequate nutrients or growth factors, they stop growing at a specific point in the cell cycle called the restriction point or START, which occurs nearly at the end of G1.Cells held up at this stage of the cell cycle are said to be in the G0 state. In contrast to the normal cells, cancer cells continue to grow and divide under conditions of high cell density, low serum concentration, or suboptimal nutrient concentration that would cause normal cells to stop at the restriction point. If the nutritional deprivation is severe, cancer cells eventually die at random points in the cell cycle rather than entering into G0.

This difference in the behaviour of normal and cancer cells has been used as a basis for devising ways to kill cancer cells selectively.

Cancer cells exhibit cell surface alterations:

Changes in the composition of plasma membrane are almost universally observed in cancer cells although the significance of such changes is often difficult to assess because similar alterations tend to occur in normal cells that have been stimulated to divide. For example, active transport systems for the uptake of sugars, amino acids and nucleosides are frequently activated in tumour cells, but a similar increase in transport activity is observed of appropriate nutrients or growth factors. It is therefore important to determine which membrane changes play unique roles in cancer cells and which changes of characteristics of dividing cells in general. Among the cell surface changes that appear to be particularly distinctive and important for the behaviour of cancer cells are those that influence the properties of adhesiveness, agglutianability, cell-cell communication and antigenic composition.

Cancer cells secrete proteases, embryonic proteins and proteins that stimulate angiogenesis:

Because they would be potentially useful for the diagnosis of cancer, a great deal of effort has been expanded in searching for the molecular 'markers' that are produced only by the cancer cells. Unfortunately none of the molecules identified thus far have turned out to be absolutely unique to cancer cells, although a number of them have provided some important insights into the behaviour of malignant tumours. Prominent among those are proteases, embryonic proteins and molecules that stimulate blood vessel formation.

It has been known for many years that malignant tumours often secrete proteases. Although, protein digestion enzymes are also secreted by certain kinds of normal cells, the enhanced production of such enzymes by cancer cells may contribute to some of the properties of malignant tumours. For example, the decrease in adhesiveness and loss of anchorage dependence that are frequently exhibited by cancer cells may be caused by proteases digestion of cell surface component. As secretion of proteases might also provide a partial explanation for the invasive properties of malignant tumours.

In addition to proteases some cancer cells manufacture and secrete proteins that are usually produced only by embryos. e.g., alpha-feto-protein, a protein made by embryonic liver cells, is found in only trace amounts in normal adults,

but its concentration in the bloodstream increases dramatically in patients with the liver cancer.

Carcino Embryonic Antigen (CEA), a glycoprotein produced in the embryonic digestive tract and fetal hormones such as chronic gonadtrophin and placental lactogen, are also secreted by certain human tumours. Testing for embryonic markers such as alpha-feto protein and CEA in the bloodstream has been used diagnostically to monitor for the presence of particular kind of cancer, but the fact that these substances are made by only a few tumour types has limited usefulness of this approach.

Some growth factors also secrete growth factors that stimulate the formation of blood vessels. The presence of an adequate blood supply is a critical factor in determining a tumours ability to grow and invade, so production of substances that stimulate the process of blood vessel formation or angiogenesis, can have a profound influence on tumour behaviour. It has been shown for example, that tumours will not grow beyond a few millimeters in diameter in the absence of newly forming blood supply. Therefore inhibitors of angiogenesis might be potentially useful tools for exhibiting tumour growth.

In recent years, the genetic changes exhibited by cancer cells have been pinpointed to the level of individual genes, and the role played by the altered genes in causing cancer is beginning to emerge. Two classes of genes are now known to play crucial roles in the development of cancers; a group of altered genes whose presence is associated with malignancy, and a group of genes whose absence (or loss of function) is associated with malignancy.

Chromosomes in Malignancies

The relationship of chromosomal aberrations to the formation and development of new growths of any kind, whether solid tumours or neoplastic processes involving haemopoietic or other free living cells, is a complex one. The basic difficulty in studying the subject is that every new growth is different and that although chromosomal aberrations are seen is tumours with great constancy, it is difficult to relate them to the type of tumour or the way in which it is behaving. There is only one notable exception to this general rule, and that is the rather constant finding of a specific chromosomal aberration, the deletion of chromosomes of the G group, in the stem cells is chronic myeloid leukaemia. This is called the Philadelphia or Ph^1, chromosomes.

The subject of chromosomes of experimental tumours has recently been reviewed by Levan, 1969 concludes virtually all neoplastic tissue shows deviation from the normal if these are carefully searched for. And in general, the longer the abnormal tissue has been growing, the greater the number of abnormalities of chromosomes that are found.

Human new growths may be divided into those which form solid tumours (Carcinomas, Sarcomas) and those in which the neoplastic cells are more or less free living and and widely disseminated throughout the body. Solid tumours do not make good experimental material, for several reasons. First, there is the difficulty that because they often grow relative slowly and contain much degenerating tissue, it is not always easy to find adequate numbers of dividing cells to study and secondly, more importantly, it is seldom of ever possible to many serial observations on their karyotypic composition, since it is necessary for the patients sake to remove any large masses of tumours which can be removed, as soon as possible (treat them by radiation where this is not possible). Hypo diploids, tetraploids and structural chromosomal changes are common. In general it is not possible to relate a specific chromosomal abnormality to a specific type of tumour. But some types of neoplasia (Chronic or Acute myelogenous leukaemia, Retinoblastoma, Meningiomas and Lymphomas) have been found to have a considerable relationship.

Chronic Myelogenous Leukaemia (CML)

Leukaemia means abnormal number of white cells in blood. The most conspicuous and well known e.g., of a constant association between chromosomal anomalies

and neoplasia is the presence of Philadelphia (Ph^1) chromosome in chromosomal myelogenous leukaemia (**Nowell & Hungerfold, 1960**). With the help of banding techniques, the abnormal chromosome was identified as a number 22 (**Casperson et al., 1970**) demonstrated that the Ph^1 chromosome does not represent a simple deletion of chromosomes 22 but rather than an apparent balanced translocation between chromosomes 9 and 22. The involvement of these two chromosomes in the genesis of the Ph^1 chromosome has been repeatedly confirmed (Berger, 1973). Blastic crisis in CML is usually accompanied by other chromosomal anomalies in addition to the presence of the Ph^1 chromosome. These changes do not follow random patterns, but frequently involve the presence of extra copies of the Ph^1 chromosome, iso chromosome for the long arm of chromosome 17, and trisomy 1, 8 and 9 (Lobb et al., 1972). The exact significance of these changes is not known.

Acute (severe) Leukaemia (AL)and other Myeloproliferative diseases:

AL either myelo or lymphoblastic, show chromosome abnormalities in bone marrow cells in approximately 50% of the cases (Sandberg and Hossfeld, 1970). Acute Lymphatic Leukaemia (ALL) tends to show hyperdilpoidy, while in Acute Myelogenous Leukaemia (AML) hypodiploidy predominants. An extra C group chromosome has been repeatedly reported to be present in bone marrow cells of leukaemia patients. The extra chromosomes may be 8 or 9 in most cases (Jonasson, 1974) and sometimes as 10 or 11 (Philip, 1975). A missing or deleted chromosome 7 has also been identified(Rowley, 1973).

Lymphomas: (Neoplasm of lymphoid tissue)

Burkitt Lymphomas is a neoplastic process in where there is a close association with the Epstein-Barr (EB) virus, possibly as a cause effect type of relationship (**Epstein & Achong, 1973**) **Manolov & Manolova,1972** reported the presence of an abnormal chromosomes 14 and 8 of 12 tumours examined. The abnormal chromosomes showed a similar anomaly in all cases, involving an extra dark band at the distal end of the long arm of chromosome 14. This finding was later confirmed by Jarvis,1974 who found that same marker chromosome in 7 cell lines derived from Burkitt lymphomas. Zech, 1975 proved that the extra dark band in chromosome 14 is the result of balanced translocation from chromosome 8. This has been confirmed by Mc caw.,1977.

Retinoblastoma

(Cancer of eye). It has long been associated with a partial deletion of the long arm of D (13–14) group chromosome (Lele, 1963). Orye,1971 applied banding techniques to chromosomes of a patient with retinoblastoma and a deletion of D group chromosome and identified the chromosome number as 13. This finding has been confirmed in several cases (Wilson *et al*.,1973; Howard, 1974). Yunis have reexamined these available information and concluded that the specific segment involved include band 13q14 and proximal portion of band 13q21.

Meningiomas

(Tumour of membrane eneveloping brain and spinal cord) Cytogenetic studies of human meningiomas have shown that the loss of G group chromosomes is a typically for the tumour (**Zang & Singer, 1967**). Banding techniques identified the missing chromosome as number 22 (**Mark et al., 1972**). In addition, loss of chromosomes 8,9,X and Y have also been reported in a few cases (**Mark et al., 1973**). In a patient with Aniridia and Wilm's tumour, a partial deletion of chromosome 8 (8p.12 8p22) has been reported (**Ladda, 1974**).

