PRINCIPLES OF GENETICS
and
CLASSIFICATION OF INHERITED DISORDERS OF SKIN

By

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Genetics is a fundamental biological discipline essential for understanding of other biological sciences.

HISTORY

Hippocrates (460–370 B. C.) mentions heredity in one of his works "The sacred disease–epilepsy". Manu forbade consanguinous marriage (Manusmruti). Its scientific study stems from the experimental studies of Mendel (1822–1884). His work on hybridization of peas and his laws were published in 1866. The significance of chromosomes as carriers of genetic information was recognised in 1902. In 1912, Johansen introduced the term genes. In 1910 to 1920 T. H. Morgan established genetics as a science. Lederberg and Beadle were awarded the Nobel prize for their work on bacterial genetics in 1959.

DEFINITIONS

Genetics is the study of heredity and its variations.

Heredity is the phenomenon whereby characteristics of parents are transmitted to their offsprings.

All the disorders that are present at birth are not necessarily inherited e. g. congenital syphilis, birth traumas. Those disorders which are transmitted through genes may not be present or obvious at birth but may develop late in life.

High incidence of a disorder in a family may suggest a genetic transmission. This is not necessarily true e. g. food poisioning, measles, scabies are obviously not hereditary diseases. Also disorders with large psychic components e. g. hysteria, alopecia areata and neurodermatitis. Even allergic disorders like asthama, eczema, infantile eczema, hay fever etc. are thought to have a hereditary basis.

"Like begets like". This is only a half truth. Genetics is also much concerned with differences between children and parents. A particular generation may escape a disease which its former generation had and vice–versa. In chronic infectious diseases, it is the susceptibility to the infection that is inherited and not the infection itself.

Genetics is a statistical science based on the phenomenon of probability of inheritance of a trait. The question therefore often asked is "what are the chances of inheritance of a trait in a sibling". Study, therefore, of smaller families is misleading because it enlarges the gulf between the expected and the actual rates of inheritance of a given trait. It is the odds of inheritance of a trait that is explained by the physician to his patients while counselling, but whether to take a chance or not must depend on the patients.

Received for Publication on 4-10-68.

PHYSICAL BASIS OF HEREDITY

The nucleus of a cell contains twisted and intermingled fine threads known as chromosomes which consist of chromatin material. These determine the inheritance ocell. The chromosomes are rod-like organized structures. Along each chromosome units called 'genes' are arranged in a single linear order like beads on a string. The human body cell contains 46 chromosomes arranged in 23 pairs Their shape and size vary, and may exhibit charactereistic knobs, constriction and unique staining properties at particular sites. All these often help in identifying and studying particular chromosomes especially in attempting to co-relate certain inherited characteristics with certain chromosomes or regions in chromosomes. According to the *classical view*, the genes are the physical roots of heredity, and are responsible for the transmission of characteristics from one generation to another.

Each gene occupies a particular position on its chromosome and the site is termed the locus of the gene. Each gene is responsible for control of one trait only. A pair of genes which control the same trait e. g. the colour of iris, but gives contrasting effects e g. one of the pair responsible for blue and the other brown, the paired genes are called "Allels" or "Allelomorphs".

MODERN VIEW

Much finer units than genes have been recognized. Benzer has introduced the term cistron as a genetic unit of function and the term muton as the genetic unit of mutation.

MOLECULAR COMPOSITION OF GENES

Chemically, nucleus contains certain proteins called nucleo-proteins.

Nucleoproteins Nucleic acid, Protein.

Nucleic acid Sugar (Pentose) + Phosphate group
+ Base + Pyrimidine or Purine

If the pentose is ribose, the nucleic aid is called Ribo-nucleic acid (RNA). If the pentose is deoxyribose, the acid is called deoxyrebonucleic acid (DNA).

