Section B and C

Volume-15

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8. INHERITANCE BIOLOGY

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G. HUMAN GENETICS

Pedigree Analysis

The study of human genetics is complicated because controlled mating of humans are not possible for ethical reasons. The inheritance patterns of human traits usually are identified by examining the way the trait occurs in the family trees of individuals who clearly exhibit the trait. Such a study of a family tree, called pedigree analysis, involves carefully assembling phenotypic records of the family over several generations. The affected individual through whom the pedigree is discovered is called the *proband.*

Pedigree analysis has its own set of symbols; figure 1, summarizes the basic symbols used here and elsewhere in the text, figure 2, present a hypothetical pedigree to show how the symbols are assigned to the family tree.

The trait presented in figure 2, is determined by a recessive mutant allele *a*. Generations are numbered with Roman numerals, and individuals are numbered with Arabic numeral; this make it easy to refer to particular people in the pedigree. The trait in this pedigree results from homozygosity for the allele, in this case resulting from cousins mating. Since cousins share a fair proportion of their offspring; in this case, one mutant recessive allele become homozygous and resulted in an identifiable trait.

Gene symbols are included in this pedigree to show the deductive reasoning possible with such analysis. The trait appears first in generation IV. Since neither parent had the trait, but they produced two children with the trait (IV-2 and IV-4), simplest hypothesis is that the trait is caused by a recessive allele.

Thus, IV-2 and IV-4 would both have the genotype aa, and their parent (III-5 and III-6) must have the genotype Aa. All other individuals who did not have the trait must have at least one A allele; that is, they must be A (either AA or Aa). Because III-5 and III-6 are both heterozygotes, at least one of each of their parent must have carried an a allele.

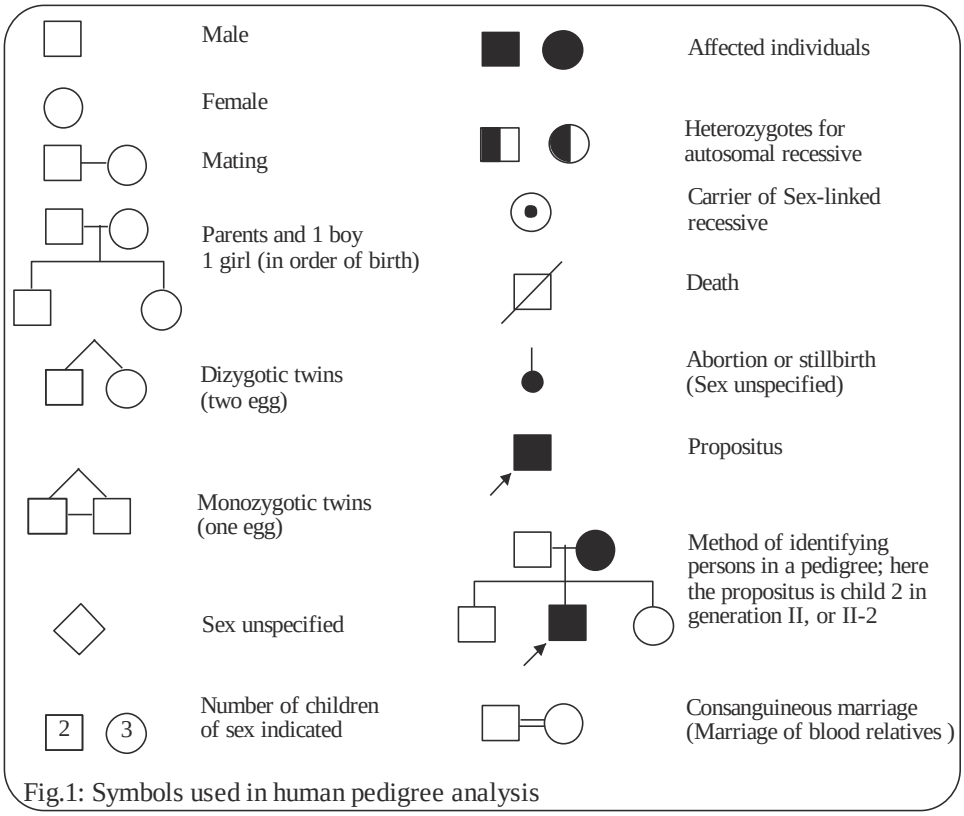

Fig.1: Symbols used in human pedigree analysis

Furthermore, because the trait appeared only after cousins had children; the simplest assumption is that a allele was inherited from individuals with bloodlines shared by III-5 and III-6. This means that II-2 and II-4 probably are both Aa and that one of I-1 and I-2 is Aa (perhaps both unless the allele is rare).

EXAMPLE OF HUMAN GENETIC TRAITS

Recessive Traits: A large number of human traits are known to be caused by homozygosity for mutant allele that is recessive to the normal allele. Such recessive mutant allele produces mutant phenotypes because of a loss of function or modified function of the gene product resulting from the mutation involved.

Many serious abnormalities or diseases result from homozygosity for recessive mutant allele. Two individuals expressing the recessive trait, individual with albinism do not produce the pigment melanin, which protect the skin from harmful ultraviolet radiation. As a consequence, their skin and eyes are very sensitive to sunlight.

