Lesson: Human Genetic Disorders
Author Name: Dr. Kiran Bala & Dr. Sudhida Gautam Parihar
Reviewer : Dr. Kamal Gupta
College/ Department: Deshbandhu College Gargi College, University of Delhi
Human Genetic Disorders

Contents

- Introduction
- Human sex anomalies
- Trisomy: autosomal and sex chromosome
  - Trisomy 21 (Down syndrome)
  - Trisomy 18 (Edward’s syndrome)
  - Trisomy 13 (Patau’s syndrome)
- Monosomy
  - Cri-du-chat syndrome
- Polysomy
  - Klinefelter's Syndrome
  - Jacob's syndrome /XYY
- Inborn error of metabolism
  - Single gene disorder
  - Albinism
  - Sickle-cell anemia
  - Brachydactyly
  - Huntington's Disease
  - Cystic Fibrosis
  - Multifactorial Disorders
- Summary
- Glossary
- Exercise
- References
Human Genetic Disorders

Introduction

A genetic disorder refers to the problem arising due to an abnormality or change in the genome of an organism. Cytochemical studies provide an insight into the pattern of their inheritance in the future generations. Majority of genetic disorders are a result of genetic mutations. These are sudden heritable changes in the genome of an organism. Mutations arise due to a number of factors: exposure to harmful radiation or chemicals, chromosomal aberration at the time of cell division/transcription or translation. A mutated gene is unable to carry out its normal function, which leads to genetic disorders either in the somatic cell or germ cells. Genetic mutations include chromosomal rearrangements (deletion, insertion, translocation), aneuploidy or polyploidy responsible for various gametic or autosomal abnormalities. These defects in the genetic composition are responsible for improper functioning of enzymes/proteins which are passed on to the future progeny.

A genetic disorder can be diagnosed by testing at both prenatal and postnatal stages. Various techniques involved in such testing include Ultrasound (high frequency sound waves are beamed into the uterus, where they encounter the dense fetal tissue, striking which, they bounce back, creating an image which tells the size of the fetus and also neural tube disorders), Amniocentesis (Fig:1, fetal cells are taken and the karyotype is studied), Chorionic villus sampling (Fig:2, cells from the chorion are taken for genetic studies), Non-invasive fetal diagnosis (maternal blood containing fetal cells is used to identify mutations), Preimplantation genetic diagnosis (helps the persons with genetic defects to have a normal healthy child) and new-born screening (testing newborn infants for genetic disorders, identification and effective treatment is provided, if needed).

Figure 1: Amniocentesis
Source: ILLL

Figure 2: Chronic Villus sampling

Institute of Lifelong Learning, University of Delhi
Human Genetic Disorders
Source: ILLL

The genetic diseases can be broadly classified into two types: (1) Autosomal disorders, where the abnormality is in the somatic chromosome(s) and (2) Allosomal disorders, where the anomalies are in the sex chromosome. Chromosomal aberrations can be as small as a single-base mutation in just one gene, or they can involve the addition or deletion of entire chromosomes.

Various types of genetic disorders are given below:

1. **Chromosomal Abnormalities**: Disorders which involve mutations/ambiguity/changes in the whole chromosome or a part of chromosome or a region coding for a specific gene on the chromosome. Eg: Trisomy, Monosomy, Cri-du-chat Syndrome (caused when a part of the chromosome 5 is missing).

2. **Single Gene Disorders** (also referred as Mendelian disorders) that are caused by a defect in just one gene. Eg: Inborn errors of metabolism (Phenylketonuria), Albinism, Brachydactyly, Huntington’s disease and cystic fibrosis.

3. **Multifactorial Disorders**: Diseases are the combined outcome of the mutations in several genes in specific environmental conditions. Some examples of these are also referred to as the life-style diseases eg; heart disease, cancer, and diabetes.

<table>
<thead>
<tr>
<th>Value addition</th>
</tr>
</thead>
<tbody>
<tr>
<td><a href="http://youtu/be/oX1v5L2O6Bo">http://youtu.be/oX1v5L2O6Bo</a> : Non disjunction of sex chromosomes during meiosis</td>
</tr>
<tr>
<td><a href="http://youtu/be/seWhCxOFVSU">http://youtu.be/seWhCxOFVSU</a> : Human genetic diseases</td>
</tr>
</tbody>
</table>

**Human sex anomalies: Trisomy**

Chromosomal anomalies occur due to structural alterations or non-disjunction during gamete formation. Chromosome non-disjunction (“not coming apart) is the abnormal separation of homologous chromosomes or chromatids to opposite poles at meiosis I (one pair of homologous chromosomes fail to separate) or meiosis II (one pair of sister chromatids fails to separate) leading to gametic abnormality. (Fig: 3). Inheritance of extra or less genetic material leads to an imbalance in the genetic constitution of an individual, resulting in abnormal/lethal consequences. The mitotic non-disjunction (during development) of egg results in aneuploid sections of the body (aneuploid sectors) whereas the meiotic nondisjunction results in aneuploid meiotic products, leading to abnormal gametes in which the entire organism is aneuploid. It leads to the formation of n-1 and n+1 gametes. "If an n-1 gamete is fertilized by an n gamete, a monosomic (2n-1) zygote is produced (Turner Institute of Lifelong Learning, University of Delhi)
Human Genetic Disorders

syndrome). The fusion of an $n+1$ and an $n$ gamete yields a trisomic $2n+1$ (Down syndrome, Patau syndrome and Edwards syndrome). A few of these disorders are discussed below.