In conclusion, the application of the banding techniques to the study of chromosomes in human tumours offers fruitful results. However, that many more studies are needed to precisely clarity the role played by chromosomal abnormalities in the genesis of human neoplasia. Now Fluorescent In Situ Hybridization (FISH) technique is developed to study chromosomes in human tissue more accurately.

Relation of oncogenes to chromosomal defects:

Oncogenes are genes that effect normal cell growth and development. If an oncogene is altered, either as a result of a mutation in the gene itself or by altered external control, the cell in which the change occurred can undergo uncontrolled growth, eventually becoming malignant.

Gene mutation Altered oncogene Cell change Uncontrolled growth of cells Formation of tumour.

Most oncogenes are mutated (activated) forms of normal genes, called proto oncogenes (Miller *et al.,* 1990). Oncogenes can be identified experimentally in DNA transfer studies by their ability to transform a non tumourigenic mouse cell line in culture to generate foci of cells with tumourigenic properties). To date more than 50 human oncogenes have been identified. The oncogenes and its counterpart proto oncogenes different in only a single base pair.

A point mutation in a somatic cell of the tumour, led to synthesis of an abnormal gene product, which was able to stimulate the growth of the cell line, change into a tumour.

Point mutation in cells of tumour abnormal gene product stimulate cell growth tumour.

Ras point mutations are observed in many tumours and the Ras genes have been shows experimentally to be target of known carcinogens, a finding that supports a role for mutated Ras genes in the development of many cancers.

Structural mutation is only one of the several mechanisms that can include activation of proto-oncogenes. Chromosome translocations are a common mechanism for proto-oncogene activation in a variety of cancers.

In Chronic Myelogenous Leukaemia (CML), increased expression and malignant transformation are related to the translocation of the abl proto - oncogene from its normal position on chromosome 9 to the break point in chromosome 22 in a haematopoietic stem cells. The 9:22 translocation directly contributes to the development of the malignant phenotype and is also a strong diagnostic indicator of CML. In addition to 9:22 translocation, the other chromosomal abnormalities are iso chromosomes for 17q and numerical abnormalities. In advanced stages of other forms of leukaemia, translocations are common. In lymphomas, translocations occur between 8;14 chromosomes and myc protooncogene is involved in this.

Another important mechanism for overexpression is gene amplification, a process that is rare or non expression in normal cells but some times common in cancer cells.

Amplified region Induced protooncogenes affects cell growth Uncontrolled growth Tumour formation.

These amplified segments are often detected as 2 types of cytogenetic changes, double minute (small accessory chromosomes) and homogenously staining regions (HSRS) that do not band normally and contain multiple amplified copies of particular DNA segment. How and why double minutes and HSRS occur is poorly understood, but amplified regions are known to include extra copies of proto-oncogenes with effects on cell growth (For e.g., the N-myc, proto oncogenes is amplified upto 200 times in 40% of Neuroblastomas).

Requirement for more than one activated gene:

An important aspect of the initiation and promotion of carcinogenesis by activated proto oncogenes is that mutation of a single gene alone seems unable to achieve transformation; rather separate genes with complementary effect seem to be required. So it means malignant transformation is a multi event process, not to be achieved by a single step or single event.

Furthermore, it is now well documented that exposure to ionizing radiation is predisposing factor. This was shown by Brill *et al.,*1962 in respect of survivors of the atomic bomb explosion at Hiroshima, by Court **Brown & Doll, 1965** in patients irradiation for Ankylosing Spondylitis. The irradiation of pregnant woman causes a risk of leukaemia for the unborn infants. Benzene can cause chromosome aberrations and can be leukaemogenic (**Tough & Court Brown, 1965**).

Two interesting reports have appeared describing individuals who were exposed to whole body irradiation and who showed abnormal deleted G group chromosomes indistinguishable from the Ph^1 chromosome. Goh,1966 reported such chromosomes in three patients who had been treated with body irradiation for Ankylosing Spondylits. Kamada *et al*., 1970 reported the same phenomenon in heavily irradiated atomic bomb survivors.

1. Finally there is also association between Downs syndrome and Leukaemia.
2. The environmental agents may cause damage to DNA.
3. The genes that are defective in the chromosome instability syndromes may be viewed as cancer genes.
4. Chromosomes instability is a hall mark of cancer.
5. Heterozygotes for these disorders may also be at an increased risk of malignancy.
6. Relatives of Ataxia Telangiectasia homozygote appear to have an increased risk of breast cancer. Upto 7.5% of all Breast cancer in young women may occur in Ataxia Telangictasia heterozytoes.
7. It is difficult to avoid a conclusion from all this evidence that leukaemia may result as a direct consequence of chromosomes breakage, but there is no firm evidence as to what the triggering event may be.
8. Finally, it should be mentioned that there appears to be a genetic factor responsible for predisposing some individuals to develop Leukaemia.

9. (**Mac Mohan & Levy, 1964**) have shown that an identical twins has an increased tendency to develop Leukaemia within a few months of his or her "other half" doing so.
10. A number of instances where the incidence of Leukaemia in a family is much higher than might be expected by chance.

Cancer as a Genetic Disorder and Cancer in Families

In the past viruses and exposure to environmental agents such as ionizing radiation were blamed for most cancers. It is now recognized that the underlying cause is gene mutation and that when carcinogenic agents are involved, they operate by causing mutations. The mutations that lead to cancer affect genes responsible for cell proliferation, cell development and other fundamental cellular activities. When normal regulation is altered, uncontrolled growth is initiated and a malignant tumour develops.

Cancer as a Genetic Disorder

Types of Cancer Genes

Genes that cause cancer of two distinct types:

Oncogenes and tumour suppressor genes. The two types have opposite effects in carcinogenesis. Oncogenes facilitate malignant transformation whereas tumour suppressor genes, as the name implies, block tumour development by regulating genes involved in cell growth.

Oncognes are genes that affect normal cell growth and development. If an oncogene is altered or overexpressed as a result of a mutation in the gene itself or by altered external control, the cell in which the change occurred can undergo uncontrolled growth, eventually becoming malignant. Most oncogenes are mutated forms of normal genes, called protooncogenes, that are involved in the control of cell proliferation and differentiation(Miller *et al.,*1990).

Whereas the products of protooncogenes promote growth, the products of tumour suppressor genes normally block abnormal growth and malignant transformation and contribute to malignancy only when the function of both alleles is lost. In other words, in contrast to mutations in protooncogenes, which are dominant in their action, mutations in tumour suppressor genes are recessive.

Two copies of every gene are present in all cells of the body and each one is called an allele. Most cancer syndromes are transmitted in a mendelian autosomal dominant manner. In these cases, only one faulty allele has to be present for an individual to have a predisposition to cancer. Individuals with one normal allele and one faulty allele are known as heterozygous.

Loss of heterozygosity (**LOH**) is a cross chromosomal event that results in loss of the entire gene and the surrounding chromosomal region.[1]

All diploid cells, for example most human somatic cells, contain two copies of the genome, one from each parent (chromosome pair); each human copy contains approximately 3 billion bases (adenine (A), guanine (G), cytosine (C) or thymine (T)). For the majority of positions in the genome the base present is consistent between individuals, however a small percentage may contain different bases (usually one of two; for instance, 'A' or 'G') and these positions are called single nucleotide polymorphisms or SNPs. When the genomic copies derived from each parent have different bases for these polymorphic regions (SNPs) the region is said to be heterozygous. Most of the chromosomes within somatic cells of individuals are paired, allowing for SNP locations to be potentially heterozygous. However, one parental copy of a region can sometimes be lost, which results in the region having just one copy. The single copy cannot be heterozygous at SNP locations and therefore the region shows loss of heterozygosity. Loss of heterozygosity due to loss of one parental copy in a region is also called hemizygosity in that region.

A heterozygous individual and a person with two normal alleles (homozygous) will have a 50% chance of producing an affected child. The mutation in the inherited gene is known as a germline mutation and a further mutation in the normal allele results in the development of cancer. This is known as Knudson's two hit hypothesis, where the first hit of the gene is the inherited mutation and the second hit occurs later in life. As only one allele needs to be mutated (as compared to both in so called "sporadic cancers"), the individual has a higher chance of developing the cancer than the general population.

The loss of heterozygosity is a common occurrence in cancer development. Originally, a heterozygous state is required and indicates the absence of a functional tumour suppressor gene copy in the region of interest. However, many people remain healthy with such a loss, because there still is one functional gene left on the other chromosome of the chromosome pair. The remaining copy of the tumour suppressor gene can be inactivated by a point mutation or via other mechanisms, resulting in a loss of heterozygosity event, and leaving no tumour suppressor gene to protect the body. Loss of heterozygosity does not imply a homozygous state (which would require the presence of two identical alleles in the cell).

Knudson Two-hit Hypothesis of Tumourigenesis

First Hit: The first hit is classically thought of as a point mutation, but generally arises due to epigenetic events which inactivate one copy of a tumour suppressor gene (TSG), such as Rb1. In hereditary cancer syndromes, individuals are born with the first hit. The individual does not develop cancer at this point because the remaining TSG allele on the other locus is still functioning normally.

