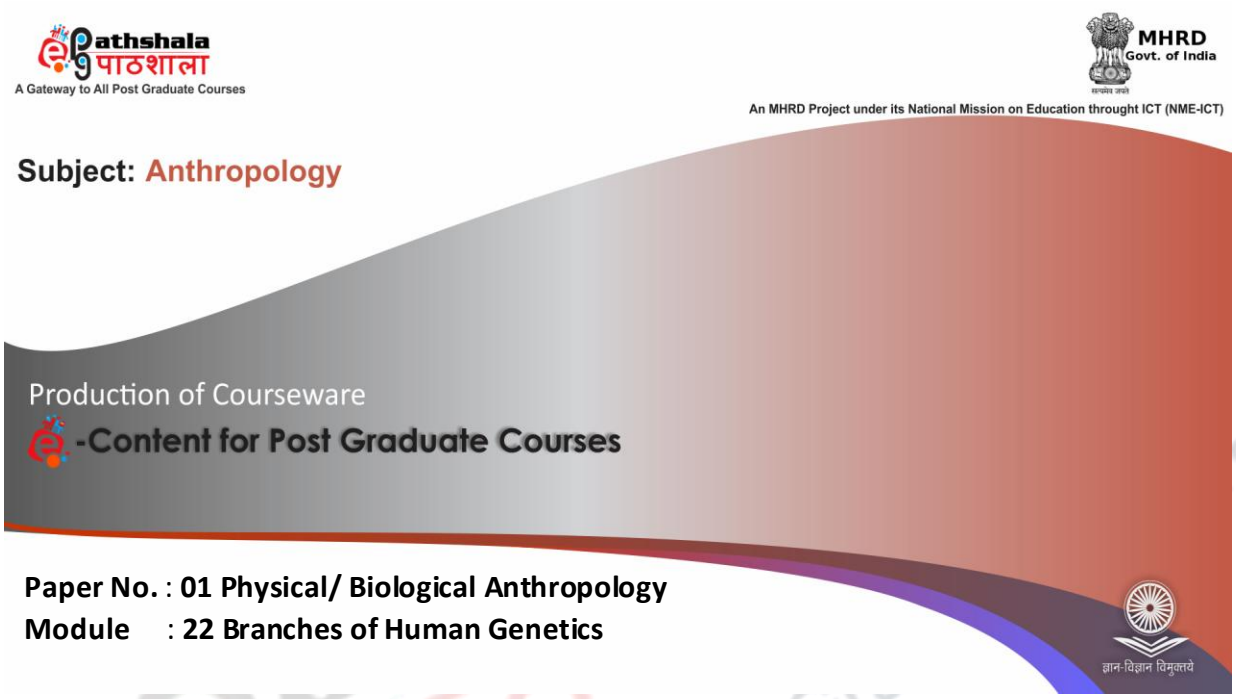

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Description of Module	
Subject Name	Anthropology
Paper Name	01 Physical/Biological Anthropology
Module Name/Title	Branches of Human Genetics
Module Id	22

Learning Objectives

- To learn about human genetics and emergence of its branches
- Rationale of the techniques in understanding the abnormalities
- To know about genetic diseases and its management

Introduction

Biological anthropology is defined as the scientific study of humankind from bio-cultural perspective in understanding the human evolution and variation. Biological anthropologists are interested in the area of human genetics to understand the origin and distribution of abnormal genes causing certain abnormalities across population groups. Thus human genetics provided wider scope for biological anthropologists to understand the evolution of certain diseases and variation in the prevalence rates in population segments. Human genetics is the scientific study of inherited human variation. In other words human genetics is the ultimate answer in better understanding of us. To achieve this goal, biological anthropologists started to understand the human genetics by learning about DNA, chromosomes, proteins and mutations. Natural selection allows different alleles more likely for survival advantage in different environments. In order to understand the survival advantage of different genotypes in various ethnic backgrounds, anthropologists started to pursue the science of genetics by mentioning anthropogenetics. Hence there is a need for anthropologists to learn about genetics in particular human genetics and its various branches to answer several questions which continues to be under investigation towards the human welfare.