![Non-disjunction Diagram](http://mitosisandmeiosis.wikispaces.com/Anaphase+I)

Figure 3: Non-disjunction

Source: [http://mitosisandmeiosis.wikispaces.com/Anaphase+I](http://mitosisandmeiosis.wikispaces.com/Anaphase+I)

Trisomy 21 (Down syndrome)

Trisomy 21 (Down syndrome) is the most commonly occurring trisomy (chromosomal abnormality), and its frequency is 1–2:1000, in human populations. It is caused due to malsegregation of chromosome 21 in meiosis during gamete formation. The meiotic I error attributes 75% and the rest of the 25% is attributed by meiosis II. An error in cell division causes the disorder and the chances of such errors are increased, due to increase in maternal age (30+). The risk of having a baby with down syndrome is 1:1250 for a 25yr old women; which increases to 1:400 if the mother's age is 35. 5 % of trisomy cases are probably due to mitotic (postzygotic) malsegregation of chromosome 21 in early embryo. Children having Down syndrome are mentally retarded (with an IQ in the 20-to-50 range); broad, flat and round face; eyes with epicanthic fold; short stature; short hands with crease across the middle; and large, wrinkled tongue (Fig: 4-5). Males are sterile and females could be fertile. Mean life expectancy is about 17 years, and only 8 percent of persons with Down syndrome survive past age 40 (Pierce, 2006).
Human Genetic Disorders

Figure 4: Common facial features of Down syndrome child.

Figure 5: Down’s syndrome, 47, trisomy21 – Typical facial features
Source: [http://felixsmum.blogspot.co.uk/2012/03/growing-up-getting-big-little-guy-is-18.html](http://felixsmum.blogspot.co.uk/2012/03/growing-up-getting-big-little-guy-is-18.html)

Trisomy 18 (Edward’s syndrome)
It is the second most common trisomy (of chromosome 18), with the frequency of 1 in 7000 newborns (Fig: 6). Individuals with trisomy 18 have many medical complications, including physical/mental problems and 50% of babies with this syndrome are stillborn. Other phenotypic characteristics are “faunlike” ears, a small jaw, a narrow pelvis, and rocker bottom feet. Early death is reported in almost all babies with trisomy 18.
Human Genetic Disorders

Figure 6: Karyotype - Edward’s Syndrome showing trisomy of chromosome 18.
Source: https://books.google.co.in/books?id=JkY8BAAAQBAJ&pg=PA516&lpg=PA516&dq=allosomal+disorder&source=bl&ots=FE5VhF4uK&sig=Trj4sNkDG&hl=en#v=onepage&q=allosomal%20disorder&f=true

Trisomy 13 (Patau’s syndrome)

Trisomy 13 (Patau’s syndrome) is the third most common defect in newborns (1 in 29,000 birth; Goldstein and Nielsen, 1988) (Fig: 7). It is rarely found and the affected individuals exhibit the following symptoms: hare lip (Cleft lip), malformed nose, and very small or undeveloped eyes. A few individuals survive until adulthood and most of the patients have a very short lifespan of up to 130 days.

Figure 7: Karyotype - Patau’s Syndrome showing trisomy of chromosome 13
Source: http://books.google.co.in/books?id=JkY8BAAAQBAJ&pg=PA516&lpg=PA516&dq=allosomal+disorder&source=bl&ots=FE5VhF4uK&sig=Trj4sNkDG&hl=en&sa=X&ei=5TMwVOuOJ0o6OuASFtoGgDA&ved=0CEMQ6AEwBw#v=onepage&q=allosomal%20disorder
Monosomy

Monosomy is the condition where one chromosome out of the total complement is absent in an organism. The genotype of the affected individual is XO (i.e., monosomy X) (Fig: 8). Some of the genetic diseases caused due to monosomy are, Turner syndrome (complete monosomy: absence of entire chromosome) Cri-du-chat syndrome (partial syndrome: absence of a part of the chromosome), etc.