DNA. is largely found in the nucleus of the cell as part of the chromosomes. It is a primary carrier of genetic information. It is also regarded as the central controlling cellular substance which ultimately directs and regulates all activities of the cell primarily by directing synthesis of proteins. It gives positive Feulgen reaction.

RNA. These acids are combined with proteins, and occur largely in the cytoplasm but also to a lesser extent in the nucleus. It gives Feulgen reaction negative.

MUTATION

Any inherited change in a trait of an organism is termed mutation. It is due to some modification in the DNA substance itself. The genes mutate at different rates and cause a wide variety of disorders varying from very slight change in function to death of the cell. On an average genes may undergo atleast a million duplication

(i. e. in course of a million successive call generation) before undergoing a change. This ability of mutation of DNA is as equally important as its stability, because mutation is the basis of all natural variations which are heritable. It is the measure which allows living systems to evolve into new genetic types. It is also this process which is responsible for the tremendous diversity of living organisms found in nature. A sudden mutation is only rarely spontaneous and is commonly due to physical or chemical agents called mutagenic agents or mutagens. They are X Rays, U. V. Rays, high temperatures, ionising radiations. Among chemicals, mutagens are nitrogen mustard, antimetabolites (particularly used in cancer).

TYPES OF CHROMOSOMES

Of the 46 chromosomes, 22 pairs are alike in males and females and are called body chromosomes or autosomes. The remaining pair is different in different sexes and therefore the two are called sex chromosomes. Their knowledge is important in the study of determination of Sex. In the human female the sex chromosomes are identical and are called X-chromosomes. In the human male the two sex chromosomes are quite different, one called X-chromosome (similar to that of female) and the other called Y-chromosome (which is much smaller).

Homozygous. When the members of a pair of Allels are identical, the individual is called homozygous for that pair of genes and,

Heterozygous. When the members of the pair are different.

Genotype. Of an individual is his full set of genes but without expression of the disease, while,

Phenotype. Is the expression of the disease (the expression may be physical, biochemical or physiological).

MULTIPLE EFFECT OF GENES

The inherited trait may bring about only very mild abnormalities of a disease in some and total disease in others e.g. in Idopathic primary xanthomatosis some siblings may have only hypercholesteraemia other may have full clinical picture of xanthomas in skin and tendons, and still others may have atheromatous changes in blood vessals. "Abortive" attacks of disease celled "Forme Frustes" are its incomplete expression.

ENVIRONMENTAL FACTOR IN GENETIC DISEASE

Xeroderma pigmentosm, the most dreaded of all hereditary cutaneous diseases, is characterised by dry pigmented skin. However the most severe expression of the disease is multiple skin cancers, and these are brought about by exposure to sunlight. Thus haliosensitivity is the environmental factor precipitating severe forms of the disease.

SPECIFICITY OF CLINICAL SIGNS

The signs of hereditary diseases are not necessarily specific e.g, certain drugs may induce bullous allergic reactions which may closely mimic hereditary disease, Epidermolysis bullosa simplex.

Dominant Gene. When an allel of its pair always expresses its trait in the phenotype, the gene is known as Dominant genes. Thus whether the individual is homozygous or heterogygous the dominant gene is expressed.

Recessive Gene. Can express itself only when both the members of the pair are recessive i.e. in a homozygously recessive individual.

PATTERNS OF INHERITANCE

The pattern of inheritance of a trait or disease in siblings will depend on how the trait is linked. This pattern can be altered or obscured by various factors. The trait may be :—

(1) Autosomal linked:- i. e. the trait is linked on any one of the 22 autosomal pairs, or

(2) It may be sex-linked i. e. the trait linked on the 23rd pair which is the pair of sex chromosomes

MENDEL'S LAWS

(1) *Unit inheritance* There is no blending of characters of two parents in their off-springs but are inherited separately as units.

(2) *Segregation.* Two members of a single pair of genes are never found in the same gametes but always segregate and pass to different gametes.