Human Genetics

Human Genetics is multidisciplinary field that connects the science of genetics and the growing number of people who can benefit from its applications. It is the science of heredity, which attempts to explain similarities and dissimilarities among the related individuals. Recent advances in Human genome project have set free an inundation of scientific, medical, and therapeutic discoveries. To understand the field of Human Genetics in toto, we need to expose to various overlapping fields in human genetics like classical genetics, population genetics, cytogenetic, behavioral genetics, molecular genetics, biochemical genetics and Epigenetics.

Classical Genetics

Classical genetics is the branch of genetics deals with the analysis of parents to offspring. It depends on visible results of characters transmitted from parents to offspring. Mendelian experiments are made it possible to identify the basic mechanism of heredity. Cell division involving chromosomes, which consists units of inheritance called genes (factors) are the key component in classical genetics. Human cell contains 46 chromosomes (22 pairs of autosomes and two sex chromosomes (XX or XY). Meiosis

in germ cells produces two gametes each with the haploid number of chromosomes (23). Thus offspring will receive 23 chromosomes from father and 23 chromosomes from mother. These chromosomes comply with the Mendelian laws.

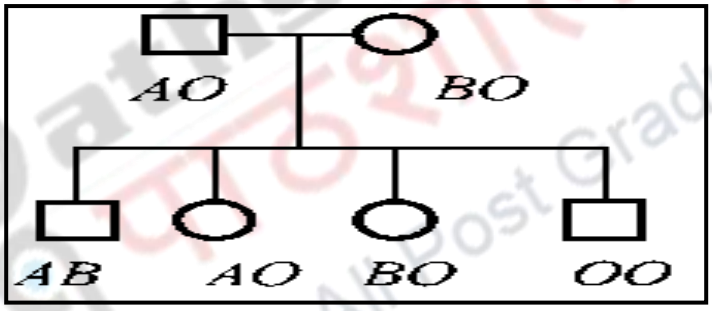
1. Law of segregation: The gene pair (alleles) segregates during meiosis, and the resultant gametes share each one allele.

2. The principle of law of independent assortment: Genes for different traits assort independently of one another.

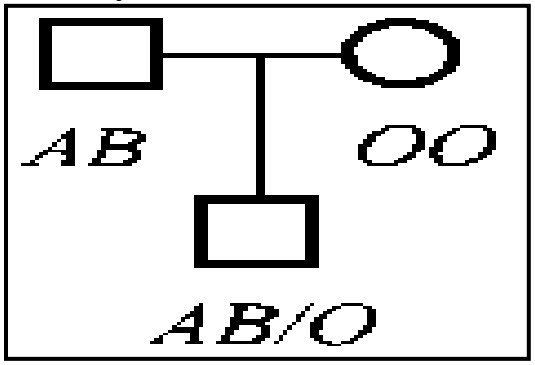
Later several modifications have been made to Mendel's laws because closely linked genes on same chromosome do not assort independently. Due to crossing over may result in new combination of genes and in non-disjuction daughter cell may receive both copies of information.

Inheritance of ABO blood group genes is the best example for classical genetics.

Segregation of genes to gametes



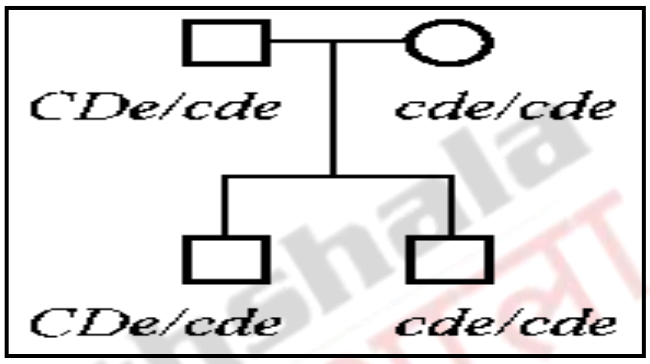
For example, the probability that a gamete will receive the *A* allele is 0.5 (from the law of segregation) and the probability that this same gamete will receive the *b* allele is similarly 0.5. Thus, the probability that a gamete will have a combined *A b* genotype is 0.5 x 0.5 = 0.25. The same probabilities are obtained for all four possible allelic combinations (*A B, a b, A b, a B*). Since the number of gametes produced by an individual is very large, these probabilities translate directly into the frequencies at which each gamete type is actually present and, in turn, the frequency with which each will be transmitted to offspring. Instead of normal segregation, nondisjuction may occur, although it is rare.Non-disjunction in the ABO system



Chromosomes have failed to segregate at meiosis so that the child inherits both *A* and *B* genes from the father (as well as an *O* gene from the mother).