Second Hit: While the second hit is commonly assumed to be a deletion that results in loss of the remaining functioning TSG allele, the original published mechanism of RB1 LOH was mitotic recombination/gene conversion/copy-neutral LOH, not deletion. There is a critical difference between deletion and CN-LOH, as the latter mechanism cannot be detected by comparative genomic hybridization (CGH)-based gene copy number counting, and requires allelic genotyping. Either way, LOH leaves only non-functioning alleles of the TSG, and the individual may go on to develop cancer.

Less often, syndromes may be transmitted as an autosomal recessive trait. Both alleles of a gene must be mutated in autosomal recessive disorders for an individual to have a predisposition to cancer. A person with two recessive alleles is known as homozygous recessive. Both parents must have at least one faulty allele in order for a child to be homozygous recessive. If both parents have one mutant allele and one normal allele (heterozygous) then they have a 25% chance of producing a homozygous recessive child (has predisposition), 50% chance of producing a heterozygous child (carrier of the faulty gene) and 25% chance of produced a child with two normal alleles.

Cancer in Families

Cancer is a common disease, so it is not surprise that many families have at least a few members who have had cancer. Sometimes, certain types of cancer seem to run in some families. In some cases, this might be because family members share certain behaviors or exposures that increase cancer risk, such as such as smoking. Cancer risk might also be affected by other factors, like obesity, that tend to run in some families. In other cases, cancers that run in families can be caused by an abnormal gene that is passed from generation to generation. Although this is often referred to as inherited cancer, what is inherited is the abnormal gene that can lead to cancer, not the cancer itself. Only about 5% to 10% of all cancers are thought to result directly from gene defects (mutations) inherited from a parent.

Many family cancer syndromes are caused by inherited mutations in tumour suppressor genes. These are genes that normally keep cells under control by slowing down how often they divide (to make new cells), repairing DNA mistakes, or telling cells to die at the right time. There are 2 copies of most genes – one from each parent. When someone inherits an abnormal copy of a gene, their cells already start out with one mutation. Often this is not a problem, as the other gene copy is still working. But if the other gene copy stops working (because of an acquired mutation, for example), the genes function can be lost altogether. When the gene that stops working is a tumour suppressor gene, cells can grow out of control, which can lead to cancer. A person born with an inherited mutation in a copy of a tumour suppressor gene would only have to acquire a mutation in the other copy of that gene for it not to work. This is more likely to happen than acquiring mutations in both copies of a gene, so this person would have a higher risk of cancer than someone born without a gene mutation.

Retinoblastoma

Retinoblastoma, the prototype of diseases caused by mutation in **tumour suppressor genes**, is a rare malignant tumour of the retina in infants with an incidence of about **1 in 20,000** births. Diagnosis of a Retinoblastoma most usually be followed by removal of the affected eye, although smaller tumours, diagnosed at an early stage, can be treated by local therapy. So that vision can be preserved.

About 40% of cases of Retinoblastoma are of heritable form, in which the child inherits one mutant allele at the Retinoblastoma locus(RBI) through the germ line, and a somatic mutation in a single retinal cell has caused loss of function of the remaining normal allele, thus initiating, development of tumour.

There are often multiple tumours, and both eyes are usually affected. The disorder is inherited as a **dominant** trait, since the likelihood of a somatic mutation occurring in at least one of more than 10^6 retinoblasts is extremely high, and thus heterozygotes for the disorder are likely to be affected. Nevertheless, penetrance of Retinoblastoma although high, is not complete since the occurrence of the second mutation is a matter of chance. Non malignant lesions of the retina(called retinomas)are present in the eyes of some relatives of index patients.

The other 60% of cases of retinoblastoma are nonheritable(sporadic),in these cases both RBI alleles in a single retinal cell have been inactivated by somatic mutation. Because this is a rare event, there is usually only a single tumour(the

retinoblastoma is unilateral)and the average onset age is later than in infants with the heritable form.

Pedigree: Comparison of Mendelian and sporadic forms of cancers such as retino blastoma.

Mendelian	Sporadic
Germ line mutation	Somatic mutation
Multiple tumours	Single tumour
Bilateral	Unilateral
Early onset	Later onset

For genetic counseling, an important further point is that **15%** of patients with **unilateral** Retinoblastoma have the **heritable** type but by chance develop tumour in only one eye.

Infants with heritable Retinoblastoma have a greatly increased(400 fold)risk of developing mesenchymal tumours such as osteogenic sarcomas, fibrosarcomas and melanomas in early adult life. The risk is much higher if the child has received radiation therapy.

The RBI gene has been mapped in chromosome 13, location is **13q14**. The inherited mutation in a few percent of retinoblastoma patients is due to deletion or translocation of this portion of chromosome 13.Other chromosomal abnormalities such as an isochromosome of chromosome 6p are found only in Retinoblastoma tumours and not in other patient tissues.

The RBI gene is expressed in many tissues other than retina, although it initiates tumour only in the retina and a small number of secondary sites leading to osteogenic sarcoma, fibrosarcoma and melanoma. As noted earlier,to gene product,described as P11ORBI (a protein 110 kilodaltons in size) is also absent for mutant in a number of cell lines derived from certain other tumours during their progression.

Loss of Heterozygosity

Analysis of DNA polymorphisms in the region close to the RBI locus in tumours from both heritable and sporadic Retinoblastoma patients led to an unusual but highly significant genetic discovery whereas individuals from whom the tumours

were taken were heterozygous at many loci, the tumours were homozygous at the same loci. Thus the tumour DNA samples contained alleles from only one of the two chromosome 13 homologs, revealing, a loss of heterozygosity for stretches of 13q in the region of the gene. In familial cases, the retained chromosome 13 is the one inherited from the affected parent, that is one with the abnormal RBI allele. Loss of heterozygosity may occur by structural deletion, but there are other mechanisms such as mitotic recombination or non disjunction. It is the most commom mutational mechanism by which the remaining normal RBI allele is lost in heterozygotes. Loss of heterozygosity is also a feature of **wilms tumour**, as well as number of other tumours, both heritable and sporadic, and is often considered evidence for the existence of a tumour suppressor gene.

Wilms Tumour

Wilms tumour, an embryonic kidney tumour, is in some ways analogous to Retinoblastoma in that it is a Mendelian disorder involving a tumour suppressor gene, although it is less commonly observed in a heritable form. It is sometimes associated with cytogenetically visible aberration at 11p13, and if so it forms part of the WAGR syndrome (high risk of wilms tumour, aniridia, genitourinary anomalies and MR),a contiguous gene syndrome involving a series of genes that map to this region. Loss of heterozygosity is a feature of the syndrome.

A gene encoding a zinc finger protein has been cloned from the 11p13region missing in wilms tumour patients and is likely to be the affected locus in atleast some cases(call et al,1990:Huang et al,1990). However this may not be the only gene predisposing to Wilms tumour, because there are multiple genes expressed in the kidney from this region of chromosome 11 and because in some wilms tumour families the predisposing locus map to 11p15, and in others, the map position is unknown.

Familial Polyposis Coli

Colon cancer is one of the most common forms of cancer, accounting for about 15% of all cancers; a small preportion of colon cases are due to **autosomal dominant** conditions such as familial polyposis coli or Gardner syndrome.

Familial polyposis coli (also known as familial adenomatous polyposis)is relatively common, with an evidence of **1 in 10,000**. In heterozygotes, numerous polyps, which themselves are benign growths, develop in the colon during the first two decades of life. In almost all cases,one or more of the polyps become

malignant. Surgical removal of the colon (colectomy) prevents the development of malignancy. Because this disorder is autosomal dominant, relatives of affected persons must be examined periodically by colonoscopy. The responsible gene has been located on chromosome 5q.One candidate for gene responsible for familial polyposis coli is MCC gene from chromosome **5q21** that is mutated somatically in atleast some sporadic colorectal carcinomas. Patients with Garden Syndrome have additional anomalies, including osteomas of jaw and desmoids, which are tumours arising in the muscle of the abdominal wall.

Neurofibromatosis Type 1 (NF1):

It is common autosomal dominant disorder that primarily affects the primary nervous system and is often characterized by large numbers of neurofibromas. Although these growths are benign, a minority of NFI patients also show an increased incidence of malignancy. The abnormal cell growth observed in NFI suggests that the normal gene may function in the regulation of cell growth in nerve tissue.

The NFI gene was mapped to the proximal long arm of chromosome 17 by family linkage studies and was subsequently cloned by application of several of the positional cloning strategies. The family studies show localization of the gene to **17q11.2**.Detailed long range mapping and cloning eventually led to isolation of a large gene that was interrupted by the two translocation breakpoints(Wallace *et al*.,1990: Viskochil *et al.,*1990). In addition, several single nucleotide substitutions were discovered in NFI patients,thus establishing the identity of the gene and its involvement in NFI(Cawthon *et al.,*1990).

Inspection of the sequence of the NFI gene and its protein product demonstrated significant homology to proteins that activate the GTPase activity of the ras oncogene product. This finding suggests that the normal NFI product interacts with ras to regulate growth stimulating activity in normal cells. The mutant NF1 gene, fail to regulate growth in normal cells from which neurofibromas are derived leading to inappropriate growth and tumour formation (Xu *et al.,*1990).