Turner syndrome occurs only in females and the zygote has one X chromosome. These females are characterized by the absence of a Barr body, therefore, having only a single X chromosome. The rate of occurrence is 1 in 2,500 to 5,000 births. The chromosomal abnormality is mostly reported among spontaneous abortions. If the embryo survives to birth, the girl child shows abnormal growth patterns like short stature (average 4 foot 7 inches adult), distinctive webbed necks (i.e., extra folds of skin), small jaws, and high arched palates. Secondary sexual characteristics are underdeveloped; they have exceptionally small, widely spaced breasts, broad shield-shaped chests, and turned-out elbows. Ovaries do not develop normally and do not ovulate; they are, in a sense, postmenopausal from early childhood and are sterile. However, they can become pregnant and give birth if fertilized eggs from a donor are implanted. Women with Turner syndrome are more prone to thyroid disease, vision and hearing problems, heart defects, diabetes, and other autoimmune disorders. Early diagnosis of this condition in childhood, regular injections of human growth hormones can increase their stature by a few inches. Hormonal therapy at the normal age of puberty can result in some breast development and menstruation. Turner syndrome women, if treated, appear relatively normal (Pierce, 2005).

Figure 8: Turner’s Syndrome- 45,XO
(Source: http://www.larasig.com/node/3485)

- **Cri-du-chat syndrome**

  Institute of Lifelong Learning, University of Delhi
Human Genetic Disorders

It is an autosomal deletion syndrome. It is a rare condition and occurs in only about 1 in 20,000 to 1 in 50,000 newborns. Affected infants produce a high-pitched cry similar to a cat. ("Cri-du-chat" means "cry of the cat" in French.) The cry is caused by a partial deletion of chromosome 5p (Fig: 9(A)) leading to an abnormal development of the child’s larynx. The syndrome is characterized by a distinctive, high-pitched, catlike cry in infancy with growth failure, microcephaly, facial abnormalities (small chin, round face, small bridge of the nose, skin fold over the eyes, abnormally wide set eyes), and mental retardation throughout life (Fig: 9(B)). The severity of a child’s symptoms depends on how much genetic information is missing from chromosome 5. Some symptoms are severe while others are so minor, that they may go undiagnosed. The cat-like cry, which is the most common symptom, becomes less noticeable over time.

![Cri-du-chat Chromosome 5 pair and Facial features](https://encryptedtbn0.gstatic.com/images?q=tbn:ANd9GcQmG2BtdDtU4pM_MrLAnyj1tUo6ObcW7zOyeM73v-g19FB_eyqEw)

Figure 9: Cri-du-chat: (A) Chromosome 5; (B) Facial features

Source: [http://4e7221.medialib.glogster.com/media/236ebbb49b2c5dd4de3f1bde47bcc099b850d4f247f66af6fc9fc650fbd31f8/images.jpg](http://4e7221.medialib.glogster.com/media/236ebbb49b2c5dd4de3f1bde47bcc099b850d4f247f66af6fc9fc650fbd31f8/images.jpg)

Polysomy

Polysomy is the addition of an extra chromosome than the normal i.e., presence of three or more number of chromosomes, than the expected value of two sets of chromosome. Poly X females (also known as triplo-X, trisomy X, XXX syndrome, 47,XXX aneuploidy) is due to trisomy of X chromosome with variable phenotypes in females (Fig:10). Females with poly X are characterized by presence of more than one Barr body. The number of Barr bodies is one less than the number of X chromosomes. 1 in 1,000 female births, is reported with this condition and is the most common female chromosomal abnormality. Individuals are only mildly affected or asymptomatic, therefore only 10% of individuals with trisomy X are diagnosed. Tall stature, epicanthal folds (skin of the upper eyelid covers the inner corner of the eye), hypotonia (reduced muscle strength) and clinodactyly (curvature of the digits) are most
Human Genetic Disorders

common features in this condition. It leads to higher rates of motor and speech delays, with an increased risk of cognitive defects and learning disabilities in children. Nondisjunction during meiosis results in trisomy (frequency), while postzygotic nondisjunction occurs in approximately 20% of cases. Pregnancy at later stages has increased the risk of trisomy X (Tartaglia et al, 2010).

Figure 10: Poly X Syndrome showing 47,XXX

Klinefelter's Syndrome

Klinefelter's Syndrome is a genetic disorder affecting only males. It was first described by Dr. Harry Klinefelter in 1942. It occurs when a boy is born with an extra X chromosome (Fig:11), which causes the boy to produce less testosterone than a normal boy. Males afflicted by this syndrome may have three (48, XXXY) or four (49, XXXXY) X chromosomes. “About 80% of the boys with Klinefelter’s syndrome will have 47, XXY in all cells of the body. About 6% will show a normal chromosome complement i.e. 46, XY in some cells and 46,XXY in the others (mosaicism). In 5% of the cases, there is 46, XX /47,XXY mosaic pattern and in the remainder, three or four X chromosomes or other arrangements of an X chromosome.” It is characterized by hypogonadism, testicular atrophy, azoospermia and a eunuchoid body with a lack of male secondary sexual characteristics. It occurs approximately in 1 in 1000 male births (Pierce, 2005). A Klinefelter male is characterized by the presence of a Barr body.
Human Genetic Disorders

Figure 11: Klinefelter's Syndrome - 47,XXY

Jacob's syndrome /XYY

Jacob's syndrome /XYY males have an extra Y chromosome (Fig:12). These "super-males" are usually tall (above 6 feet), light weight compared to stature, larger craniofacial areas, appearance and behaviour is normal, while they have high levels of testosterone. They often are slender, have severe facial acne during adolescence, and are poorly coordinated. They are usually fertile and lead ordinary lives as adults. Frequency is 1 in 1000 male births.