Rh blood group system is the best example. Dd, Cc, Ee loci are closely linked on a chromosome, hence crossing over does not occur.

Inheritance in the Rh system



Because crossing over cannot occur, the genotype *Cde/cde* is impossible in a child from this mating. Even though the father has *C*, *d*, and *e* genes, the *Cde* and *cde* on each chromosome are always transmitted to offspring together.

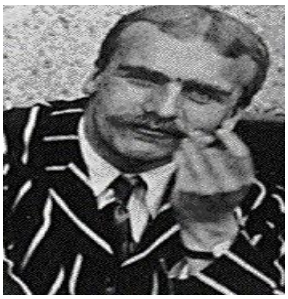
In transfusion medicine these principles are applied to identify the hemolytic diseases of new born. Currently the science of genetics includes a broad spectrum of inquiry from molecular studies on gene regulations to analyses of allele frequencies in natural populations.

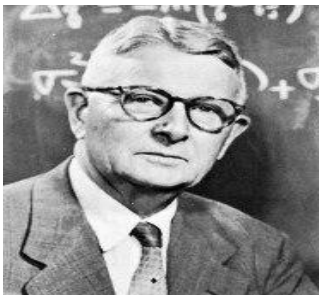
Population Genetics

Population genetics is the study of the frequencies of alleles in a population. The discipline grew out of the need to establish Darwinian Theory of evolution by natural selection on Mendelian heredity principles. Mendelian principles of inheritance (population genetics) are crucial to follow the Darwinian hypothesis that natural selection will play a significant role in evolution and generating diversity of life. Early population geneticists, R A. Fisher, JBS Haldane, Sewall Wright used single locus algebraic models to describe the changes in gene frequencies at population level. Population genetics studies the origin of variation, the transmission of variants from parents to offspring generation after generation, and the temporal changes that occur in a population because of systematic and random evolutionary forces.


Gregor Mendel (1822-1884)

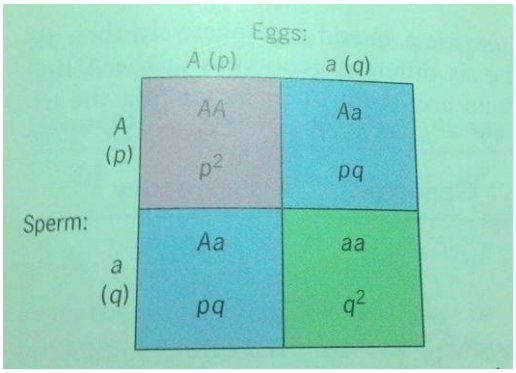

RA Fisher (1890-1962)


JBS Haldane (1892-1964)


Sewall Wright (1889-1988)

In 1908, Hardy (a British Mathematician) and Weinberg (a German Medical Doctor) independently formulated theorem of population genetics popularly known as Hardy-Weinberg Law (law of equilibrium). This law allows us to predict a population's genotype frequencies from its allele frequencies. The law states that allele frequencies remain constant through generations in large random mating population provided if the population is free from mutation, migration, genetic drift and natural selection. This allows quantifiable analysis of changes, and the equations can be extended to predict the changes in allele frequency resulting from continuing those changes. Thus evolutionary outcomes of particular scenario can be predicted.

