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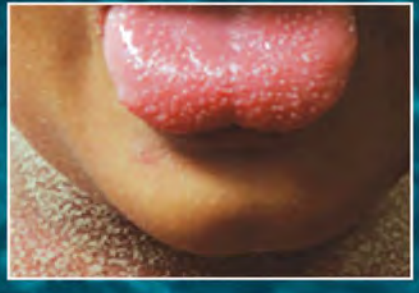

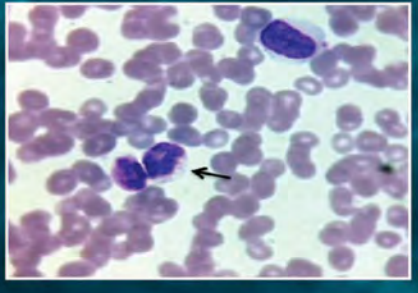

Foreword
Howard I Maibach

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2 SECTION

Skin and Genetics

2 CHAPTER

Principles of Genetics

Priya Bishnoi, Ravi Hiremagalore

INTRODUCTION

Understanding of genetic disorders is incomplete without the basic understanding of human genetics. Each cell in human body has a nucleus which contains the essential information in the form of genes, which is required for the normal functioning of cells. Genes are made up of DNA, which are made up of a unique sequence of bases. All the information in DNA is transcribed into mRNA which later gets translated into proteins. Chromosomes are linear structures in the nucleus which are made up of genes. Every cell has diploid number of chromosomes that is two pairs of 23 chromosomes each (44 autosomes and two sex chromosomes). The reproductive cells in an individual undergo cell division (meiosis) and from male and female gametes which fuse together to give rise to the offspring. Every gene exists in two or more forms known as alleles and thus individuals can have the same alleles *(homozygous)* for a particular character or they can have two different alleles *(heterozygous)*. If only a single allele is required for expression of a particular character, then this allele is the dominant allele and if two similar alleles are required, then this allele is the recessive allele for that character.

GENETIC DISORDERS

Genetic disorders can be either inherited from one generation to the other or they can occur *de novo* due to mutations. Inherited genetic diseases can be due to single gene defects, multiple gene defects, or can even be due to chromosomal anomalies. These disorders can be classified according to the type of inheritance:

- Autosomal dominant—affected individuals are heterozygous for the defective allele and both males and females are affected
- Autosomal recessive—both males and females are affected and affected individuals are homozygous for the defect
- X-linked recessive—defect lies on X chromosome and thus only males are affected and females are always carriers
- X-linked dominant—defective allele is present on X chromosome and this allele is dominant. Both males and females can be affected but in males the mutation is lethal and hence only females are seen with this group of disorders.

Mutation is an irreversible change anywhere along the DNA sequence which causes defective flow of genetic information. If a mutation occurs in the reproductive cells, it is known as *germ line mutation* and can be passed on to the next generation. Germ line mutations again can be heterozygous, homozygous, or even compound heterozygous (both alleles are mutated but with a different mutation in both the paternal and maternal alleles). If the mutation occurs in somatic cells, it is known as somatic mutation and is not passed on further. Mutations can be of many different types:

- Point mutation occurs if a single base in the sequence is replaced by another base. The consequence of a point mutation depends on the type of point mutation and it need not always be disastrous. Types of point mutation are as follows:
  - *Nonsense mutation:* When the mutation results in a codon which does not translate into a functional protein
  - *Missense mutation:* When mutation results in a stop codon and results into truncation of protein
  - *Silent mutation:* Mutation does not lead to any abnormality, either because the mutation is in the noncoding area or the base mutated does not cause any alteration in the amino acid
  - *Neutral mutation:* Due to the mutation the amino acid formed is different but chemically similar to the original amino acid.
- *Insertions*: Insertion of a base would cause either alteration in splicing of mRNA (splice mutation) or shift in the reading frame (frame-shift mutation)
- *Deletions*: It is due to removal of a base from the sequence and thus could lead to a shift in the reading frame.