Figure 12: Karyotype- Jacob’s Syndrome showing 47, XYY
Source: http://suncfb1.wikispaces.com/Jacobs+Syndrome

Hermaphrodite is a condition in which cells have a mosaic of cell types i.e. 44+XX/44+XXY or 46,XX/46,XY in a person. The afflicted are characterized by ambiguous external genitalia and abdominal gonads consisting of ovotestis and a primitive testis (Minowada et al, 1982).
Human Genetic Disorders

### Value addition

- Autosomes and sex chromosomes) [Video](http://youtu.be/o66aXZmVkd4?list=PLbIMzi0gjFdP8CoujKv4qBoGY7B2oIJZ)
- Homologous and homologous chromosome and karyotype from metaphase plate: [Video](http://youtu.be/o66aXZmVkd4?list=PLbIMzi0gjFdP8CoujKv4qBoGY7B2oIJZ)
- [Link](http://curious.com/craigsavage/genetics)
- [Video](http://youtu.be/oXIv5L2O6Bo)

### Inborn errors of metabolism

In the early 20th century (1908), the phrase, “Inborn errors of metabolism”, was coined by the British physician, Archibald Garrod (1857–1936). A disruption of normal metabolic pathways leads to inborn errors of metabolism (IEM). Metabolism helps in breaking down of the food to yield energy. These congenital metabolic disorders result from the absence or abnormality of an enzyme or its cofactor, leading to either accumulation or deficiency of a specific metabolite. These can be easily treated by the removal of toxic metabolite(s).

There are various approaches which classify IEM depending upon the metabolite: amino acid disorders, urea cycle disorder, fatty acid oxidation disorder, carbohydrate disorder etc. Few common IEM are listed below:

- **Phenylketonuria (PKU)** is an autosomal recessive disorder (Fig:13). It is one of the most common aminoacidurias, with an occurrence of 1 in 20,000 live births. Affected persons show high levels of phenylalanine in the blood (hyperphenylalaninemia). PKU results from defect in phenylalanine hydroxylase enzyme which converts Phenylalanine to Tyrosine. “In this pathway phenylpyruvate is formed when phenylalanine undergoes transamination with pyruvate (Fig:14). Accumulation of Phenylalanine and phenylpyruvate in the blood and tissues and are excreted in the urine, and, hence the name, "phenylketonuria." Phenylpyruvate is either decarboxylated to phenylacetate or reduced to phenyllactate and is then excreted. The characteristic odor of urine is due to Phenylacetate, which is traditionally used to detect PKU in infants. Restriction of phenylalanine intake in diet can decrease the toxic effects of phenylalanine accumulation and patients can develop with normal intelligence (Poustie and Rutherford, 1999; Nelson and Cox, 2008).
Phenylketonuria can also be caused by a defect in the enzyme that catalyses the regeneration of tetrahydrobiopterin. The treatment in this case is more complex than restricting the intake of phenylalanine and tyrosine. Tetrahydrobiopterin is also required for the formation of \( \text{L-dopa} \) and \( \text{5-hydroxtryptophan} \)-precursors of the neurotransmitters norepinephrine and serotonin, respectively—and in phenylketonuria of this type, these precursors must be supplied in the diet. Supplementing the diet with tetrahydrobiopterin itself is ineffective because it is unstable and does not cross the blood-brain barrier (Lanpher et al., 2006; Nelson and Cox, 2008).

Maple sugar urine disease (MSUD): It is another metabolic disease in which the body is unable to breakdown amino acids such as Leucine, isoleucine, and valine. It is a life-threatening neurological disorder characterized by maple syrup odor of the urine.

Hyperammonemia: It is caused due to defect in urea cycle enzymes. Thus, absence of
ammonia detoxification to urea.

- **Fructose intolerance:** It is a genetic disorder caused by mutation in the gene encoding aldolase B. It is an autosomal recessive disorder characterized by fructose malabsorption.

- **Galactosemia:** It appears because of the inability to breakdown galactose to glucose. It is most commonly diagnosed in milk fed neonates, as milk contains a high fraction of galactose. Besides, retarded mental growth, enlargement of spleen and liver are also seen in the afflicted infants. The patients are asked to avoid dairy products and use galactose/lactose –free milk substitutes.

- **Glycine encephalopathy:** This is caused by deficiency of the glycine cleavage multi-enzyme system. Short arm of the chromosome 9 bears the gene responsible for the disorder.