This model suggests that NFI is a tumour suppressor gene. By analogy with other dominantly inherited tumour suppressor gene mutations, loss or inactivation of the remaining normal alleles at the NFI locus would be required to explain growth of either neurofibramos or other solid tumours in NFI patients. Alternatively, it may be that multiple mutations in other genes have additive effects and stimulate unregulated cell growth, as seen in the clonal progression of colon cancer.

Li-Fraumeni Syndrome

These are rare "cancer families" in which there is a striking history of a variety of forms of cancer (including several kinds of sarcoma,breast cancer and other neoplasms) affecting a number of family members at an unusually early age, in an **autosomal dominant** pattern. Because the tumour suppressor gene P53 is inactivated in the sporadic forms of many of the cancers found in Li-Fraumeni Syndrome (LFS), **P53** was considered as a candidate for the gene defective in LFS. DNA analysis of several LFS families has now confirmed this hypothesis; affected members in LFS families carry a mutant form of the P53 gene as a germline mutation (Malkin et al., 1990) Thus LFS is an extreme form of a group of cancers that occur in both sporadic and a familial form; as seen also in Retinoblastoma, in the familial form one of the two mutations necessary to inactivate the P53 gene is present in the germline, but in the sporadic form both mutations are somatic events.

Familial Breast Cancer

Breast cancer has long been recognized to have a strong genetic component. Population based epidemiological studies have shown that upto **10%** of all women in North America will develop breast cancer in their life time. Further more, a women's risk of developing breast cancer is increased upto 3 fold if one first degree relative is affected and upto 10 fold if more than one first degree relative is affected. This familial risks are increased even more if the onset of disease in the proband is at 40 years of age or less (Claus et al., 1990). Although as much as **20%** of all breast cancer cases may have a significant genetic component as a part of a **polygenic or multifactorial** mode of inheritance, a small proportion of cases appear to be due to **dominantly inherited** Mendelian predisposition to breast cancer. These families share same characteristic features of familial(as opposed to sporadic) cancer.

Population studies have indicated that 2–5% cases of breast cancer are due to inheritance of a major susceptibility gene (Claus et al., 1991). Genetic linkage studies in families with early onset familial breast cancer have localized dominant gene for increased susceptibility to breast cancer to the long arm of **chromosome 17** (Hall et al.,1990).This susceptibility allele has an estimated frequency 0.003.Thus the frequency of carrier females can be estimated to be nearly 1%.

Comparison of breast tumour tissue with normal tissue from the same women has shown loss of heterozygosity from a number chromosomal regions, including **1p,3p,11p,13q,16q and 17p** suggesting that there may be a number of genes important for breast tumour progression. Although the gene on chromosome 17p is likely the p53 tumour suppressor gene shown to be defective in Li-Fraumeni syndrome, the other genes have not been identified.

Tumoursuppresor gene	**Chromosome**	**Tumours**
P^{53}	17	Carcinoma of lung and breast, sarcoma
Retinoblastoma (Rb)	13	Retinoblastoma, sarcoma, some carcinomas
NF1 tumours	17	Neurofibromas, malignant peripheral nerve
APC	5	Colonic carcinoma
WT1	11	Wilms' tumour, bladder cancer

P^{53} gene: This gene codes for a nuclear phosphoprotein, which is expressed in increased Amounts following cellular damage,e.g.irradiation. P^{53} has been called the 'Guardian of the genome'. Abnormalities of P^{53} are found in at least 30% of all cancers. Germ line P^{53} mutation is a feature of the Li-Fraumeni syndrome.

Heritable Fragile Sites and Oncogenes

There are at least 17 sites on human chromosome at which there is an inherited predisposition to breakage. Ten of these sites are at or near regions involved in chromosome aberrations in Leukaemias or Lymphomas & some of these are at or near the sites of proto oncogenes. But the possible association of hereditary fragile sites with predisposition to cancer remains unproved.

Chromosomal Instability Syndromes

There is now a considerable body of evidence to the effect that circumstances predisposing to chromosome breakage leads to an increased incidence of Leukaemia. The examples are Fanconi's pancytopenia (Fanconi anemia), Bloom syndrome, Ataxia telangiectasia, Xenoderma pigmentosum, are all associated with an increased risk of malignancy, particularly Leukaemia.

Fanconi Anaemia

Fanconi anaemia (FA) is an autosomal recessive disease characterised by congenital abnormalities, defective haemopoiesis, and a high risk of developing acute myeloid leukaemia and certain solid tumours. Chromosomal instability, especially on exposure to alkylating agents, may be shown in affected subjects and is the basis for a diagnostic test. FA can be caused by mutations in at least seven different genes. Interaction pathways have been established, both between the FA proteins and other proteins involved in DNA damage repair, such as ATM, BRCA1 and BRCA2, thereby providing a link with other disorders in which defective DNA damage repair is a feature. This review summarises the clinical features of FA and the natural history of the disease, discusses diagnosis and management, and puts the recent molecular advances into the context of the cellular and clinical FA phenotype.

Rare, congenital disorder, characterized by aplastic anaemia in child hood or early adult life, bone abnormalities, chromatin breaks and developmental anomalies.

Bloom Syndrome

Bloom syndrome (BSyn) is a rare genetic disorder characterized by short stature; a sun-sensitive, red rash that occurs primarily over the nose and cheeks; mild immune deficiency with increased susceptibility to infections; insulin resistance that resembles type 2 diabetes; and most importantly, a markedly increased susceptibility to many types of cancer, especially leukaemia, lymphoma and gastrointestinal tract tumours. Diagnosis typically involves identification of the characteristic clinical features and/or molecular testing to identify changes to the *BLM* gene. BSyn is inherited in an autosomal recessive pattern, meaning that it occurs when a person inherits two changed (mutated) copies of the *BLM* gene. Because the most common BLM mutation is present at a high frequency in the Eastern European Jewish (Ashkenazi) population, it is often included among the Jewish genetic diseases. The genetic abnormality in Bloom syndrome causes problems with DNA repair, resulting in a high number of chromosome breaks and rearrangements. The abnormal DNA repair is responsible for the increased risk for cancer.

A rare genetic disease occurs mainly in Jews. It is transmitted as an autosomal recessive trait and is characterized by growth retardation, telangiectatic erythrema (inflammation of skin,redness) of the face and arms, sensitive to sunlight and an increased risk of leukaemia.

Ataxia-telangiectasia

Ataxia telangiectasia (AT) is a complex genetic neurodegenerative disorder that may become apparent during infancy or early childhood. The disorder is characterized by progressively impaired coordination of voluntary movements (ataxia), the development of reddish lesions of the skin and mucous membranes due to permanent widening of groups of blood vessels (telangiectasia), and impaired functioning of the immune system (i.e., cellular and humoral immunodeficiency), resulting in increased susceptibility to upper and lower respiratory infections (sinopulmonary infections). Individuals with AT also have an increased risk of developing certain malignancies, particularly of the lymphatic system (lymphomas), the blood-forming organs (e.g., leukaemia), and the brain.

AT is inherited as an autosomal recessive trait. The disorder is caused by changes (mutations) of a gene known as ATM (for "AT mutated") that has been mapped to the long arm (q) of chromosome 11 (11q22.3). The ATM gene controls (encodes for) the production of an enzyme that plays a role in regulating cell division following DNA damage.

A rare, genetic disease involving immunoglobulin metabolism that is transmitted as an autosomal recessive trait. The onset usually occur in infancy and progresses slowly with increasing cerebellar degeneration and recurrent sinopulmonary infections. Telangiectasias are most prominent on the ears, facial skin and bulbar conjunctiva. There is increased risk of malignancies especially Leukaemia. Also called Louis-Bar syndrome.

Xenoderma Pigmentosum

Xeroderma pigmentosum (XP) is a rare inherited skin disorder characterized by a heightened sensitivity to the DNA damaging effects of ultraviolet radiation (UV). The main source of UV is the sun. The symptoms of XP can be seen in any sun-exposed area of the body. The effects are greatest on the skin, the eyelids and the surface of the eyes but the tip of the tongue may also be damaged. In addition, approximately 25% of XP patients also develop abnormalities of the nervous system manifesting as progressive neuro-degeneration with hearing loss. People with XP have a 10,000-fold increased risk for developing skin cancer including basal cell carcinoma, squamous cell carcinoma and melanoma. They also have a 2000-fold increased risk for cancer of the eye and surrounding ocular tissues.

These symptoms appear early in life, typically before age 10 years.

Xeroderma pigmentosum is an autosomal recessive genetic condition caused by alterations (mutations) in nine different genes. Eight of the genes make up the nucleotide excision repair pathway (NER) that identities and repairs UV induced DNA damage. The ninth gene acts to bypass unrepaired damage.

Is a rare, inherited skin disease characterized by extreme sensitivity to ultraviolet light exposure to which results in telangiectasia, carcinoma, papilloma, melanoma, keratitis (inflamation of cornea), and tumour develops in the eye lids and cornea may result in blindness.

