Lecture 34: DNA & Disease Association

We have already studied structure of DNA in earlier lectures. DNA is selected as genetic material by nature due to self replicating property and repair mechanism. There are several experiments which prove that the DNA acts as genetic vehicle for transfer of information from one to next generation.

There is a range of diseases which have certain genetic background (except, diseases caused by microorganisms). Since, DNA is the genetic material and carries all the informations required for the growth and development of an individual, any change in the DNA leads to some abnormality. DNA is present in form of chromosomes inside the nucleus so, the change in DNA can be explained in terms of change in chromosomes or chromosomal aberration.

Chromosomal aberrations:

Any change in normal chromosome of the cell, referred as chromosomal aberration. This may be due to structural or numerical change.

Structural change: Following structural changes can lead to a disease (Fig. 1)

1. **Deletion:** This is due to loss of a part of a chromosome.

Wolf-Hirschhorn syndrome: Partial deletion of the short arm of chromosome no. 4.

Jacobsen syndrome: Deletion of terminal part of long arm of chromosome no. 11.

Cri du chat syndrome: Partial deletion of the short arm of chromosome no. 5.

2. **Duplication:** This is due to addition or duplication of a part of chromosome.

Bar eye in drosophila: Duplication of 16A region of X chromosome of Drosophila.
Charcot-Marie-Tooth Disease type 1A: Duplication of a large region in chromosome 17p12.

3. **Translocation:** This is due to movement of a part of chromosome to other chromosome. It may be reciprocal or robertsonian type.

Leukemia (acute myelogenous leukemia & chronic myelogenous leukemia) and Ewing's sarcoma is generally caused by translocation.

4. **Inversion:** This is due to reverse orientation of a part of chromosome. It may be paracentric (centromere is not included) or pericentric (centromere is included).

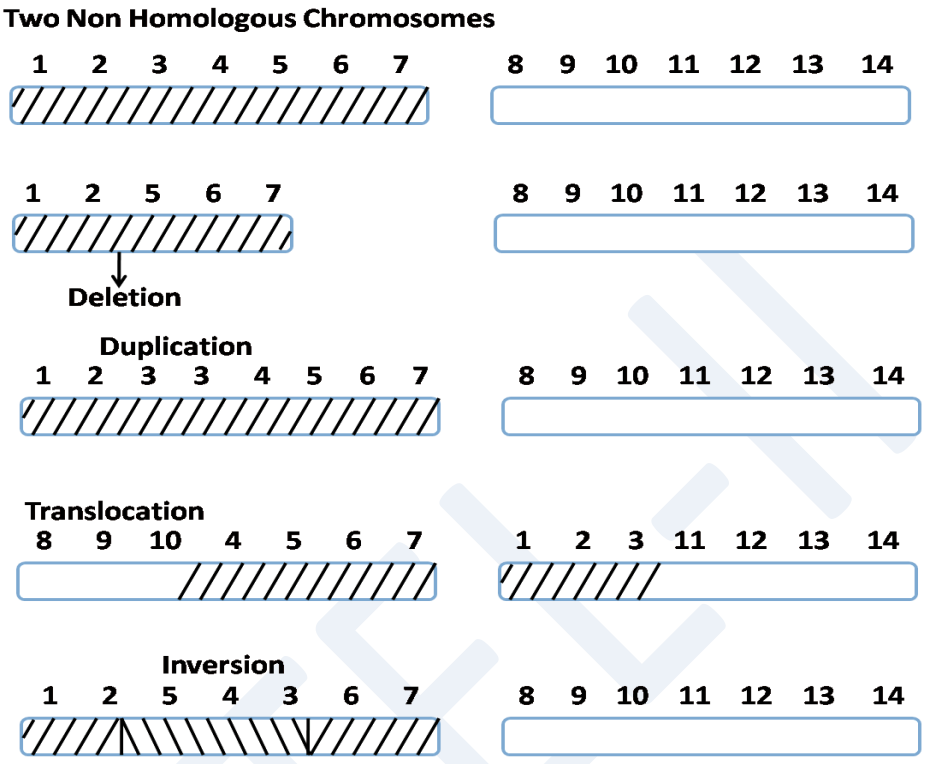

Figure 1: Possible structural changes in chromosomes.

Numerical change: Numerical changes in chromosome can also lead to a diseased condition. The numerical changes are mainly of two types.

A. Aneuploidy: Change (increase or decrease) of one or two chromosome from a chromosome pair.

Monosomy (2n-1): Turner syndrome (XO): Loss of one X chromosome.