### Single gene disorders

#### Albinism

Albinism (from a Latin word albus = white) is a rare autosomal recessive genetic disorder leading to decreased production of melanin in the body. People suffering from this disease have little or no pigment in their hair, skin and eye (Fig: 15 (A);(B)). It is, as mentioned above, an autosomal recessive disease, that is, the trait should be passed on from both the parents for the disease to occur.

![Autosomal Recessive Inheritance](http://learn.genetics.utah.edu/content/disorders/singlegene/sicklecell/images/autosomal-recessive.jpg)

**(A)** Inheritance pattern  
**(B)** Albino: Absence of eye pigment

Figure 15: (A) Recessive inheritance pattern; (B) Albino (observe the absence of color pigment in eye, hair and skin.

Source:  
[http://learn.genetics.utah.edu/content/disorders/singlegene/sicklecell/images/autosomal-recessive.jpg](http://learn.genetics.utah.edu/content/disorders/singlegene/sicklecell/images/autosomal-recessive.jpg)  

#### Types of albinism:

Different gene defects are responsible for the various types of albinism which are as follows:

- **Oculocutaneous Albinism (OCA):** OCA affects the skin, hair, and eyes. This is the most
**Human Genetic Disorders**

severe form of albinism. There are several subtypes of OCA, which include:

- **OCA1** is caused by a defect in the tyrosinase enzyme (TYR gene located on chromosome 11 at position 14.3). There are two subtypes of OCA1.
  - **OCA1a**: People with OCA1a have a complete absence of melanin. They have white hair, very pale skin, and light eyes.
  - **OCA1b**: People with OCA1b produce some melanin. They have light-colored skin, hair, and eyes. Their colorcoding may increase as they age.
- **OCA2** is less severe than OCA1. It is caused by a defect in the OCA2 gene on chromosome 15 that results in reduced melanin production. People with OCA2 are born with slight colorcoding and have light skin, and their hair may be yellow, blonde, or light brown. It is common in Sub-Saharan Africans, African Americans and Native Americans.
- **OCA3** is a defect in the TYRP1 gene (chromosome 9 at position 23), and it usually affects dark-skinned people, particularly in black South Africans. People with OCA3 have reddish-brown skin, reddish hair, and hazel or brown eyes.
- **OCA4** is caused by a defect in the SLC45A2 protein (chromosome 5) that results in the minimal production of melanin, commonly found in people of East Asian descent. People with type OCA4 have similar symptoms as people with OCA2.

**Ocular Albinism (OA):** OA is caused by a gene mutation (gene GPR143) on the X chromosome (position 22.3) and occurs almost exclusively in males. This type of albinism only affects the eyes. People with OA have normal hair, skin, and eye colorcoding, but have no colorcoding in the retina (the back of the eye).

**Hermansky-Pudlak Syndrome (HPS):** HPS is a rare form of albinism that is caused by a defect in HPS1 gene located on chromosome 10 (position q23.1-q23.3). It produces symptoms similar to OCA, and occurs with lung, bowel, and bleeding disorders.

**Griscelli Syndrome (GS):** GS is an extremely rare genetic disorder that is characterized by albinism (may not affect the entire body), immune problems, and neurological problems. Griscelli syndrome is caused by mutations in different genes: Type 1 results from mutations in the MYOSA gene (chromosome 15), type 2 is caused by mutations in the RAB27A gene (chromosome 15), and type 3 results from mutations in the MLPH gene (chromosome 2). GS usually results in death within the first decade of life and is recognizable in infants.

**Waardenburg syndrome** is usually inherited as an autosomal dominant trait that includes deafness and pale skin and hair color. Mutations in different genes involved in the development and formation of pigment producing cells causes this disorder.

**Sickle-cell anemia**

*Sickle-cell anemia* (also known as sickle cell disease) or drepanocytosis, is an autosomal recessive (Fig: 16(A)) inherited blood disorder affecting the structure and function
Human Genetic Disorders

haemoglobin (carrier of oxygen) in the blood. As a result, the erythrocytes of these individuals are sickle shaped. The abnormally shaped cells (RBC) accumulate in blood vessels, obstructing the blood flow and leading to severe pain and tissue damage in the body. The haemoglobin in sickle shaped RBCs (called haemoglobin S) is clumped together which aggregates into tubular fibers (Fig: 17 (A);(B)). These fibers of clumped deoxygenated haemoglobin S cause the deformed, sickle shape of the erythrocytes, and their number increases greatly in the tissues, as blood is deoxygenated (Fig:17(B)).