The theory of population genetics is the theory of allele frequencies. Each gene in the genome exists in different allelic states (allele is an alternative form of gene). A diploid individual is either homozyge or heterozyge. Within the population of individuals we can calculate the frequencies of homozygotes and heterozygotes of a gene, and from these we can estimate the frequency of each gene's alleles. Let's suppose that in a population a particular gene is segregating two alleles, A and a, and that the frequency of A is p and that of a is q. Under the assumption that the members of the population mate randomly, then the diploid genotypes of the next generation will be formed by random union of haploid eggs and haploid sperms. The probability that an egg/sperm carries A is p, and the probability that it carries a is q. The probability of producing homozygote is p x $p=p^2$, and the probability of producing aa homozygote is q x $q=q^2$. For Aa heterozygote there are two possibilities: A can unite with a or a can unite with A. Each of these occur with probability of p x q, and they are equally likely, the total probability is 2pq.



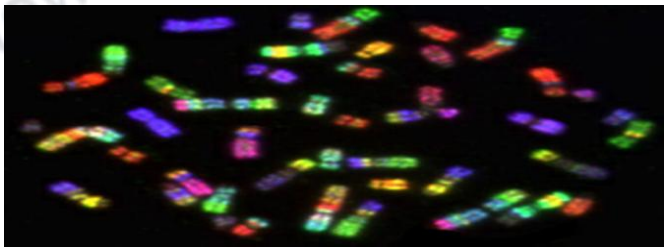
Genotype	Frequency
AA	p^2
Aa	2pq
Aa	q^2

Punnet square showing the Hardy-Weinberg Principle.
Source: Snustad DP and Simmons MJ. Principles of Genetics. Jhon Sons, Inc. 2003

The predicted frequencies are the terms in the expansion of the binominal expression $(p+q)^2=p^2+2pq+q^2$ and termed as Hardy-Weinberg genotype frequencies. Thus, Hardy and Weinberg principle demonstrates that, given the assumptions above, after one generation of random mating, stable genotype frequencies will result and be maintained provided if the population is free from selection, mutation, migration, or random drift, then variation will be preserved in a population.

Cytogenetic

Cytogenetic deals with the physical basis of heredity (cell). It can also be termed as the study of chromosomes, which are the visible carriers of the heredity material. Cytogenetics describes the chromosome structure and identifies the abnormalities related to disease. The scope of cytogenetics includes several technologies besides Fluorescence in situ hybridization (FISH), comparative genomic hybridization (CGH), and multicolor FISH etc.

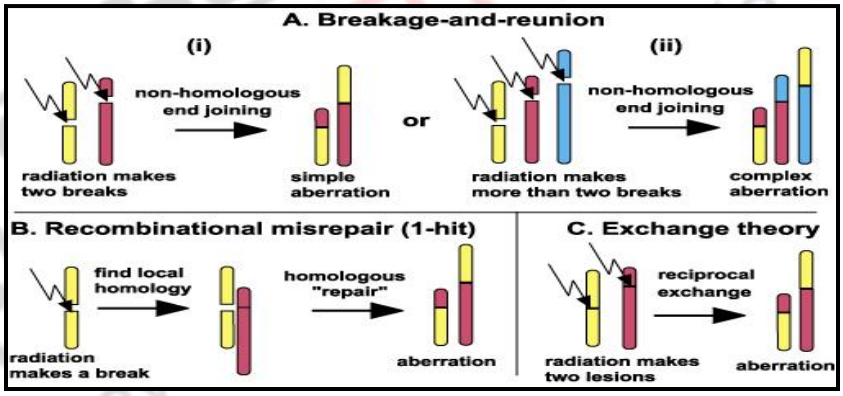


FISH remains the single most important technology in cytogenetics. Several innovations are described of which the most important are single copy FISH (imaging of nucleic acids in living cells) and nanotechnology-based FISH. The unique character of peptide nucleic acid (PNA) allows these probes

to hybridize to target nucleic acid molecules more rapidly and with higher affinity and specificity compared with DNA probes. PNA-FISH is more suited for rapid diagnosis of infections.

Chromosomal aberrations can be detected based on microarray/biochip based technologies. Whole genome expression array and direct molecular analysis without amplification are other important technologies. Analysis of single-cell gene expression promises a more precise understanding of human disease pathogenesis and has important diagnostic applications. Optical Mapping can survey entire human genomes for insertions/deletions, which account for a significantly greater proportion of genetic variation between closely-related genomes as compared to single nucleotide polymorphisms (SNPs), and are a major cause of gene defects.