Nullisomy (2n-2): Loss of one complete set of chromosome (patient will not survive).

Trisomy (2n+1): Down syndrome or Mongolism: Trisomy of 21st pair of chromosome.

Edwards syndrome: Trisomy of 18th pair of chromosome.

Patau syndrome: Trisomy of 13st pair of chromosome.

Klinefelter syndrome (47,XXY) : Extra X chromosome in male sex chromosome set.

Tetrasomy (2n+2): 48(XXXX): Two extra X chromosome.

B. Euploidy: Change (increase or decrease) of complete set of chromosome.

Haploid (n): Have single set of chromosomes.

Diploid (2n): Have two set of chromosomes.

Mutation related Genetic Disorders:

DNA contains its hereditary information in a unit gene which normally resides inside the DNA stretch. These are basic unit of life which governs all the traits and thus any aberration or mutation inside it, leads to harmful effects. Some of the disorders are cited below which are caused due to genetic defects.

Cystic Fibrosis:

Cystic fibrosis is the recessive genetic disorder develops when neither copy in the two genes works normally. Although most of the normal people without CF have two working copies of the CFTR gene, only one is needed to prevent cystic fibrosis. It is caused by a mutation in a gene for the protein cystic fibrosis transmembrane conductance regulator (CFTR) due to deletion of three nucleotides, results loss of one amino acid (phenylalanine) at 508^{th} position in the protein. This protein is required to regulate the components of sweat, digestive juices, and mucus.

Duchenne Muscular Dystrophy:

DMD is X linked recessive form of muscular dystrophy. This disease is caused by a mutation in the dystrophin gene which is located at the X chromosome in humans (Xp21). Dystrophin is an important component of muscle tissue which provides stability to dystroglycan complex (DGC), located on cell membrane. Since males only have one X chromosome, they only have one copy of DNA that makes this protein and there is no backup. Females have two X chromosomes and so have two copies of the gene. Because males only have a single copy of the gene, this disease is much more common in males. Affected individuals experience muscle weakness throughout their bodies that eventually leads to paralysis and expected life is fewer than 35 years.

Pompe Disease:

Pompe disease is an inherited disorder caused by mutation in GAA (acid alpha-glucosidase) gene. GAA gene is for production of an enzyme acid alpha glucosidase also known as acid

maltase. This enzyme is active in lysosomes which act as recycling centres inside the cells. Mutation in GAA gene prevents acid maltase enzyme to break down glycogen effectively which allows this sugar to accumulate upto the toxic level which further damage tissues and organs throughout the body.

Sickle cell anaemia (SCD):

It is an autosomal recessive disorder of haemoglobin gene characterized by a sickle shape of RBC with hard and sticky structure. SCD occurs due to a point mutation which leads to conversion of seventh amino acid of Hb protein i.e. glutamic acid to valine.

Hemophilia:

It is an X linked recessive disorders mainly affecting males because of presence of single copy of X chromosome in males. It is a group of hereditary genetic disorder that impairs the blood clotting ability. Haemophilia A is caused due to factor VIII deficiency and haemophilia B is caused by factor IX deficiency. Haemophilia lowers blood plasma clotting factor levels needed for a normal clotting process. Thus when a blood vessel gets injured, a temporary scab does form, but the missing coagulation factors prevent fibrin formation, which is necessary to maintain the blood clot. A haemophiliac does not bleed more intensely but it bleeds for longer time than a normal person.

Purine and Pyrimidine metabolism related disorders

Disorders of purine salvage pathway:

Lesch-Nyhan syndrome:

This is a caused by deficiency of hypoxanthine-guanine phosphoribosyl transferase (HPRT) and a rare X-linked, recessive disorder. HPRT deficiency results in failure of the salvage pathway for hypoxanthine and guanine and these purines further degraded to uric acid. Additionally, a decrease in inositol monophosphate and guanosyl monophosphate leads to an increase in conversion of 5-phosphoribosyl-1-pyrophosphate (PRPP) to 5-phosphoribosylamine, which further enhances uric acid overproduction. Hyperuricemia predisposes leads to gout.

Adenine phosphoribosyltransferase deficiency (APRT):

This is a rare autosomal recessive disorder that cause by deficiency of APRT enzyme. APRT catalyse the reaction between adenine and phosphoribosyl pyrophosphate and forms AMP. Deficiency of APRT leads adenine accumulation which is oxidized to 2,8-dihyroxyadenine and precipitates in the urinary tract. Diagnosis is by detecting elevated levels of 2,8-dihyroxyadenine, 8-hyroxyadenine, and adenine in urine.