(A): Inheritance of Sickle cell anaemia          (B): Chromosome 11 mutation

Figure 16: (A) Inheritance of Sickle cell anaemia; (B) Chromosome 11 showing the mutation to valine

(A): Deformed RBC                                        (B) RBC in blood

Figure 17: (A) Deformed red blood cells with sickle shape: (B) Blood circulation

(Source: http://www.tutorvista.com/content/biology/biology-iii/human-genetics/genetic-diseases.php
http://t3.gstatic.com/images?q=tbn:ANd9GcRdE5_J7fBhlHb33c0G_162uE8hRuEuYejABen9KZ88Fg2evvBRq)

Value addition:

Institute of Lifelong Learning, University of Delhi
Haemoglobin S is formed due to single amino acid substitution (valine instead of a glutamate residue) at position 6 in the two β chains of haemoglobin (Fig: 16(B)). Since valine has no electric charge and glutamate has a negative charge (at pH 7.4) therefore, haemoglobin S has less negative charge than haemoglobin A (one fewer on each β chain). Sickle cell anaemia is sometimes life threatening due to clogging of the blood vessels. Such clogging leads to episodes of severe abdominal or joint pain in patients and leading to failure of blood supply. The inadequate blood supply causes kidney damage, strokes, heart damage and frequent cases of pneumonia (Nelson and Cox, 2008).

**Brachydactyly**

“Brachydactyly (derived from ancient Greek word: brachy-short; dactylοs-digit) is an autosomal dominant disorder characterized by short digits and abnormal development of phalanges, metacarpals, or both (Temtamy and Aglan, 2008).” It results in disproportionately short fingers and toes, and forms part of the group of limb malformations characterized by bone dysostosis. Dysostosis refers to abnormalities of individual bones, either in isolation or in combination with various abnormally formed bones. It may also result in short stature accompanied by other hand malformations, such as syndactyly, polydactyly, reduction defects, or symphalangism. The various types of isolated brachydactyly are rare, except for types A3 and D, which are the most common types, affecting an estimated 2% of people (Fig:18). It can occur either as an isolated malformation or as a part of a complex malformation syndrome. It usually occurs well before birth, at some point during the first 8 weeks of development in the womb. Sometimes, it can be caused by exposure to medications taken during pregnancy or by blood flow problems to the hands or feet. There are 5 main types of brachydactyly, types A through E. The type A group of brachydactyly is divided into subgroups. The specific type of brachydactyly a person has is determined by which specific digits are affected and how they are affected. Brachydactyly can be diagnosed by physical evaluation and X-ray (Table: 1). There is no treatment for brachydactyly. The patient may feel a little self-conscious, but has no health problems as such. The afflicted person has difficulty in gripping due to shorter fingers and toes. However, in severe cases, the patient may have impaired walking. The brachydactyly pattern generally remains the same among family members. The appearance of brachydactyly can vary, depending upon the bones which are affected. Shortening as well as complete absence of the digits can be observed.
Human Genetic Disorders

Figure 18: Types of brachydactyly
(Source: https://www.peds.ufl.edu/divisions/genetics/teaching/hand_malformations.htm)

Table 1: Types of brachydactyly

<table>
<thead>
<tr>
<th>Type A</th>
<th>affecting middle phalanges</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1: Middle phalanges of all fingers are shortened</td>
<td></td>
</tr>
<tr>
<td>A2: Index finger</td>
<td></td>
</tr>
<tr>
<td>A3: Only little finger</td>
<td></td>
</tr>
<tr>
<td>A4: Index finger /little finger</td>
<td></td>
</tr>
<tr>
<td>A5: Absent middle phalanges</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Brachydactyly-Type</th>
<th>B- E (Fingers affected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type B</td>
<td>Type C</td>
</tr>
<tr>
<td>End of each finger either shortened or completely missing, nails absent, short but intact thumbs</td>
<td></td>
</tr>
<tr>
<td>Index, middle and little finger. Ring finger is unaffected and often longest</td>
<td></td>
</tr>
<tr>
<td>Most common and affects only the thumbs The end bones of the thumbs are shortened but all the fingers are normal.</td>
<td></td>
</tr>
<tr>
<td>Rare form having shortened metacarpals and metatarsals. Small hands and feet.</td>
<td></td>
</tr>
</tbody>
</table>

Huntington's Disease

It is an autosomal dominant disorder (Fig:19(A) caused by mutation in the HTT gene on chromosome 4 (position 16.3). CAG trinucleotide repeat is responsible for HTT mutation. In normal condition, the CAG (cytosine, adenine, guanine) segment is repeated 10 to 35 times within the gene. CAG repeats range from 30-120 in the genome; 36-39 CAG repeats (people may or may not develop the disease), whereas, the people with 40 or more repeats almost always develop the disorder (Fig:1 9(B)), the reason being, production of an abnormally longer version of the huntingtin protein. This elongated protein gets cut into smaller, toxic pieces that bind together and accumulate in neurons, disrupting the normal functioning of these cells. It eventually leads to death of neurons in certain areas of the brain, which underlie the signs and symptoms of Huntington's disease.
Cystic Fibrosis

It is an autosomal recessive disease (Fig: 20) that develops because of CFTR gene mutation in chromosome 7. CTRF gene produces a protein which functions as a channel across the cell membranes that produce mucus, sweat, saliva, tears, and digestive enzymes. The main purpose of this channel is to transport negatively charged particles like the chloride ions, in and out of the cells. Thus, controlling the movement of water in the tissues, necessary for free flow of the mucus (helps to lubricate/protect the lining of airways, digestive system, reproductive system etc) (Fig: 21). An affected individual suffers from blocked airways, digestive tubes and reproductive tracts.