Nanotechnology has facilitated the development of technology for single molecule imaging. Atomic force microscope (AFM) has become a well-established technique for imaging single bio-molecules under physiological conditions. The scanning probe microscope (SPM) system emerged as an increasingly important tool for non-intrusive interrogation of bio-molecular systems in vitro and has been applied to improve FISH.



There are connections between cytogenetics and biomarkers of genetic disorders as well as cancer. Biomarkers are very important for molecular diagnostics. As a means to understand the pathomechanism of disease and as links between diagnostics and therapeutics, biomarkers will play a major role in personalized medicine. Application of cytogenetics extends beyond genetic disorders and cancer to diagnosis of several other diseases.

Behavioral genetics

Behavioral genetics is a field in which genetic methodologies from twin and adoption studies through DNA will be applied to understand the individual differences in behavioral traits. It studies the inheritance of behavioral traits. In this field emphasis will be given to understand how important are genetic and/or environment influence on certain human behavioral traits (gene environmental interaction). A strong correlation for certain behavioral traits found in parents and offspring to think

whether it is parenting or genes?. The science of behavioral genetics focuses to distinguish the effects of environment and genes.

Human behavioral genetics use several methodologies to address the nature and mechanism of genetic influence on behavior. Twin studies and adoption studies are best examples to understand the importance of genetic and environmental effects. Heritability estimates the proportion of phenotypic variation in a population that is attributed to genetic influence. Heritability is a characteristic of population not of an individual. Stature estimation is the best example of heritability. One individual may experience nutritional deficiency during development and keeps shorter; on the other hand, the other one is free from nutritional deficiency and attained full height. For the first one environment is important but in the later genes was important. Thus the level of genes and environment varies considerably at the level of individuals with in a population.

Twin studies are much help in understanding gene nutrient interaction. Identical (monozygotic) twins are alike in their genetic information on the other hand; fraternal (dizygotic) twins though they are alike share only half of their genes. Both kinds of twins exposed to similar degree of environment. The differential share of DNA in identical and fraternal twins is an evidence for a shared environmental contribution to the trait. The studies of children who have adopted at an early age provide an opportunity to segregate genetic effects from shared environmental effects.

Molecular genetics

Molecular genetics deals with the chemical basis of heredity. It is the advance field of genetics. Genomics and proteomics are the key components in molecular genetics. During the last half century, geneticists have determined the molecular structure of Mendel's factors and the mechanism by which they control the characteristics of an organism. Molecular genetics allows us to understand the DNA

structure (nucleotides, DNA polynucleotides, the double helix, complementary base pairing) RNA structure and interrelation between DNA and RNA molecules.

Molecular genetics research has given us powerful tools to study genes. In 1985, Kary Mullis developed a technique called polymerase chain reaction (PCR) that allows us to take a minute sample of DNA and produce millions of copies of DNA for molecular analysis. With the use of PCR, DNA isolated from a small sample of tissue perhaps a single sperm or white blood cell or a hair follicle recovered from any crime scene can be subjected to molecular analysis. Forensic scientists use a type of DNA analysis called DNA fingerprinting to examine the variation in the sequence of DNA. A major component of DNA technology is cloning, which is the process of making multiple, identical copies of a gene by incorporating in an organism like bacteria to use in different applications.

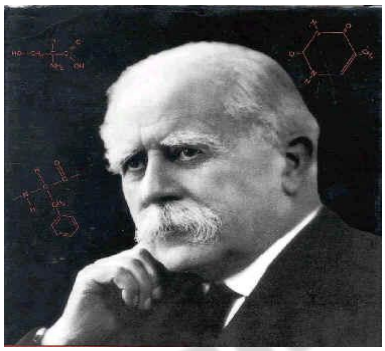
DNA recombinant technology allowed us to alter the DNA with the help of restriction end nucleases, and can be inserted into another matched DNA to understand the variable pattern. This technique helpful in merging the genes into molecular devices and can transport these genes to various cellular destinations (gene therapy). In this technique corrected genes can be delivered into individuals with defective genes that cause specific disease. DNA chip technology facilitates gene expression profiling to understand the specific gene up and down regulation. The up and down regulation of gene allows us to estimate the cancer risk.