One important conclusion to be drawn from the study of patients with chromosome breakage syndromes is that there is extensive variation in inborn resistance to DNA damage by environmental agents. Clinically, radiography must be used with extreme caution if at all in ataxia telangiectasia, fanconi anemia and blooms syndrome. Furthermore, prolonged exposure to sunlight must be avoided in xeroderma pigmentosa.

The gene that are defective in the chromosome instability syndrome may be viewed as cancer genes. Chromosome instability is a hallmark of cancer. The enzymes defective in these syndromes must be intimately involved in DNA repair and the maintenance of chromosome integrity. The genes for two of these defects(two forms of xeroderma pigmentosa)have been isolated. However, precise involvement of the predicted gene products in DNA repair is still unknown.

Heterozygotes (consisting of two different alleles at a locus) for these disorders may also be at an an increased risk of malignancy. Relatives of ataxia telangiectasia homozygotes (consisting of two identical alleles at a given locus) appear to have an increased risk of breast cancer; upto 7.5% of all breast cancer in young woman may occur in ataxia telagiectasia (Swift et al.,1987).Thus cloning of ataxia telangiectasia gene (one of which has been mapped by family linkage studies to chromosome 11q)may allow preclinical identification of a class of individuals with a dramatic genetic predisposition to atleast one of common cancers.

Inherited Versus Sporadic Cancers

Most cancers are caused by changes in genes, called mutations. Genetic mutations can interfere with how the body normally works, such as stopping cells from growing out of control or repairing any damage to the cells.

If a person inherits a particular cancer-causing mutation from their parents and develops cancer as a result, that type of cancer can be called hereditary cancer. Other names for this type of cancer include inherited cancer or family cancer.

Cancer is a common disease, so most families will have some members who have had cancer. Cancer that is not due to an inherited gene mutation (change) is called sporadic cancer. It is believed that most—perhaps 80%—of all cancers are sporadic. This means even if cancer does not run in a family, a family member can still be at risk for some type of cancer in his or her lifetime.

Hereditary Cancer

Cancer that results from genetic changes that are passed on from one generation to the next is considered hereditary. Approximately 5–10% of all cancers fall into this category.

Sporadic Cancer

Most cancers develop due to genetic damage sustain over a lifetime. When the genes acquire defects that alter the cells ability to grow and divide properly, tumours form. Cancers that occur because of these genetic changes are considered to be sporadic. Approximately 70–80% of all cancer is deemed sporadic.

Family Clusters of Cancer

When cancer occurs in a family more often than what would be expected by chance, it is considered a familial cancer cluster. Familial clusters have been reported for many types of cancer and are believed to be due to a combination of risk factors which include inherited susceptibility, environmental factors and chance.

"Hereditary Cancer Type" Characteristics

Hereditary cancers are caused in part by gene mutations passed on from parents to their children. Other blood relatives may share these same gene changes.

Apparently autosomal dominant transmission of specific cancer type(s):

1. An inherited gene mutation is present in the egg or sperm cell that formed the child. When the egg is fertilized by the sperm, it creates one cell that then divides many times and eventually becomes a baby. Since all the cells come from this first cell, this kind of mutation is in every cell (including eggs or sperm) and so can be passed on to the next generation (germ line mutation).
2. Earlier age of onset of cancers than is typical.
3. Multiple primary tumors in an individual.
4. Clustering of rare cancers.
5. Bilateral or multifocal cancers.
6. First degree relatives of mutation carriers are at 50% risk to have the same mutation.
7. Incomplete penetrance and variable expressivity, such that obligate carriers of the family mutation may be cancer-free and the age of diagnosis of cancer among relatives will vary.
8. Hereditary cancers can sometimes be more aggressive than the sporadic form of the same cancer. For example, hereditary prostate cancers tend to be more aggressive and more likely to spread than sporadic prostate cancers.
9. Hereditary cancers may respond to different treatments than sporadic cancers. For example, PARP inhibitors are drugs that were designed to treat cancers associated with BRCA mutations.
10. Individuals who have inherited a gene change may be at a higher risk for more than one type of cancer.

"Sporadic Cancer Type" Characteristics

Sporadic cancers are believed to arise from gene damage acquired from environmental exposures, dietary factors, hormones, normal aging, and other influences. Most acquired gene changes are not shared among relatives or passed on to children.

Cancers in the family are likely due to nonhereditary causes;

1. An acquired (somatic) mutation does not come from a parent, but is acquired some time later. It starts in one cell, and then is passed on to

any new cells that are created from that cell. This kind of mutation is not present in egg or sperm cells, so it is not passed on to the next generation. Acquired mutations are much more common than inherited mutations. Most cancers are caused by acquired mutations.

2. Age of onset later than the hereditary cancer.
3. More than one primary tumour is rare.
4. Even if there is more than one case in the family, there is no particular pattern of inheritance.

"Familial Cancer Type" Characteristics

More cases of a specific type(s) of cancer within a family than statistically expected, but no specific pattern of inheritance.

1. Age of onset variable.
2. May result from chance clustering of sporadic cases.
3. May result from common genetic background, similar environment and/or lifestyle factors.
4. Does not usually exhibit classical features of hereditary cancer syndromes.

Cell Cycle Regulation

Every cell is the product of a cell cycle. Different phases of cell cycle are G_1, S, G_2, M- the four phases constitute are complete round of the cell cycle. First in 1970 Lee Hartwell and Colleagues showed that the cell cycle regulation could be dissected genetically in the single celled yeast *S.Cerecisiac*. Genetic analysis was used extensively to identify the genes encoding the essential components of the cell division machinery and to clarify the functional relationships of the gene products. The logic behind screening for cell division control (cdc) mutant was to identify colonies in which growth was arrested at a particular stage when the culture was transferred to the non permissive temperature. The arrest phenotype of the cdc mutant identified how far the cell cycle could progress without the presence of the wild type gene product, the termination or arrest point. Biochemical analysis, particularly in combination with cell biology, also provides powerful tools that researches have used to examine the function of specific proteins involved in cell cycle regulation.

Two techniques often used together are analysis of phase specific protein extracts and biochemical complementation. Finally a series of cell fusion experiments were performed, first with human cell lines by Potu Rao and Robert Johnson and later also with plant cells by Denes and Dudits. The above experimental observations demonstrate that S phase cells contain a labile activator that can stimulate G_1, nuclei (but not G_2 nuclei) to enter S phase. Cells also contain a repressor of mitosis, which is active in S phase cells and inhibit DNA replication before mitosis.

G1 nucleus replicated DNA, where as G2 nucleus did not replicate together, these observations demonstrate that S phase cells contain a labile activator that can stimulate G1 nuclei but not G2 nuclei to enter S phase. Cells also contain a repressor of mitosis which is active in S phase cells and inhibits DNA replication before mitosis.

Genetic analysis, biochemical complementation and cell fusion experiments allowed scientists to identify cdc mutants and indicated that regulatory molecules were involved in coordinating a complex events required for cell division.

DNA replication is strictly controlled during cell cycle:

Initiation of DNA synthesis is inhibited in wild type cell during G_2, M, G_1. This inhibition suppresses two different types of cell division errors. Although DNA

synthesis remains inhibited during late M and G_1, the assembly of the protein complexes that mediate initiation of DNA synthesis is promoted. As a result, the cell becomes competent to initiate DNA synthesis. In contrast DNA synthesis is promoted during S phase, while assembly of protein complexes that facilitate the initiation of DNA synthesis is inhibited.

DNA synthesis in S phase is initiated at discrete origins of replication distributed at regular intervals throughout the genome occurring on average events 36 kb yeast, 66 kb in dicotyledons, 47 kb in monocotyledons. So origin of replications are important in the regulation of DNA synthesis and a large number of proteins interact directly and indirectly with the origins to control pregression through the chromosomal cycle. Not all origins initiate DNA synthesis simultaneously at the beginning of S phase, rather DNA synthesis is initiated through out S phase therefore origin of DNA replication are classified into early, intermediate and late types.

Many molecules involved in controlling S phase progression

Origin of DNA replication are bound throughout the cell cycle by an **origin recognition complex (ORC).** In budding yeast this complex consist of 6 proteins orc1 to orc6. ORC serves as a **docking point** for additional proteins that recognize pre and post replicative states of origins. ORC also interacts with the **DNA polymerases** that **catalyze DNA synthesis**. Additional proteins eg cdc6p, MCM proteins, cdc45p,cdc46p and the cdc7p/Dbf4p protein kinases are required in yeast to organized the proper function of origins of replication**.**

The association of Sc **Cdc6p with ORC** is required to establish the prereplication complex. Sc Cdc6p is a unstable protein, so stabilization of this protein complex, which binds weekly to the ORC requires **Cdc45p**. **MCM proteins** change their sub cellular localization during the cell cycle, being localized in the nucleus during G1 but exported to the cytoplasm during S phase and remaining there in G_2. This redistribution and their interaction with the **cdc6p- ORC** complex suggest that MCM proteins are involved in ensuring that the replication origins fire (initiation replication) only once during the chromosomal cycle. This activity has been called **licensing factor**, to indicate that nuclear localized MCM proteins give the cell a licence for one round of DNA replication. MCM proteins are conserved in plant is. The cdc7p/Dbf4p protein kinase is also highly conserved.