(3) *Independent assortment.* Members of different pairs of genes assort to the gametes independently.

AUTOSOMAL INHERITANCE

(a) Simple Genetic Inheritance:—

Example:— (i) T = Dominant gene for ability to taste a substance.
t = inability to taste.
TT = Homozygously dominant (Homozygous tasters)
tt = Homozygous nontasters.
Tt = Heterozygous tasters.
i) TT x Tt

TT
∧
T T

Tt <		
T	TT	TT
t	Tt	Tt

Therefore, phenotypically 100% are tasters; Genotypically 50% are homozygous and 50% heterozygous.

Possible cominations of parents :—

TTxTT; TTxTt; TTxtt; TtxTT; Tt; Tt; Ttxtt; ttxTT; ttxTt; ttxTt; ttxtt.

Example-ii) Tt x tt
Therefore 50% tasters
50% nontasters.

Tt
∧
T t

t t <		
t	Tt	tt
t	Tt	tt

Thus diagnosis of Autosomal dominant inheritance may be summarized as follows:–

(1) The trait appears in every generation.
(2) The trait is transmitted by an affected person to half of his offsprings.
(3) Unaffected persons do not transmit the trait to their children.
(4) The occurence and transmission of the trait are not influenced by sex of the offsprings.
(5) Sufferers will transmit the disease and vice versa.

Counselling. Normal person in a family can marry safely. Abnormal persons should not marry. This will lead to ultimate eradication of the disease except that caused by mutation.

(b) *Autosmal Recessive Gene.*

Example. Aa x Aa

	Aa	
	A	a
A	AA	Aa
a	Aa	aa

AA = 25% will not suffer and will not transmit.
Aa = 50% will suffer and will transmit, and
aa = 25% will suffer and will transmit.

Thus one in four will suffer from the disease. Tracing of families with carriers is very difficult. Only families in which there is a case can be studied. Though the distribution of carriers in general population is 1 in 25, the carrier with rare genes runs in families. Therefore, there is concentration of carriers in families. Hence chances of this abnormality are much more if a carrier marries in related family than if he marries a person from general population.

Criteria for Autosomal Recessive inheritance:—

(1) The trait appears only in sibs not in their parents.
(2) One fourths of the sibs of the propositus (index-case) are affected.
(3) The parents of the affected child may be consanguinous.
(4) There is no sex bias in distribution of the disease.

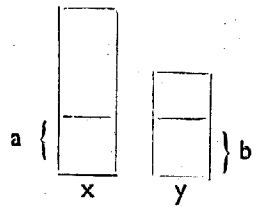
Penetrance. The term is used to designate the frequency with which a characteristic will appear in a population of individuals having that particular gene. When a gene is fully penetrant all the possessors will show signs of the abnormality but the degree to which the severity of signs will appear will vary e.g., Primary hypercholesterimic xanthomatosis.

Incomeplete or irregular dominance. Means incomplete penetrance e. g., neurofibromatosis.

Genetic Carrier is one who only transmits the hereditary disease without himself or herself suffering from the defect.

Thus the genetic carriers may be normal persons having genes with incomplete dominance or recessive genes.

Sex-Linked Inheritance. X = female chromosome; Y = male chromosome; XX = Female; XY = Male.



"a and b" are "Pairing segments" of X and Y and are equal. Extra segments on X and Y are "differential segments".

Genes on the differential segments cannot cross over and hence always have definite transmission. These genes are "completely" sex linked. When the trait is on pairing segment, *usually* the trait is more common in one sex than other However, there may *sometimes* be crossing over giving rise to defect in different sex than would be customary. Therefore this sex-linked chromosomal transfer is not complete but "partial".

Thus Sex-linkage may be partial or complete. Complete may have X-linkage (female) or Y-linkage (male).