Figure 20: Inheritance of cystic fibrosis
Source: ILLL
**Multifactorial Disorders**

Multifactorial genetic disorders involve a multiple number of genes, generally acting in relation with the ambient environmental conditions. Being the single largest class of inherited disorders affecting the human populations, they are also referred to as lifestyle diseases. Some common conditions as obesity, heart disease, and diabetes are now considered to be multifactorial disorders. Multifactorial inheritance disorders are caused by a combination of both genetic and other factors that may include internal factors such as ageing and exposure to external environmental factors such as diet, lifestyle, and exposure to chemicals or other toxins (Fig: 22). Since the environment plays a crucial role, exact genetic factor and the risk of recurrence are usually arrived at, empirically. Risk of reoccurrence of multifactorial diseases is much lower than single gene diseases; mostly the risk varies with the number of relatives affected and the closeness of their relationship. Moreover, close relatives of more severely affected individuals (e.g., those with bilateral cleft lip and cleft palate) are generally at greater risk than those related to persons with a less-severe form of the same condition (e.g., unilateral cleft lip). It cannot predict whether one will develop the disease. For instance, a woman who inherits an alteration in the BRCA2 gene is more likely than other women to develop breast cancer, but she may also remain disease-free. The altered gene is only one risk factor, among many. Lifestyle, environment, and other biological factors also play a part. The inherited faulty gene(s) make the person at increased risk for developing the condition (predisposed or susceptible) but unless other factors are present, the condition may never
Human Genetic Disorders

It might be possible to determine if family members are at risk for a particular multifactorial condition by examining the family health history.

Human disorders attributed to multifactorial inheritance:

1. **Coronary heart disease**: Genetic or lifestyle factors cause plaque to build up in one’s arteries as one ages. With increasing age, the risk of CHD is more (men after age of 45yrs and female after 55yrs). By the time one is middle-aged or older, enough plaque has built up to cause signs or symptoms. High levels of a protein called C-reactive protein (CRP) in the blood may raise the risk of CHD and heart attack. High levels of CRP are a sign of inflammation in the body. Risk is more if one of the parents has been diagnosed with the disease. Type 2 diabetes also has a similar genetic component too.

2. **Diabetes**: Insulin deficiency leads to elevated blood glucose levels or diabetes. Type 1 diabetes develops if the body cannot produce insulin. It accounts for around 7% of all people with diabetes, and usually appears before the age of 40. Type 2 diabetes develops when the body can still make some insulin, but not enough, or when the insulin produced does not work properly (known as insulin resistance). In most cases this is linked with being overweight. Major symptoms of diabetes are weight loss, frequent urination with presence of glucose in the urine, nocturia, excessive thirst, and lethargy. The development of symptoms is usually much more rapid in type 1 than type 2. Studies reveal a 3% chance of developing type 1 diabetes below the age of 20 years if a parent or sibling is affected. The chance of developing type 2, is much higher, with a potential 40% chance by age 80 years if one parent or sib has type 2, and an 80% chance if both parents have type 2. For type 1 diabetes, the HLA (human leukocyte antigen) and MHC (major histocompatibility...
Human Genetic Disorders

complex) regions are thought to contain the main susceptibility genes. For type 2 diabetes, there are thought to be many different susceptibility genes. Cancer is uncontrolled growth of abnormal cells in any part of the body. Different genes that influence breast cancer susceptibility have been found on chromosomes 6, 11, 13, 14, 15, 17, and 22. General signs and symptoms are not very specific but are as follows: fatigue, weight loss, pain, skin changes, change in bowel or bladder function, unusual bleeding, persistent cough or voice change, fever, lumps, or tissue masses.

Summary

Mutations are the sudden heritable changes responsible for genetic diseases. Changes in the DNA of somatic cell can also result in genetic disorders. Thus, genetic diseases can be broadly classified into two types: (1) Autosomal disorders which are result of changes in the somatic chromosome and (2) Allosomal disorders responsible for changes in sex chromosome. Abnormalities can be as small as a single-base mutation in just one gene, multiple genes or they can involve the addition or subtraction of the entire chromosomes. Various techniques like ultrasound, amniocentesis, pre-post natal screening etc are now being used to study the genetic disorders. Autosomal disorder is a result of meiotic non-disjunction Institute of Lifelong Learning, University of Delhi
Human Genetic Disorders

in the autosomes. Non-disjunction of the chromosomes are causing (Trisomy 21) Down’s syndrome, Edward syndrome and Patau Syndrome (Trisomy 13). Major sex anomalies in humans are Turner Syndrome, Poly X Syndrome, Klinefelter’s Syndrome, XXY males and Hermaphrodite. Inborn errors of metabolism are rare genetic disorders due to abnormal metabolism of an intermediate in a metabolic pathway leading to either its accumulation or deficiency. Mostly the carrier of these non-disjunction die during development. Chromosomal Abnormalities involve mutations/ambiguity/changes in whole chromosome or part or a region coding for a specific gene on the chromosome. Eg: Cri-du-chat Syndrome (Loss of the short arm of chromosome 5).