The cdc6p-ORC complexes can form only after M phase is complete and before S phase begins. During this period, the **ORC-cdc6p pre-replication complex** serve as a **docking center** and flat form for assembly of MCM proteins.

The association of MCM protein with the ORC-cdc6p pre-replication complex remodels the replication origin which then assumes primed pre replication state. In late G1phase, the cell makes the decision whether to proceed with proliferation at the restriction point (or start in the budding yeast). Once the cell has passes this point in the cell cycle, it is committed to S phase. Although replication origins are competent to initiate DNA synthesis at this time, cells are not able to enter S phase before the expression of **S phase genes**(eg histone genes) has been **activated.** S phase is then initiated when primed pre-replication complexes are activated by **phosphorylation** of cdc46p (MCM5), which is catalyzed by Dbf4p – dependent kinase, cdc7p. **Phosphorylation** is a biochemical process that involves the addition of phosphate to an organic compound. Examples include the addition of phosphate to glucose to produce glucose monophosphate and the addition of phosphate to adenosine diphosphate (ADP) to form adenosine triphosphate (ATP). High activities of S phase kinases and later of M phase kinases, are required to maintain the post-replicative state of DNA until telophase, at which time new cdc6p-ORC complexes can assemble. If mitotic, kinase activity is experimentally suppressed in S or G_2 phase, prereplication will occur without intervening mitosis.

Mitosis

Less is known about molecules involved in mitosis in plants. But experimental evidence indicate that regulation of mitosis in plants resembles that in animals and yeast. Mitosis is suppressed during phases G_1,S and G_2. The step wise process that promotes mitosis is initiated in S phase. Mitosis commence with the initiation of chromosome condensation and disassembly of the nuclear envelope that separate the nuclear matrix from the cytoplasm**.** This is often referred as the onset of M phase, but cells are not yet competent for chromosome segregation. Full competence for separation of the duplicated DNA is achieved only when condensed chromosomes are aligned along a plane in the centre of the cell, with each chromosome comprising 2 chromatids that, although attached to each other,are connected by microtubules to opposite ends of the cell. Cells have evolved similar principles for regulating DNA replication and mitosis. Each process requires a sequence of multiple preparatory steps that takes place during a period in the cell cycle when DNA replication or mitosis is prevented. Structural and regulatory molecules are involved in controlling the initiation of mitosis. Proliferating cell synthesis proteins collectively called condensins and cohesions, which are essential for assembling the long chromatin fibers into chromosomes and thereby permit the replication of DNA to be segregated without damage.

The molecular details of how chromosome condensation and cohesion are achieved are still poorly understood. Cohesion protein such as Scclp and Smclp, which have been identified in yeast and animals, are synthesized during S phase. These proteins interact with both sister chromatids of a chromosome to establish and maintain their linkage until anaphase. Sister chromatid condensation and cohesion are tightly coupled. The high degree of DNA packing density in early M phase involves a complete remodelling of chromatin structure. Histones HI, which in interphase binds to linker DNA between two nucleosomes, is phosphorylated and subsequently is unable to bind DNA condensing chromosomes are assembled around a central axis of scaffold proteins, Presumably arrays of cohesin and condensin molecules, which binds to long loops of DNA. During the early steps of chromosome condensation, the two sister chromatids condense together as one large cylinder. On further condensation in late prophase and early metaphase, topoisomerases introduce super coiling into the DNA helix. Super coiling increases the packing density of DNA ever further and at this point the sister chromatids become distinguishable in the light microscope. The more organized chromosome structure at this phase of the cell cycle exposes the cohesins to regulatory factors that break the linkage between sister chromatids and therefore triggers chromosome separation at the onset of anaphase.

A second large complex, the kinetochore attaches to the centromeres of chromosomes and the microtubules network which is ultimately responsible for congregation of the chromosomes along the metaphase plate and their subsequent movement towards the cell poles attaches to the kinetochore**.** Kinetochore assembly is coupled to the completion of DNA replication. The molecular composition of kinetochore complex is poorly understood.

Proteases regulate the initiation of chromosome separation:

The capacity of the cell to undergo ordered mitosis is established during S phase and continue until mitosis is complete. Ordered mitosis begins with the insertion of cohesins into the newly replicated helices and the removal of catenations (binding of an element to itself through covalent bonds to form chain or ring molecules) that would preclude chromosome separation. Once the chromosomes are disentangled and condensed, they are fully competent for segregation. An in DNA synthesis, mitosis is initiated by protein phosphorylation. The metaphase to anaphase transition is activated by phorphorylation of APC, which is catalyzed by cyclin activated kinase and by the kinase encoded by CDC5.

Activation of APC results in the ubiquitination of pdslp. Ubiquitinated Pdslp is recognized by the 26s proteasomes as a substrate and is degraded. Destruction of Pdslp activates cutlp, which breaks the cohesion established linkage between sister chromatids once these bonds are broken, the mechanical forces generated by motor proteins along the kinetochore microtubules draw each sister of the formerly paired chromatids to opposite ends of the cell**.**

Mechanism of Cell Cycle Control

Specific kinase complexes advance the cell through the cell cycle. The molecular mechanisms of cell cycle control in eukaryotes are remarkably well conserved. Cell cycle progression is controlled by activity changes of cyclin dependent kinase (CDKS). Cyclin dependent protein kinase complexes are composed of 2 different subunits is functioning as a catalyst, the other activating catalyst. The catalytic subunit alone lacks activity; association with cyclin is the first step in activation of the kinase complex. Many single celled eukaryotes such as yeast have a single CDK catalytic subunits, where as all multicellular eukaryotes appear to have multiple CDKs. All eukaryotic cells have multiple classes of cyclins, each of which is required for specific regulatory steps during the cell cycle. In yeast these different cyclins interact sequentially with the CDK catalytic subunit, thereby changing the substrate specificity of the enzyme complex during the cell cycle. In multicellular organism, certain CDKs can interact with certain classes of cyclins. These interactions determine the activity and specificity of the enzyme complexes at particular points in the cell cycle. Thus the association of CDKs with specific cyclins is generally thought to be key regulatory mechanism, advancing the cell through various stages of the celll cycle. At the start of the cycle, proteases are required to initiate DNA replication, and at the metaphase-anaphase transition, proteases degrade the cohesion proteins that connect sister chromatids. **Protesase function in all cell cycle regulation at two critical committing steps.**

Multicellular eukaryotes have a complex pathway of CDKs

CDKs are a highly conserved class of protein kinases in eukaryotes complexed with cyclin, they phosphorylate substrates on serine or threonine residues. CDKs have several characteristic features located close to the N terminus of the protein are the amino acids required for ATP binding, followed by a small PSTAIRE domain (named for the single letter codes of the amino acids it comprises), which is involved in cyclin binding. Several variants of this sequence motif are known,

and the differences among the variants have been used to classify CDKs into different subgroups. CDKs also contain a flexible domain called the T-loop, which can be either mask the catalytic site to prevent substrate binding or swing open to permit substrate phosphorylation.

Complex CDK gene families have evolved in multicellular eukaryotes. Multiple CDK genes have been identified in all plant species. In most plants, several CDK genes encode proteins with the N- terminal PSTAIRE motif and additional CDK genes encode variant PSTAIRE motifs. However in animals distinct CDKs are required at different phases of the cycle. CDK1 is essential for transmission from G2 to M. CDK2 and CDK3 are required for the G_1 to S transition, with CDK2 also being required during S phase, CDK4 and CDK6 function during G1 to control the decision about whether to enter a new cell cycle.

In addition to CDK2 atleast two other protein kinases are essential for the chromosomal cycle and mitosis. In yeast, these are encoded by the genes CDC5 and CDC7.The Cdc7 protein associated with a regulatory subunit encoded by DBF4 to activate DNA syntesis at replication origins. ACDC7 homolog has been identified in plants during genome sequencing efforts. CDC5 protein kinase activity is required in M phase to activate APC to regulate the motor proteins required for chromosome segregation. Genes homologous to CDC5 have been identified also in animals as in yeast they are necessary for M phase progression.

Cyclin determine the specificity of subcellular localization of CDKs:

Association with cyclins is required for CDK protein kinase activity cyclins also confer substrate specificity to the cyclin CDK complex and are involved in targeting CDKs to specific subcellular compartments during the cell cycle. Cyclins an be classified into two groups - Mitotic cyclins and G1 cyclins. These are again subdivided.

Cyclins			
Mitotic cyclins		**G1 cyclins**	
A type cyclins (S cyclins) (S phase)	B type cyclins (M cyclins) (G2 & M)	D type cyclins (Unstable proteins) (G1 &S)	E type cyclins (Late G1 & early S phase)

B type cyclins also known as M cyclins and A type cyclins also known as S cyclins. Proteins in the first group are characterized by a large conserved central Domain, called the cyclin box, that interacts with the kinase subunit. They also carry a protein domain called the mitotic destruction box, which mediates cyclin degradation late in mitosis. B type cyclins commit the cells to mitosis at the G2 to M transition. A type cyclins, which have essential function in S phase also contain destruction boxes. Animals and yeast genomes encode approximately 10 different types of Atype and B type cyclins. Plants, however appear to have a much larger number of genes for these types of cyclins. The significance of these is not well understood.