Frequencies of harmful recessive mutant alleles usually are higher than frequencies of harmful dominant mutant alleles because heterozygotes for the recessive mutant allele not at a significant selective disadvantages. Nonetheless, individuals homozygous for recessive mutant allele usually are rare. In the United State approximately 1 in 17,000 of the white population and

1 in 28,000 of the African- American population have albinism. Among the Irish about 1 in 10,000 have albinism.

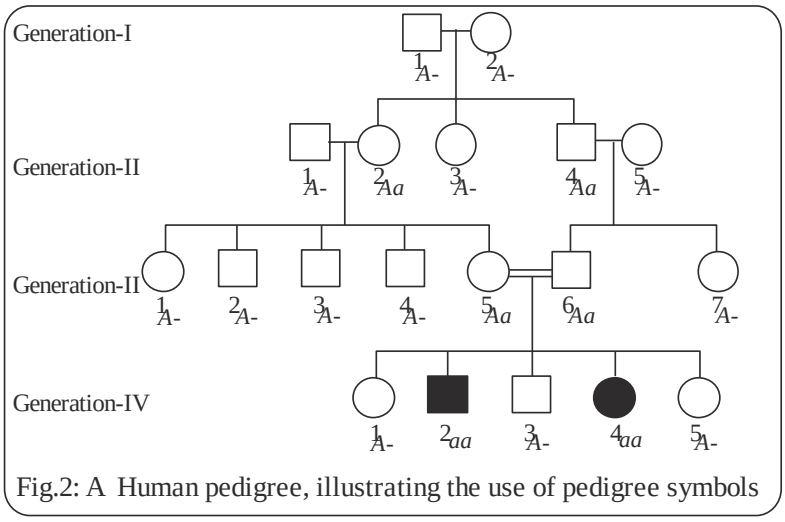

Fig.2: A Human pedigree, illustrating the use of pedigree symbols

The following are some general characteristics of recessive inheritance for a rare trait:

(i) Most affected individuals have two normal parents, both of whom are heterozygous. The trait appears in the F_1 because a quarter of the progeny are expected to be homozygous for the recessive allele. If the trait is rare an individual expressing the trait is likely to mate with a homozygous normal individual. The next generation from such a mating would be heterozygote who does next express the trait. In other words, recessive traits often skip generations. In the pedigree in figure, for example, II-6 and II-7 must both be aa, and this means both parents (I-3 andI-4) must be Aa heterozygotes. I-1 is also aa, so II-4 must be Aa. Since II-4 and II-5 produce some aa children, II-5 also must be Aa.

(ii) Mating between two normal heterozygotes should produce an approximately 3:1 ratio of normal progeny exhibiting the recessive trait. However, in the analysis of human populations, it is difficult to obtain a large enough sample to make the data statistically significant.

(iii) When both parent are affected they are homozygous for the recessive trait, all their progeny usually exhibit the trait.

Dominant Trait: There are many known dominant human traits. Dominant mutant allele may produce mutant phenotypes because of a gain of function of the gene product resulting from the mutation involved. In other words, the dominant mutant phenotype is a new property of the mutant gene rather than a decrease in its normal activity. Figure 2, illustrates one such trait, called wooly hair, in which an individual's hair is very tightly kinked, is very brittle and breaks before it can grow very long. The best example of pedigrees for this trait comes from Norwegain

families; one of these pedigrees is presented in figure 2. Since it is a fairly rare trait and since not all children of an affected parent show the trait, most wooly-haired individuals probably are heterozygous for the dominant allele involved rather than homozygous.

Dominant mutant alleles are expressed in a heterozygote when they are in combination with what is usually called the wild-type allele, the allele that predominates in the population found in the "wild". Since many dominant mutant alleles that give rise to recognizable traits are rare, it is extremely unusual to find individuals homozygous for the dominant allele. An affected person in a pedigree is likely to be a heterozygote, and most pairings that involve the mutant allele are between a heterozygote and a homozygous recessive (wild type). Most dominant mutant genes that are clinically significant fall into this category.

The following are some general characteristics of dominant inheritance for a rare trait:

(i) Every affected person in the pedigree must have at least one affected parent.

(ii) The trait usually does not skip generations.

(iii) On average, an affected heterozygous individual will transmit the mutant gene to half of his or her progeny.

If the dominant mutant allele is designed A and its wild type allele is a, then most crosses will be Aa x aa. From basic Mendelian principles, half the progeny will be aa (wild type) and the other half will be Aa and show the trait.

KARYOTYPE

Chromosomes can simply be described as the carriers of heredity units *i.e.* genes. They are the vehicles which facilitate reproduction and maintenance of a species. Their behavior at the somatic cell division in mitosis and during gamete formation in meiosis provides answers to a number of questions about genetics. Therefore, the study of chromosomes has a prime importance in the study of genetics. This study of chromosomes is called *cytogenetics*.

A karyotype is the chromosomal constitution of an individual. It can be defined as the photomicrograph of an individual's chromosomes, arranged in a standard manner. This photomicrograph is generally of the metaphase stage; when the chromosomes are maximally condensed and therefore easy to see and study.

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