Molecular genetics has revolutionized biology and is having an ever increasing impact in pharmacology, genetic engineering in disease prevention, in increasing agricultural growth, in detection of disease and crime (forensics) etc. Further it helps us in tracking DNA evolution, migratory patterns and species evolution over the ages. The advances brought in molecular geneticists have profound implications for the future of medicine for they have placed us at the threshold of new methods of diagnosis, prevention, and treatment of numerous human diseases. Hormones, vaccines, therapeutic agents, and diagnostic tools are already greatly enhancing medical practice.

Human Biochemical Genetics

Biochemical genetics is an important branch of Human Genetics, which provides a base to understand the genetic variation and disease occurrence. Human biochemical genetics expose how the study of human systems led to advances in basic biology. Recent development in the whole human genome project has been driving force for identifying genetic disorders. This is true in the area of inborn errors of metabolism. From Garrod's understanding of alkaptonuria to today's ability to detect single nucleotide changes, we have technology driven discoveries. Various technologies like amino acid analysers, gas chromatography/mass spectrophotometers led to identify the analytes of amino acids, organic acids and fatty acids. Identification of these disorders at an early stage may provide an

opportunity to initiate therapies like dietary modifications, enzyme inhibitors, enzyme replacement therapy and bone marrow transplantation.



AE Garrod (1857-1936)

Amino acid metabolism disorders: Phenylketonuria is a rare genetic disorder where body can not break down the essential amino acid phenylalanine. In the body phenyl hydoxylase enzyme converts phenylalanine to tyrosine. Tyrosine is necessary to activate neurotransmitters like epinephrine, norepinephrine and dopamine. The increased levels of phenylalanine in the blood cause damage to the nervous system and brain. Phenylketonuria is inherited as autosomal recessive pattern. An infant with phenylketonurea may appear normal for the first few months of his/her life. If the condition is not treated in time, abnormalities like mental retardation, tremors or jerky hand and leg movements, hyperactivity and stunted growth etc will precipitate.

Maple syrup urine disease is another inherited disorder in which the body unable to process certain amino acids properly. The condition is named as maple syrup urine due to distinctive sweet odor of affected infant's urine and also characterized by poor feeding, vomiting, lethargy and developmental delay. If untreated, the condition leads to seizures, coma and death. This condition is inherited as autosomal recessive pattern.

Carbohydrate disorders: Galactosemia is a disorder that affects how the body processes a simple sugar called galactose. The signs and symptoms of galactosemia result from an inability to use galactose to produce energy and affect different enzymes involved in the breaking down the galactose. If the condition is not addressed with low galactose diet, severe complications may arise few days after birth. This condition is inherited as autosomal recessive pattern.

Fatty acid oxidation disorders: Medium chain acyl CoA dehydrogenase (MCAD) is a condition where body fails to convert certain fats to energy during starvation or fasting. MCAD may include the symptoms of vomiting, lethargy and low blood sugar. The condition is inherited as autosomal recessive pattern.

Organic acid disorders: Isovaleric acidemia is a rare disorder in which body is unable to convert certain proteins properly and helps to buildup of particular acids known as organic acids. Abnormal levels of organic acids in the blood, urine and tissues can be toxic and can result in serious health problems. The condition is inherited as autosomal recessive pattern.

Lysosomal storage diseases: Fabry disease is X linked inherited disorder resulting from the buildup of a particular type of fat, called globotriaosylceramide. The condition causes signs and symptoms that affect many parts of the body. The disease also involves life threatening complications.

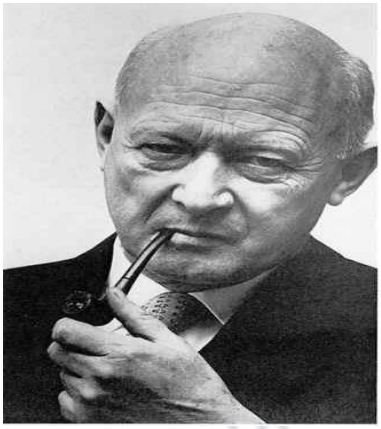
Mitochondrial disorders: Mitochondrial encephalomyopathy, lactic acidosis and stroke like episodes (MELAS) affect different parts of the body, particularly brain and nervous system and muscles. People with MELAS characterized by increased levels of lactic acid, causing acidosis. An increase of acidity in blood may lead to vomiting, abdominal pain, fatigue, muscle weakness and breathing problems.