The second group of cyclins, called G1 cyclins is composed primarily of D type cyclins, but also including E type cyclins that are synthesized in late G1 and early S phase. D type cyclins contain a distinct central cyclin box, but it is less well conserved than that of B type cyclins Dtype cyclins are generally unstable proteins, but destruction boxes do not mediate their degradation. Some D type cyclin accumulates only in G1 and are degraded, rapidly at the beginning of S phase, whereas others are present at low concentration, throughout the cell cycle. In animals, the accumulation of D type cyclin is stimulated by growth hormones, indicating that this class of cyclins is important for the advancement of cells into G1 and S phage. In Arabidopsis the G1 cyclin D3 is regulated by cytokinins and probable couple the control of plant growth to the cell cycle. In yeast D type cyclin are encoded by CLN1, CLN2 and CLN3. CLN3p required for cell cycle regulated gene expansion in G1 and S phases, whereas cln1p and cln2p are required to initiate S phase.

CDK Activity is regulated by kinases, phosphatases and specific inhibitors

The activity of CDK cycle in complexes are controlled by specialized kinases and phosphatases, which have important functions in regulating cell cycle progression. Weel type kinase which are named for the small cell phenotype of fusion yeast mutant for this protein**,** phophorylate adjacent threonine and tyrosine residues near N terminus of the CDK molecule. This phosphorylation of Thr14 and Tyr15 inhibits CDK activity.

The yeast cdc25 gene encodes a multifunctional phosphatases that removes phosphate groups from tyrosine, threonine and serine residues. The most important reaction catalyzed by cdc25p is the removal from the N terminus of the CDK phosphatases added by weel p. This dephosporylation results in the abrupt increase

in CDK activity observed at the onset of the breakdown of the nuclear envelop. Cdc25p activity is controlled in part by pathways that prevent damaged cells from replicating. In the event of DNA damage, cdc25p gene in yeast is not activated, which allows cell to pause and repair the damage before initiating mitosis.CDK inhibitors(CKIs) have also been identified.

Under certain conditions, CKI proteins associate with the activated CDK cyclin complex to prevent it from phosphorylating substrates**.** This inhibition of CDK activity is reversible and does not alter the composition or phosphorylation state of CDK cyclin complex. CKIs are used by the cell to control CDK cyclin complex activity before undergoing cell cycle transition and to arrest the cell cycle temporarily in response to DNA damage or to other signaling pathway.

In humans at least three classes of CKIs are known the INK4 gene product, which serves an important function in controlling the G1 to S transition is frequently mutated in neoplastic cell that have lost the ability to control proliferation. Clp1 gene product p21 is an important effector of cellular damage control pathways activities by other key regulatory proteins and klp1 gene p27 inhibits premature activation of S phase CDK activity late in G1.

Ubiquitin dependent proteolysis occurs at key transitions in the cell cycle

Proteolysis of CKIs is necessary to trigger the G1 to S transition. similarly, degradation of the cohesin proteins that connect sister chromatids is required for the irreversible transition from metaphase to anaphase. How are these and other proteins which are degraded at key transition points in cell cycles selected and marked for destruction,a common feature of all such proteins is their modification by covalent attachment of polyubiquitin to the side chains of lysine residues. Ubiquitinated proteins are recognized by the 26s proteasome which functions throught out the cell cycle. The SCF complex and APC regulate uniquitination of cell cycle regulatory molecules at G1 to S transition and M phase respectively.

SCF-3 Proteins

SKP1P	cdc53p	cdc34p
(Contain F box, that can interact with Individual selector proteins Which recognize Specific substrates.)	(Forms scaffold, attaches cdc34p and SKP1P)	(E3, Ubiquitine ligase attaches ubiquitin to target protein)

The SCF complex is composed of three proteins skpIp, cdc53p and cdc34p. cdc34p is the ubiquitin ligase(E3) that attaches ubiquitin to target proteins. Cdc53 forms a scaffold to which both cdc34p and skp1p attach. Skp1p contains a domain called the F box that can interact with individual selector proteins, which themselves recognize specific substrates.

SCF complex recognizes only phosphorylated proteins as substrates for ubiquitination. Therefore SCF activity complements G1 CDK activity to mediate the G1 to S phase transition. Proteins that are phosphorylated by CDKs can be permanently removed by the proteosome after binding to the selector protein and being presented to the SCF complex.

Anaphase onset is triggered by the activation of APC, a protein complex with ubiquitin ligase (E3) activity. APC which comprises atleast 12 proteins, including proteins that contain the mitotic destruction box like SCF, APC may exist in several forms that have different selector proteins. Atleast 2 different selector proteins have been identified. The protein encoded by CDC20 in yeast and fizzy gene in Drosophila associate with APC to mediate the ubiquitination of pds1p and S cyclins at the metaphase to anaphase transition. APC recognizes M cyclins and the M phase kinase cdc5p. These proteins are degraded only in late M phase. APC is activated by CDKs and cdc5 in late metphase. Unlike SCF, however, APC recognize protein that are not phosphorylate. Identification of the genes that encode proteins to subunits of the SCF and APC complexes suggests that the G1 to S phase and metaphase to anaphase transition in plants and mediated by mechanisms similar to those of animals and yeasts. Inhibition of CDK activity by CKIs is important mechanism of CDK regulation.

The logic of cell cycle control

Cell cycle progression is regulated by intrinsic and external signals. The discovery of conditional cell division control mutants in yeast raised the question of whether cell cycle progression was governed by activity state of the protein substrates, which execute specific steps in the cell cycle or by the sequential activation of cell cycle regulators.

In the first model, the **domino model** progression through each step of the cell cycle depends on completion of the preceding step. The second model the **clock model**, suggests the existence of an independent timer mechanism that entrains the separate events of the cycle Initial analysis of CDC mutants at restrictive temperatures**,** indicated that the domino model was generally valid. However in later observations with fertilized frog eggs, drugs that blocked spindle assembly were unable to inhibit the continued oscillation of a previously identified MPF activity now known as the CDK cyclin complex. Additional observation have reinforced the notion that the regulatory pathways controlling the biochemical reactions of the cell cycle represents a combination of both domino and clock models. Regulatory mechanism based on the state of the execution substrate can prevent cell cycle steps from occurring in an inappropriate sequence, and the existence of additional independent mechanisms can make the decision to divide conditional on environmental factors.

In living systems, biochemical reactions do not always proceed to completion and a cell undergoing division can experience adverse condition that could damage its DNA or spindle apparatus. To account for these factors, the cell cycle contains dedicated check points at which the cell can monitor the completion of specific reactions (e.g., DNA replication, chromosome condensation) or the integrity of complex structures (e.g., spindle apparatus, sister chromatid adhesion complex). Additional monitoring is required to link entry into the cell cycle and cell cycle progression with internal and external cues (signals) that control growth, development and the social context of the cells.

Regulation of cell cycle progression depends on CDK and protease activities

Cells have evolved elaborate mechanisms to safeguard that S phase and M phase occur only once per cell cycle and in the correct order. However, these mechanisms

do not instruct the cell when to initiate a new cycle or when to initiate S phase and M phase. Such intrinsic mechanisms are unable to couple cell cycle control to the cells environment, growth and metabolism. The overriding control of cell cycle progression is established through the interplay of CDKs and ubiquitin dependent proteases. To best illustrate the basic principles of this control, let us consider the operate in budding yeast and animal cells.

CDK activity requires association with other G_1, S or M cycle. Experiments with yeast show that the activity of one type complex (e.g., S phase CDK- cyclin complex) suppresses the synthesis or activity of the type (e.g., M- phase CDK-cyclin complex), while simultaneously activating controlling the mechanism its own destruction. This ensures temporal attention of the defferent types of CDK cyclin complexes during the cell cycle. The sequential transitions between the CDK cyclin complexes are enforced by proteolysis of the components that were required for the preceding phase.

Once cell division is completed how does the cell regulate its entry into a new cell cycle?

In somatic cells G_1 cyclins (D type and E type) play an important role in this process. The abundance of G_1 cyclins is rate -limiting for G_1 progression and their synthesis is coupled to cell growth. This establishes that cells proceeds into S phase only when they have achieved adequate mass.

The CDK cyclin D complex phosphorylates substrates to activate four important processes. First the phosphorylation turns of APC mediated proteolysis of cyclins that contained destruction boxes (S and M cyclins), which permits a buildup of S cyclin/CDk complexes. Second it activates the transcription of genes required for S phase, leading to enhanced expression of essential biosynthetic and structural gene products such as histones**.** Third phosphorylated inhibitors of the S cyclins/CDK complex (CKIs) are recognized as substrate by the SCF dependent proteolysis machinery and subsequently degraded; this results in a strong and abrupt activation of pre accumulated CDK activity in S phase, which is required to activate DNA synthesis at the origins of replication. Fourth, the phosphorylated G_1 cyclins are targeted for destruction by proteolysis, there by completing the irreversible transition from G_1 CDK activity to S phase CDK activity and thus from G_1 to S phase.