FEW TERMINOLOGIES IN GENETICS

- *Genetic heterogeneity:* When diseases with very similar phenotypes are a result of various different alleles, e.g., ichthyosis, epidermolysis bullosa, psoriasis
- *Pleiotropy:* Single defective gene is responsible for multiple phenotypic expressions in a single disease. This could be because the gene could code for a product which is required by various different types of cells for their function, e.g., albinism
- *Genomic imprinting:* This is a very rare phenomenon where inheritance does not follow the Mendelian laws and is rather dependent on the parent of origin. Only one of the genes would be expressed depending on the paternity, e.g., Angelman syndrome, Prader-Willi syndrome

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- *Uniparental disomy:* When a person receives two copies of chromosomes from the same parent, due to any error in meiosis.

CUTANEOUS MOSAICISM

Mosaicism refers to the presence of two or more genetically different populations of cells originating from one genetically homogeneous zygote.

How to Recognize Mosaicism of Skin

Mosaicism is usually present in different shapes and patterns. They typically follow lines of Blaschko or may have flag-like patterns with a sharp superior and inferior border and midline separation. Other patterns include checkerboard, phylloid, block type, zosteriform or dermatomal and garment-like. Figs 1 to 4 shows the various patterns of hypopigmented patterns of mosiacism. Figs 5 to 7 shows the hyperpigmented patterns. Archetypal patterns are more likely to have extracutaneous involvement than nonarchetypal patterns. Another example of cutaneous mosaicism is incontinentia pigmenti as shown in Figs 8 to 10.

GENETIC MECHANISM

Mosaicism can be due to:

- *Genetic*: Mutations occur during embryonic development
- *Epigenetic*: This happens due to modifications in gene expression.



FIG. 3: Flaglike pattern with sharp midline cut-off.



FIG. 1: A large nevus depigmentosus.

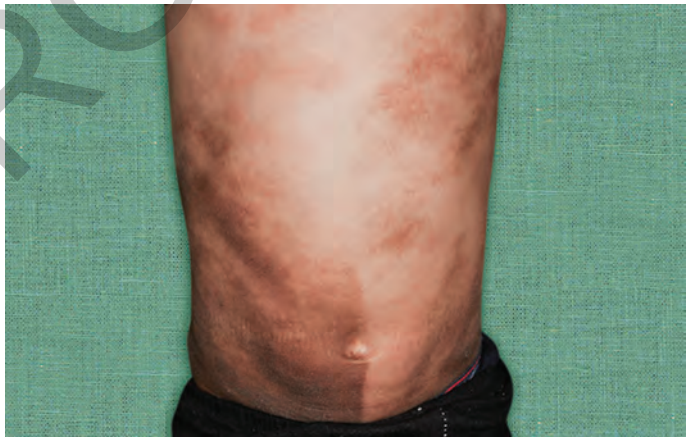

FIG. 4: Block like patterns seen on the anterior chest and abdomen.

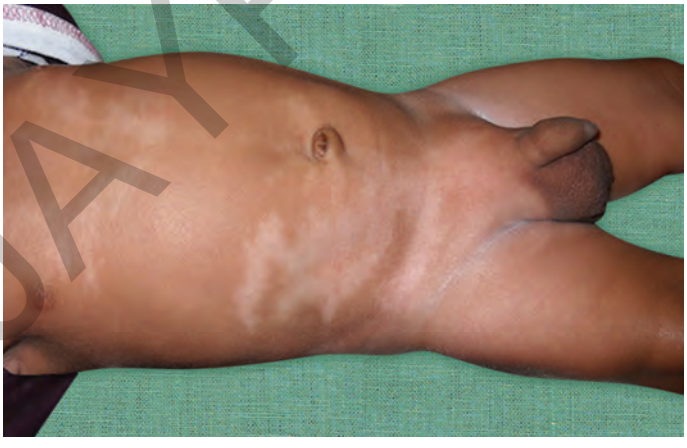

FIG. 2: Phylloid pattern of pigment mosaicism.



FIG. 5: Blaschkoid pattern on the back.

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FIG. 6: Hyperpigmented variant in a zosteriform distribution.



FIG. 9: Incontinentia pigmenti in papular stage showing some vesicles and hyperpigmentation.



FIG. 7: Hyperpigmented variant in blaschkoid distribution.



FIG. 10: Final stage of incontinentia pigmenti showing whorled pattern of hyperpigmentation.



FIG. 8: Incontinentia pigmenti in the vesicular stage.