Urea cycle disorders: The disorder Citrullinemia inherits in autosomal recessive pattern causing ammonia and other toxic substances to accumulate in the blood. Infants affected with citrullinemia appear normal at birth, but as ammonia accumulates in the blood, they experience progressive lack of energy, poor feeding, vomiting, seizures and loss of consciousness.

Epigenetics

Epigenetics involves change in phenotype without changes in genotype. It can also be referred as the changes in organism caused by alteration in gene expression rather than alteration in genetic code (DNA). Epigenetic changes will be influenced by several factors such as age, life styles and diseases. Epigenetic changes will be more rampant that can end up with diseases like cancers. The term Epigenetics was first introduced by Waddington in 1942, and described the influence of genetic processes on development. The concept of genetic assimilation has gained interest during 1990s, which paved the way to understand the molecular basis of Waddington's observations in which environmental stress caused genetic assimilation of certain phenotypic characters in Drosophila fruit flies. There after efforts towards identifying epigenetic mechanisms related to external factors has been attenuated. DNA methylation, histones modifications and non–coding RNA (ncRNA)-associated gene silencing are currently considered to be important in initiating constant epigenetic changes.

The science of epigentics is quickly growing by understanding both the environment and life styles which may directly interact with genome to influence epigenetic change. These changes may precipitate any stage of human journey and may see in later generations also. Prenatal and post natal environmental factors influence the adult risk of developing various chronic diseases. Research results show that starvation in early stage or poor nourishment in the womb may result in obesity and hypertension in later life. A few epigenetic mediated disorders are mentioned below.



CH Waddington (1905-1975)

Cancer: Feinberg and Vogelstein (1983) linked cancer with Epigenetics. The scientists observed that genes of colorectal cancer cells substantially hypomethylated compared with normal tissue, which can activate oncogens and initiate chromosome instability, whereas DNA hypermethylation initiate silencing of tumor suppressor genes. Addition of genetic and epigenetic errors can transform a normal cell into metastatic tumor cell. Similar pattern of changes can be seen in other cancers also. Hence epigenetic changes can be used as biomarker for early diagnosis of cancers.

Immunity: Research evidence shows that epigenetic modifications are one of the prime reasons in developing autoimmune disorders. Recent evidence clearly indicates that autoimmune diseases occur more often in female, suggesting a key role for the X chromosome by highlighting the relation between autoimmune diseases like systemic lupus erythematosus and the X chromosome. X chromosome inactivation- a major epigenetic feature in female cell that provide dosage compensation of X-linked genes in avoiding its over expression. When frequent episodes of cellular stress occur, the inactive X chromosome may be disrupted and involuntarily involved in the nucleolar stress response. Developments of autoantigens, which are aid in nucleoprotein complex in the nucleolus, increase further during cell stress and appear to have an important role in autoimmune diseases process (Brooks and Renaudineau, 2015).

Several other diseases like neuropsychiatric disorders, pediatric syndromes, mental retardation disorders also show a potential link with epigenetic modifications. The increased knowledge and techniques in Epigenetics allows us in better understanding the interplay between epigenetic change, gene regulation and human diseases, and will lead to the development of the new approaches for molecular diagnosis and clinical management.

Summary

Human genetics provides wider scope for biological anthropologists to understand the evolution of certain diseases and variation in the prevalence rates in population segments. Human genetics is the scientific study of inherited human variation. Hence there is a need for anthropologists to learn about human genetics to answer several questions which continues to be under investigation towards the human welfare. To understand the field of Human Genetics in to, we need to expose to various overlapping fields in human genetics like classical genetics, population genetics, cytogenetics, behavioral genetics, molecular genetics, biochemical genetics and Epigenetics. In all these specialties newer technologies has been developed and continue to be under investigation to provide more and more sophisticated tools with which we can understand evolutionary pattern of variation and disease occurrence in different population groups.