Male Linkage. Here the abnormal gene is in the differential segment of Y chromosome and hence the affected individual are always males. Thus father passes on his defect to his sons, and the sons to their sons and so on. Female do not have Y chromosome; therefore, they neither suffer nor transmit the trait. Clinically, this pattern of inheritances is extremely rare in dermatology.

Female Linkage. The abnormal gene is on the differential segment of X-chromosome. It would be in females as well as males. The pattern will depend now on whether the X-linked chromosome is dominant or recessive. If dominant, X-linked trait:- and if the father be affected e.g. X_1 Y therefore,

$$X_1Y \times XX \rightarrow X_1Y \lessdot \begin{matrix} & XX \\ X & X_1X \mid X_1X \\ Y & XY \mid XY \end{matrix}$$

Thus the father transmits the trait to all his daughters. The sons neither suffer nor transmits the trait.

If the mother is affected, say, XX_1

$$XY \times XX_1 \rightarrow XY \lessdot \begin{matrix} & XX_1 \\ X & XX \mid XX_1 \\ Y & XY \mid X_1Y \end{matrix}$$

Thus half the number of sons and half the number of daughters suffer and transmit the trait.

If the female-linkage, and if the gene is recessive:-
e. g. xX

$$xX \times XY \longrightarrow XY$$

	X	Y
x	xX	xY
X	XX	XY

25% (XX) = normal daughters;
25% (XY) = normal sons;
25% (xX) = phenotypically normal daughters but genotypically abnormal and therefore able to transmit the trait.
25% (xY) = geno-and phenotypically abnormal sons. Example of the disease is haemophilia.

Bacterial Genetics. Its aspects are that study of bacterial genetics has systematized and developed human genetics and resistance of bacteria to certain drugs is heritable.

Chromosomal Anomalies. Their incidence is 3 to 5 per 1000 of live-births and they are a significant cause of physical and mental defects. There may be abnormality of number of chromosomes or structure of chromosomes.

Numerical abnormality. e. g. 47 instead of 46 chromosomes in Mongolism.

Structural changes in a chromosome could be either deletion of a portion of chromosome, or presence of extra piece of chromosome or a section of a chromosome may be inverted. In translocation, there is transfer of the material from one chromosome to a non-homologous chromosome.

Causes of Chr. Aberrations are not definitely known. Late maternal age (for Mongolism), autoimmune disease, ionizing radiation, viruses are some of the causes. Twenty percent of abortions occuring spontaneously in the first trimester of pregnancy are caused by chr. aberrations.

Biochemical Genetics. This area deals with aspects of biochemical nature of the genetic material itself, and with inherited biochemical disorders.

Pharmacogenetics. It is a branch of Biochemical genetics concerned with the study of the inherited nature of variations of human beings in their response to drugs.

Immunogenetics. It is that area of genetics which deals with genetically determined antigens and serum proteins. Of importance are antigenic substances on blood and tissue cells. There are three aspects of immunogenetics:-

1. Detection of blood groups and problems of blood group incompatibilities.
2. Tissue transplantation and
3. Autoimmune disease.

USES OF GENETICS

I. Genetics in clinical Practice. A positive family history helps in diagnosis of genetic conditions and also in understanding true nature of disease. It also helps in early diagnosis in siblings.

II. Helpful in transfusions, transplantations.

III. Forensic Medicine. In case of disputed paternity, it is always possible to say when a person is not the father of a child. However when he is indeed the father, it is possible to determine the paternity with great probability but not with absolute certainty. This evidence is acceptable in the court of law. This is possible by study of blood groups and serum and serum proteins of genetic origin of the child and parents. Similarily the problem of rare cases of children being inter-changed in a nursery may be solved by similar aid.

IV. Genetics in Pubilc Health. Genetic is useful in the overall health problems of a community. Health programme must be planned to meet the needs of a genetically diverse population especially because many of genetically caused conditions are amenable to treatment, and many such conditions place a load on the public health services of the community.

Genetics can be useful in Public Health in control of mutagens and in organising curative and preventive medical services.