Disorders of purine nucleotide synthesis

Phosphoribosylpyrophosphate synthetase superactivity:

This X-linked recessive disorder causes purine overproduction. Excess purine after degradation, resulting in hyperuricemia, gout, neurologic and developmental abnormalities.

Disorder of purine catabolism

Adenosine deaminase deficiency:

ADA converts adenosine and deoxyadenosine to inosine and deoxyinosine, which are further broken down and excreted out from the body. Enzyme deficiency results in accumulation of adenosine which is further converted to its ribonucleotide and deoxyribonucleotide (dATP) forms by cellular kinase activity. The increase in dATP results inhibition of ribonucleotide reductase and underproduction of other deoxyribonucleotides. As a result, DNA replication is compromised. Immune cells are especially sensitive to this defect because ADA is most active in lymphocytes. Thus adenosine deaminase deficiency causes one form of severe combined immunodeficiency (SCID).

Disorders of pyrimidine metabolism

Uridine monophosphate synthase deficiency:

Uridine monophosphate is the enzyme that catalyzes formation of UMP. Its gene is present on 3q13 location. This bifunctional enzyme has 2 subunits-orotate phosphoribosyltransferase and orotidine-5′-monophosphate decarboxylase. These enzymes work in the last 2 steps of UMP synthesis. With its deficiency due to mutation, orotic acid accumulates in body, causing megaloblastic anemia, orotic crystalluria and nephropathy, cardiac malformations, strabismus, and recurrent infections.

DNA mutation leads to Immunodeficiency:

DNA repair and Cancer:

Large distortion in the helical structure of DNA is repaired by nucleotide excision repair system. Genetic defects that inactivate nucleotide excision repair system leads to many genetic defects as Xeroderma pigmentosum. It is caused by pyrimidine dimer formation in humans which symptoms are extremely light sensitivity further leading to skin cancer. Nucleotide excision repair is the only repair mechanism for photoreactivation of pyrimidine dimers.

There are so many other diseases related to chromosomal defect as Severe Combined Immunodeficiency (SCID) where defect is in 11p13 locus causing defect in RAG-1/RAG-2 deficiency and transmitted as autosomal recessive disorder.

In Digeorge syndrome, 22q11chromosomal defect leads to impaired development of T and B lymphocytes and inherited as autosomal dominant disorder.

Autosomal 11q22 locus recessively inherited defect in cell cycle kinases leads to Ataxia Telangiectasia which results low immunoglobin level of IgA and IgE.

DNA in Cancer development:

Cancer by Gain of Function of Genes:

One type of cancer causing genes are proto-oncogenes which are basically involved in the secretion of growth factor or its product functions as transcription factor. They work in a regulated manner in normal cells. Mutation in proto-oncogene changes it into more active oncogenic form and now they behave abnormally by stimulating cell proliferation in an uncontrolled manner. Few examples are myc, jun and fos oncogenes which codes for transcription factors and their overactivity resulted unregulated proliferation leading to cancer.

Chromosomal translocation of c-myc proto oncogenes in Chronic Myelogenous Leukemia (chromosome 9→22 translocation) and Burkitt Lymphoma (chromosome 8→14 translocation) enhances the activity of c-myc and thus transcription factor production too, which leads to cancer.

Cancer by Loss of Function of Genes:

Another category is tumor suppressor genes or anti-oncogenes which encodes protein for inhibiting cell proliferation. Inactivation of these genes results excessive proliferation of cells. The protype of this gene is retinoblastoma (Rb) gene which inactivation leads to tumour develop in neural precursor cells of retina. The other gene is Guardian of genome p53 gene which encodes a nuclear phosphoprotein that inhibits formation of small cell lung cancer and colon cancer.

Inborn Error in Metabolism:

A. E. Garrod (1909) described certain hereditary diseases which lead to certain defects in metabolism. Most of these diseases are due to mutation in genes responsible for production of certain crucial enzymes of metabolic pathways. Inactivation of enzymes leads to accumulation of their substrates which results several abnormalities.

Phenylketoneuria: Phenylalanine metabolism (phenylalanine hydroxylase)
Alceptoneuria: Phenylalanine and Tyrosine metabolism (homogentisate 1,2-dioxygenase)
Zellweger syndrome: Deficiency or absence of functional peroxisomes