Human Diseases and Their Genetic Basis

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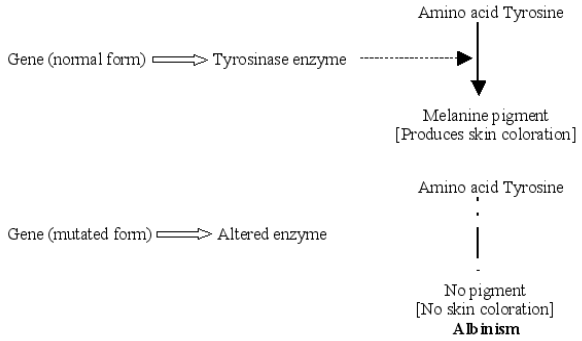
Vast number of the ailments that human suffers can be categorized into three groups viz. (A) ailments resulting from body's adverse reactions in response to pathogenic infections such as from bacteria, viruses etc., (B) ailments that are symptomatic of some physiological imbalances, and (C) ailments that are due to inborn genetic defects. Even several of the afflictions belonging to group-A, and, mostly of group-B are caused due to pre-disposing factors that have genetic basis.

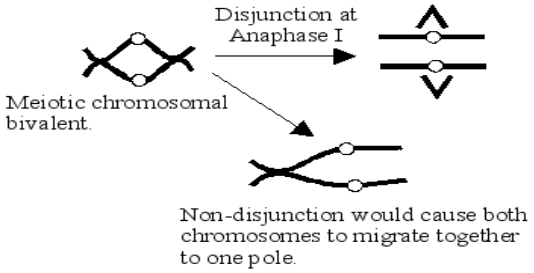
Mendelian disorders and inborn errors of metabolism

These are defects arising due to malforming nuclear genes that show vertical inheritance from parents to children following Mendelian mode of inheritance. Such defects are single-gene disorders resulting from the lack of or under-production of some enzyme/protein which is required to carry out a specific biochemical conversion in the system. Pathological condition in these cases is caused by the fact that the gene responsible to produce the required enzyme or protein has a mutated structure that codes for aberrant non-functioning protein/enzyme.
Example: **Albinism (non-pigmentation in skin).**



Human genome mapping has now located a number of such defect-prone nuclear genes on our 24 chromosomes. The knowledge of the location of these mutant genes is definitely going to help in the prevention and management of these genetic ailments.
In addition to nuclear single-gene disorders, several of the human defects are caused by -

1. Chromosomal aberrations (Structural alterations in chromosomes),
2. Aneuploidy (Change in chromosome number)
3. Alteration in mitochondrial genes,
4. Somatic mutations, and
5. Alteration in multi-gene interaction pattern (Polygenic disorders).



Chromosomal aberrations

All structural aberrations in chromosomes result from chromosome breakage. Two sticky ends arise when a chromosome breaks. Repair mechanism tends to correct it immediately by rejoining the sticky ends. However, if more than one breaks have occurred, it falters and joins wrong ends in most cases causing aberrations. Such aberrant chromosomes would be inherited creating a lineage of these disorders in the family.

Aneuploidy

Aneuploidal changes in chromosomes are the result of :

- Non-disjunction of chromosomes during gametogenesis in parents,
- Chromosome lagging during cell divisions, and
- Chromosomal endoduplication.

Mitochondrial defects

Human mitochondrial genome consists of a single, circular and double stranded DNA with 16569 base pairs. It is present in multiple copies per mitochondrion. 37 genes of this genome code for 22 transfer RNAs, two types of ribosomal RNA needed for mitochondrial protein synthesis and 13 proteins required for oxidative phosphorylation process. Mutation rate in the mitochondrial genome is 10 times higher than that in the nuclear genome.

As mitochondria are in inherited from the mother's side in multiple copies, the impact of a mitochondrial gene mutation is very high. The severity of mtDNA induced defects depends on whether the patient is homoplasmic (with all copies of the gene defective) or heteroplasmic (many copies of the gene defective but with few normal copies).
Leber's heriditary optic neuropathy (LHON) is a maternally inherited mutant mtDNA induced mid-life blindness caused by bilateral central vision loss due to atrophy of the optic nerve.

Somatic mutations and cancer

Cancers are mostly individual specific and result of somatic mutations (not inherited). Three groups of genes that induce cancer by mutations are-
1. Oncogenes (mutated versions of retroviral genes that were employed by the human cells to carry out some normal cellular functions),
2. Tumour suppressor (TS) genes (that inhibit cell proliferation), and
3. Mutator genes (genes responsible for correction of DNA damages).

Polygenic defects

These are the disorders caused through complex interaction of several genes and environmental components (i.e. pre-disposing factors). This group constitutes the major chunk of diseases that we suffer with. e.g. hypertension, diabetes, arthritis, multiple sclerosis etc. These diseases do not show a particular inheritance pattern and may be found more in one family than in others.

Translational genomics research

It is the research area that makes use of the knowledge and innovative approaches arising from the Human Genome Project for their application to the development of diagnostics, prognostics and therapies for cancer, neurological disorders, diabetes and other complex diseases. Human genome mapping has led the researchers to work out and translate variations in human genes to discover the underlying cause of individual-specific susceptibility, disease progression and resistance to therapy.