Genetic (Somatic) Mosaicism

Mutational event occurs in the embryo stage. Lethal autosomal mutations can survive secondary to mosaicism. Keratinocyte epidermal nevus syndrome is an example of this type of mosaicism. Likewise, lethal autosomal recessive mutations appear in a normal carrier heterozygous individual due to mosaicism. This can be secondary to loss of heterozygosity resulting from a second mutation or a loss of normal allele during embryo development.

Nonlethal autosomal dominant mosaicism can be of two types:

1. *Type 1:* This is usually a postzygotic new mutation and can have a generalized counterpart. A parent with a linear epidermal nevus of the epidermolytic hyperkeratosis type, can have a child with bullous ichthyosiform erythroderma due to mosaicism
2. *Type 2:* A heterozygous embryo with a generalized disease can have an areas of skin far more severely affected. This is due to loss of heterozygoisity.

Mosaicism can be seen in polygenic inflammatory disorders secondary to loss of heterozygosity during the development of embryo. The common disorders with this pattern include psoriasis, lichen planus and vitiligo.

PROGRESS IN MOLECULAR GENETICS

With the techniques of polymerase chain reaction (PCR) and sequencing, it has been possible to identify the genes that are mutated in more than 350 genodermatosis. Developments in molecular analyses have enabled genotype-phenotype correlation. This has helped in understanding the pattern of inheritance. For example, previously it was difficult to determine

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if a child with moderately severe blistering and scarring, born to unaffected parents was due to sporadic autosomal dominant inheritance or an autosomal recessive trait.

DNA-based Prenatal Diagnosis

The major immediate benefit of advances in molecular analysis is prenatal diagnosis to couples in whom there is an increased risk of recurrence of a particular genodermatosis. This is accomplished by obtaining fetal DNA from chorionic villus sampling (CVS) between 10 and 12 weeks of gestation. The first step involved in DNA based prenatal diagnosis is to identify the pathogenic mutation in the proband. This is accomplished by direct sequencing the target gene which is a very laborious process. In the case of large genes like collagen VII A 1 (Col 7A1), it is preferable to have an algorithm for testing by screening for the hot spots first and then proceed to whole gene sequencing if no known mutations are identified. This is followed by sequencing the parents DNA for this specific mutation. This strategy establishes the pattern of inheritance which thereby helps in counseling. Finally, the fetal DNA taken from CVS would be tested for the mutation and parents are again counseled regarding the possibilities and thus a rationalized decision can be taken. The most common skin disorder for which a DNA based prenatal testing has been established is Hallopeau-Siemens recessive dystrophic epidermolysis bullosa (EB) and Herlitz junctional EB. In the conditions where there is considerable genetic heterogeneity, like junctional EB and lamellar ichthyosis, it is pertinent that the mutation is accurately identified in the proband. This problem can be approached by recent advances in techniques like Next-gen sequencing and exome sequencing. This involves screening the entire genome or exome which generates enormous data that require training in bioinformatics to interpret accurately.

Ethical Issues in Prenatal Diagnosis

The development of DNA based prenatal testing has raised several ethical issues. With the advances in molecular genetics, it is not only possible to do DNA-based prenatal testing for severe phenotypes of certain genodermatosis but also in milder forms, which is considered unjustified by some health care personnel. On the contrary, society perceive that every couple at risk have the right to know the options available and hence the right to prenatal diagnosis with termination of an affected pregnancy. Such decisions are often complex and very personal and may vary with the region and religion.

Gene Therapy

Advances in molecular genetics have been responsible for the initiation of research in gene therapy. Classically, EB has been the most common genodermatoses where gene therapy has been studied. There are two approaches.

1. *Ex vivo:* In this strategy, cells are harvested from the patient and they are propagated in a vector and gene corrected and cells are expanded in a culture and finally transplanted back to the patient. This approach has been tried in junctional EB. The major limitation is carcinogenesis
2. *In vivo*: This approach involves topical application or injection of gene therapy compound into the skin.

CONCLUSION

Genodermatoses form a major part referral to pediatric dermatology services. Hence understanding of some of the basic terminologies in genetics is imperative. Cutaneous mosaicism is common and awareness amongst dermatologists is necessary for early diagnosis and alleviate patient anxiety and to avoid unnecessary use of topical medications. Advances in molecular genetics have enabled DNA-based prenatal diagnosis and evidence-based genetic counseling.

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