GENETIC COUNSELLING

(1) Marriage counselling: whether a prospective baby will develop a heritable disease.
(2) If the parents have already an abnormal child whether a later born child will have the disease.
(3) The onset age of the illness i.e. whether it will be present at birth, during early childhood, or late in life.
(4) Rh. incompatihility.
(5) Determination of paternity.
(6) Carrier detection.
(7) History of chromosomal aberration as for example in families with unusually high rates of still births or abortions, infertility, cancer especially leukemia, mental retardation, and hence the advice for family restriction.
(8) Drug sensitivity of genetic origin, e.g. INH slow inactivator in a family. Patients with porphyria should not be given barbiturates or sulphonamides.

SOME INFORMATION

(1) A part from Monozygotic twins, no two persons are identically similar.
(2) Virtues are heritable.
(3) Age is no bar for transmission of a trait.
(4) No genetical difference between legitimate and illegitimate chilldren initially.
(5) Not all characters are rigidly determined by heredity.

(6) A character determined by heredity can be influenced and modified by environmental factors.

(7) Conversly, even if causative agent for a disease is known genetics can still play a role in determining susceptibility (chronic infections)

(8) A condition can be hereditary even in absence of a positive family history.

EUGENICS

The term Eugenics covers all aspects of the improvement of the human race by selective breeding and prevention of reproduction by the unfit. The idea of Eugenics though laudable theoretically, presents many practical difficulties. Some countries have Eugenic sterilisation laws especially for the mentally retarded and the psychotic. The philosophical argument concerning pros and cons of Eugenics will continue for many years.

Classification of genetically determined disorders of skin:—

I. Autosomal Dominant Abnormalities:—

(A) Complete dominance:—

Neurofibromatosis (Penetrance variable)
Piebaldness (sometimes incomplete dominance or even recessive; sometimes by mutation)
White forelock (rarely male-linkage or sex-linked recessive)
Freckles (pigment trait combined with red hair trait)
Hereditary haemorrhagic telangectasia.
Encephalotrigeminal angiomatosis.
Benign familial pemphigus (irreguiar dominance)
Epidermolysis bullosa simplex.
Recurrent bullous eruptions of feet.
Darier's disease.
Ichthyosis vulgaris
Keratosis palmaris et plantaris
Porokeratosis (more in males)
Primary hypercholesterimic xanthomatosis
Pachyonychia congentiale (? two dominant genes)
Premature grayness of hairs.
Trichoepithelioma
Keloids (? dominant)
Monilethrix (formerly regarded as Incomplete Dominant)
Allergic predisposition (? Inherited).

(B) Incomplete Dominance:—

Epiloia, Albinoidism, Milroy's disease, Pilitorti
Pili annulati, Keratinous cysts.
Tuberous sclerosis.
Pityriasis rubra pilaris

II. Antossmal Recessive Abnormalities.

Complete Albinism, Ochronosis, Congenital porphyria, Pseudoxanthoma elasiticum, Dystrophic epidermolysis bullosa, Lipoid Proteinosis, Xeroderma pigmentosum, Congenital ichthyosis, Congenital ichthyosiform erythrodermia, Werner's syndrome, Rothmund–Thomson's Syndrome, Niemann–Pick's disease (Formerly regarded Dominant) Gaucher's disease (-do-)

III. Sex-Linked Abnormalities:—

Completely sex–linked:—

(a) Male (Y)–linked–rare; example–Bizare forms of congenital ichthyosis.

(b) Female (X)–linked–

(i) Dominant–No dermatological disease.

(ii) Recessive—Anhydrotic ectodermal displasia.
Ichthyosis vulgaris (Sometimes) Incomplete albinism and Rare variants of Darier's disease and Dystrophic epidermolysis bullosa.

ACKNOWLEDGEMENTS

I am deeply indebted to the authors and publishers of the books listed in references, which have made this revision article possible.

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