Single Gene Disorders (Mendelian disorders) are caused by a defect in just one gene. Eg: Huntington’s disease (degeneration of the nervous system) and cystic fibrosis (affects the mucus and sweat glands leading to lung infection). Albinism leads to absence of pigmentation in the skin, eye and hair color of the affected individual. Hermansky-Pudlak Syndrome (HPS), Griscelli Syndrome (GS), Waardenburg syndrome are different types of albinism.

Glutamic acid is replaced by valine at sixth position in the beta haemoglobin chain leads to sickle cell anaemia. The shape of the red blood cells changes to sickle shape as a result the red blood cells break apart causing anaemia. Shortening of the fingers and toes leads to disproportionate limbs causing Brachydactyly.

Multifactorial inheritance refers to the pattern of inheritance of common health problems and rarer conditions. Multifactorial conditions have in common that they do not always develop despite the suggested presence of a faulty gene(s). Various lifestyle diseases eg; heart disease, cancer, and diabetes which are the combined outcome of the specific environmental conditions and gene mutations. Multifactorial inheritance disorders are caused by a combination of small inherited variations in genes, often acting together with environmental factors. Heart disease, diabetes, and most cancers are examples of such disorders. Behaviors are also multifactorial, involving multiple genes that are affected by a variety of other factors. Researchers are learning more about the genetic contribution to behavioral disorders such as alcoholism, obesity, mental illness and Alzheimer’s disease.

Glossary

**Aneuploid:** A cell with one or more extra or missing chromosomes.

**Centromere:** Chromosomal region to which the spindle fibers attach during mitosis or meiosis. It appears as a constriction at metaphase. It contains chromosome-specific repetitive DNA sequences.

**Chromatid:** A single, very long DNA molecule and its associated proteins forming half of a replicated chromosome.

**Chromosomal mosaic:** An individual in whom some cells have a particular chromosomal
Human Genetic Disorders

anomaly, and other do not.

**Cytogenetics**: A discipline that matches phenotype to detectable chromosomal abnormalities.

**Deletion**: A missing sequence of DNA or part of a chromosome.

**Dicentric**: A chromosome that is abnormal because it has two centromeres.

**Diploid cell**: A cell containing two sets of chromosomes.

**Duplication**: An extra copy of a gene or DNA sequence, usually caused by misaligned pairing in meiosis; a chromosome containing repeats of part of its genetic material.

**Gamete**: A sex cell.

**Gene**: A sequence of DNA that instructs a cell to produce a particular protein.

**Haploid cell**: A cell containing one set of chromosome (half the number of chromosomes of somatic cell).

**Karyotype**: A chart that displays chromosome pairs in the order of size.

**Meosis**: A type of cell division that takes place during gamete formation in which chromosomal number is halved to form haploid gametes.

**Mitosis**: Division of somatic (nonsex) cells.

**Mutation**: A change in a protein encoding gene (that has an effect on the phenotype).

**Non-disjunction**: The unequal partitioning of chromosomes into gametes during meiosis.

**Pachytene**: The third stage of the prophase of meiosis during which the chromosomes become shorter and thicker and divide into chromatids.

**Phenotype**: The expression of a gene in traits or symptoms.

**Trisomy**: A human cell with 47 (one extra) chromosomes.

---

**Exercise**

Q.1. Explain the following.

(a) Trisomy 13.

(b) Trisomy 18.

(c) Down’s syndrome.

(d) *cri du chat* syndrome.

Q.2. Answer the following question in short.

(a) Name the human disorder produced by the lack of one sex chromosome.
Human Genetic Disorders

(b) Which disorders is caused in man by presence of one extra sex chromosomes?
(c) Give an account of Turner syndrome.
(d) Name three genetic disorders of different kinds found in man. Describe any one.

Q.3. Answer the following question in detail.
(a) Down syndrome is caused by trisomy for 21-chromosome. A few cases of Down syndrome are reported with 46-chromosomes? How?
(b) What is the cause of Down’s syndrome?

References

- [http://genome.wellcome.ac.uk/doc_wtd020863.html](http://genome.wellcome.ac.uk/doc_wtd020863.html)
- [http://genome.wellcome.ac.uk/node30079.html](http://genome.wellcome.ac.uk/node30079.html)
- [http://genome.wellcome.ac.uk/doc_WTD020862.html](http://genome.wellcome.ac.uk/doc_WTD020862.html)

Books

Human Genetic Disorders