Once DNA replication is complete, how does the cell complete mitosis and return to G_1?

The synthesis of M phase cyclins in late G_2 prepares the cell for mitosis. The rapid increase of mitotic CDK activity at the G_2 to M transition initiates mitosis and cytokinesis, beginning with chromosome condensation and alignment of the chromosomes at the metaphase plate. The activation of APC, for which both mitotic CDK activity and CDC5P protein kinase are required, initiates the separation of sister chromosomes and destruction of the mitotic cyclins. The decline in mitosis CDK activity relives the repression of G_1 cyclin synthesis allowing accumulation of D type cyclins, which had been suppressed from S phase through telophase. Thus G_1 CDK activity can gradually accumulate which permits the assembly of new replication complexes and maintains APC activity to prevent any residual mitotic CDK activity.

Check points controls are activated by DNA damage of incomplete cell cycle events:

Cell proliferation often occurs under unfavourable conditions frequently; therefore cells may incur DNA damage or may lag in completing DNA synthesis or in attaching the chromosomes to the spindle apparatus. All cells are capable of restoring normal cell cycle activities by using special repair mechanisms, but cell cycle progression must be arrested to prevent the damage from progressing to a mitotic catastrophe. When damage occurs, cell cycle progression is arrested at a checkpoint, of which 3 major ones have been discovered. Arrest at a check point can occur prior to the restriction point at the G1 to S transition, prior to the S to M transition that couples mitosis to the completion of DNA synthesis or prior to sister chromatid separation at the metaphase to anaphase transition. Each of these checkpoints immediately precedes a committing event that is irreversible checkpoint controls have not been studied extensively in plants, but the basic mechanism discovered in other eukaryotes are likely to operate in plants as well.

The highly conserved proteins involved in checkpoint control and the regulatory network in which they function can be grouped into three classes:

Those involved in perceiving damage or incomplete cell cycle events; those that transduce this information and orchestrate the cellular response; and those that mediate cell cycle arrest. For example DNA damage is perceived (mechanism not yet fully understood) and this signal is initially transmitted by a group of proteins encoded by RAD genes. These genes were originally identified in yeast and are

required for resistance to ionizing radiation. RAD3 a DNA dependent protein kinase plays a central role in the initial steps of the pathway; it is activated by binding to single stranded DNA, a hall mark of damaged DNA. A human homolog of RAD3 is encoded by the ATM(ataxia telangiectasia mutated) gene which when defective, predisposed the cell to cancer. In most eukaryotes, the signals resulting from incomplete DNA replication and DNA damage converge as the DNA dependent protein kinase (RAD3).

Activated RAD3 stimulates further protein kinases, notably the chkl(checkpoint kinases) protein. These kinases couple the perception of genome distress to cell cycle arrest and also activates repair mechanisms. Chklp targets the genes that control CDK activity at the G2 to M transition where as a different protein kinase, RAD 53 mediates arrest at START. Chklp inhibits the activity of CDK1 by phosphorylating the tyrosine residue at position 14, near the N terminus of the proteins. Active chklp also inhibits the CDC25 phosphatase required to remove the inhibitory Tyr14 phosphate, thus maintaining the CDK cyclin complex in an inactive state. Active chklp also stimulates the tyrosine protein kinases such as weel p responsible for the inhibitory Try14 phosphorylation of CDK1 thereby reinforcing the inactivation of the CDK cyclin complex.

Accessory proteins are required to enforce CDK control of cell cycle progression:

In animals, members of the E2F transcription factor family, particularly E2F1, E2F2 and E2F3 are required for the transcription activation of genes for proteins that are essential during DNA replication. Thus E2F transcription factors are critical effectors of the decision to pass the G1 to S restriction point and allow the cell to proceed into S phase. Certain E2F proteins bind to their own promoters, thereby creating an autocatalytic transcription loop that results in a very rapid and decisive commitment in entering S phase**.** However, such autocatalytic control mechanisms operate efficiently only if a sufficient amount of performed E2F is present in the cell more over without a mechanism to dampen and reverse such signal amplification, E2F autoactivation can disrupt the normal cell cycle regulation in adverse conditions or when mutated. Thus there is a strong requirement for an inhibition that can inactivate E2F transcription factors, analogous to CDK inhibitors. Such proteins are encoded by members of the Retinoblastoma (Rb) gene family. The Rb protein, which was first identified because of its ability to cause oncogenic cell growth when mutated, binds to E2F proteins and suppresses their activity. In

mammalian cells, PRb and PRb-related proteins control the transition from G1 to S but their function in other cell cycle stages is still not well understood. Homologs of Rb and E2F proteins have been identified in monocots and dicots, suggesting that a similar G1to S regulatory mechanism is functioning in plants.

PRb can interact with members of the E2F transcription factors family and suppress their activity only when it is not phosphorylated. During G1 PRb becomes progressively phosphorylated on multiple sites by CDK4 cyclin D complexes. When PRb is fully phosphorylated, E2F factors dissociate from it and are active. Later in S phase the CDK2 cyclin A complex phosphorylates E2F protein, abolishing their ability to bind DNA. By this mechanism, Rb proteins enforce the decision to proliferate activating cell cycle dependent transcription to produce the DNA synthesis machinery at the transition from G1 to S.

Rb proteins are targets in additional pathways for control of cellular growth and therefore are often mutated when proliferation spins out of control in cancer cells. cellular parasites, such as DNA viruses that depend on host replication machinery for multiplication, may target Rb for inactivation. Rb inactivation is sufficient to activate DNA synthesis pathways and thereby allow viral replication. The recent discovered plant Rb homologs have also been shown to interact with protein encoded by gemini viruses which suggests that these plant viruses exploit a mechanism for initiating their replication in ways similar to animal oncoviruses.

Cell cycle control in multicellular organism, intercellular communication controls the cycle during growth and development:

In single celled organisms, nutrients limitation is the single most important factor of restricting cell growth, therefore cell size is the major cue (signel) for division. In multicellular eukaryotes with specialized cell types and functions cell division control necessarily becomes more complex. In plants, only a few stem cells organized into meristem divide to produce the plant body. These cells depend completely on nutrients provided by the rest of the plant; although cell size signals are also required, they are insufficient to direct the complex patterns and rates of cell division in multicellular organisms. Furthermore, control of cell proliferation is only one aspect of development. Cell cycle control is integrated with the regulation of cell expansion, differentiation and cell death. Other type of growth controls called social controls evolved to regulate development and proliferation within complex organisms. In most multicellular organisms, social control prevails over nutritional control of the cell cycle.

The emergence of social controls resulted in the loss of cellular autonomy over proliferation control. This had important consequences for dividing and differentiating cells. First, cells in multicellular organisms are normally quiescent (a state often termed $G_{0)}$ and quiescent cells do not proliferate without stimulation. Second the stimuli that mediate cell proliferation for e.g., growth factors, provide the signalled cell with information about the status of the whole organism rather than just its individual cells. Third, if only a few cells permanently retain the capacity to divide the majority of cells that have lost this capacity must somehow be instructed to do so.

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Notes

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About The Authors

Dr. V. Lakshmi Kalpana, M.Phil., Ph.D, is an Associate Professor, Department of Human Genetics at Andhra University. Besides being an accomplished academician, she is also a meticulous administrator who served as Head for 4 departments - Human Genetics, Microbiology, Bio-technology and Food, Nutrition and Dietetics simultaneously. Presently, she is the chairperson of the Board of Studies for Human Genetics Department, Andhra University. She has authored multiple National and International publications, books, and book chapters on clinical cytogenetics, molecular genetics, and molecular cytogenetics. Her research areas of interest include human cell culture and karyotyping, genetic counseling, gene polymorphisms and population genetics. In addition to research, she has a longstanding commitment to teaching, training, and mentorship at all levels, including postgraduate students, doctoral and postdoctoral fellows. Many of whom have gone on to highly successful academic careers in related areas.

Dr. A. Anuradha, M.Phil., Ph.D., is a Research Scientist, at Andhra Medical College. She completed her Ph.D. under the guidance of Dr. V. Lakshmi Kalpana, Department of Human Genetics at Andhra University in 2014. She was also a recipient of the prestigious Women Scientist–B, Department of Science and Technology, New Delhi. Her research has been reflected in both National and International publications and book chapters. She assisted Dr. V. Lakshmi Kalpana in composing and editing the books.

Salient Features

- The book deals with genetics of the various disorders at the molecular level and discusses their prognostic, diagnostic and management/treatment aspects.
- Cancer is detailed in the perspective of genetics i.e., the alteration of proto-oncogenes and oncogenes at the cellular level.
- This book provides better insight into the genetic disorders and inherited versus familial cancers.
- This book will benefit Postgraduate students of both Human genetics and Medicine to develop an understanding of Medical Genetics.

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Dr. V. Lakshmi Kalpana, M.Phil., Ph.D.
Dr. A. Anuradha, M.Phil., Ph.D.

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