Review Article

Basic genetics for dermatologists

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ABSTRACT

During the past few decades, advances in the field of molecular genetics have enriched us in understanding the pathogenesis of diseases, their identification, and appropriate therapeutic interventions. In the last 20 years, genetic basis of more than 350 monogenic skin diseases have been elucidated and is counting. The widespread use of molecular genetics as a tool in diagnosis is not practiced routinely due to genetic heterogenicity, limited access and low sensitivity. In this review, we have presented the very basics of genetics so as to enable dermatologists to have working understanding of medical genetics.

Keywords: Definitions, Medical genetics, Mosaicism, Mendelian inheritance, Polygenetic inheritance

"I see a bright future for genetics in dermatology and for dermatology in genetics….."

- Victor A McKusick

INTRODUCTION

Since the basics of human evolution have been understood, man has been curious to know how heredity works. This stimulated many advances in this field which has helped us to comprehend the basic genetics of several inherited skin disorders. In this aggrandize era of robust genomic sequencing, it has become important for the clinicians to understand the basics of genetics so as link basic sciences to clinical medicine.

Chromosomes, the basic structural units of inheritance, occur in pairs (23 pairs) in normal human individuals. Genes carried on the chromosomes are the functional units of trait or character. Genes determine the biological character of a person, an individual gene normally appears on each member of a pair of chromosomes. At a given loci, the pair of genes may or may not be identical but are complementary to each other. They are called alleles.

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HISTORY

Before Gregor Johan Mendel, (honored as the 'Father of genetics'), a number of theories had been proposed for the mechanism of inheritance but none stood the test of time. His simple experiments on pea plants revolutionized the concept of genetics. He proposed three principles:[1]

- First principle: The law of segregation- The allelic genes in zygote do not blend or contaminate each other but segregate and pass into different gametes.
- Second principle: The law of independent assortment- During meiosis, one of the chromosomes in the pair contributes independently to the gamete without being influenced by other chromosomes or cytoplasmic factors.
- Third principle: Law of dominance- It emphasizes that two alleles of a particular gene may not be identical and may impart different characters to a particular trait.

Although this pattern of inheritance could be observed for only a few traits, Mendel's work suggested that

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heredity was particulate, not acquired, and that the inheritance patterns of many traits could be explained through simple rules and ratios. William Bateson, a proponent of Mendel's work, coined the word 'genetics' in 1905 (adjective genetic, derived from the Greek word *genesis*). Although genetics plays a vital role in the appearance and behavior of organisms, it is the combination of genetics with how an organism interacts with nature that determines the ultimate outcome. For example, genes play a role in determining an organism's size but the nutrition, environment and health it experiences also have a profound effect on the appearance and behavior of the organism.

MEDICAL GENETICS

Medical genetics is the subspecialty of medicine that involves the diagnosis and management of hereditary disorders. Medical genetics differs from human genetics: human genetics is a field of scientific research that may or may not apply to medicine, but medical genetics refers to the application of genetics to medical care. Medical genetics encompasses different areas; including clinical practice of physicians, genetic counselors, and nutritionists, clinical diagnostic laboratory activities, and research into the causes and inheritance of genetic disorders.

DEFINITIONS IN GENETICS

Genotype: This is the internally coded, inheritable information or the basic genetic constitution that a person receives from their parents.[1] Thus it is the blue print of the structure and function for an individual. It remains constant from birth to death.

Phenotype: It is the appearance or performance of an organism as a result of genotype interaction with the given environment.[1] Phenotype changes with place, age, food etc. It is temporary and not transmitted to the next generation.

Proband: it is one of several terms used to indicate the first member of a family who comes in contact with the doctor or researcher in a study.

Heterozygote: Individuals who carry two different alleles at the same genetic locus are called heterozygotes, e.g. 'Aa.'

Homozygote: Those individuals who carry identical pairs of alleles like 'AA; and 'aa' are called homozygotes.

Gene interaction: A situation wherein one gene influences the expression of another gene controlling a similar character is known as gene interaction. A classic example of gene interaction was demonstrated by Batson and Punnett in fowl.[2] They studied two varieties of fowls, one with 'Rose' comb and the other with 'Pea' comb. The cross between them gave rise to a new strain called the 'Walnut' comb in F1 (first filial generation). Intercross between F1 generation yielded lineage in proportion of 9/16 Walnut, 3/16 rose, 3/16 pea and 1/16 single type of comb.

Mutations: A mutation is defined as any permanent change in a DNA sequence that makes up a gene, which may range in size from a single DNA to a large section of a chromosome.[3] Mutations can lead to various genetic disorders or disease. Most mutations are recognized by the change in phenotype (change in characteristics displayed by an organism). There are different types of mutations, which can occur in the form of chromosomal mutations or they may be the result of a single base pair change in the DNA sequence. Mutations can occur within a gene thus preventing the synthesis of actual protein or they may occur at gene promoter areas thus changing the interpretation levels of the protein. Moreover, they can occur near the splice sites in introns causing disruption to the splicing process and hence production of an incorrect protein.

Mutations in gene manifest in two ways: they can be inherited from a parent or one can pick them up during a person's lifetime. Hereditary mutations or germline mutations are those in which mutations are passed from parent to the child. This mutation persists throughout an individual's life in virtually every cell of the body.[3]

Mutations occurring only in egg or sperm cell, or those which occur just after fertilization are termed de novo mutations. De novo mutations elucidate a genetic disorder wherein the affected child displays mutation in every cell, but there is absence of family history of the similar disorder.[3]

Acquired (or somatic) mutations appear in the DNA of individual cells any time during a person's life. The promoting factors include environmental factors such as ultraviolet radiation from sun and smoking, or a mistake made in DNA copies itself during cell division. Acquired mutations in somatic cells cannot be passed on to the next generation.[3]

MOSAICISM

Cutaneous mosaicism was first proven in a case of linear hyperpigmentation caused by trisomy 18 mosaic.[4] Rudolf postulated the new genetic concepts on mosaicism in skin.[5] For the physician the essential question is how to recognize a cutaneous mosaicism? A careful complete clinical examination is important for the diagnosis. The term mosaicism refers to the presence in an individual of 2 (or more) genetically distinct cell populations derived from the same homozygous zygote.[6] Best example for mosaicism is all mammalian females with karyotype 46,XX. They are functional mosaics as one of their X chromosomes is randomly inactivated during embryogenesis. The nomenclature used to describe mosaicism in skin remains puzzling for most clinicians who are familiar with genetics because the underlying mechanisms and significance of different patterns are not completely elucidated.[5]

- Genetic or epigenetic mosaicism as suggested by Christina[5]

Genetic mosaics result from post zygotic mutation that may occur in any cell and at any time involving chromosome or genes. However, to persist and be propagated, the mutation must target a proliferating self-renovating cell. If the postzygotic mutation affects an undifferentiated cell earlier during the development, it is transmitted to the deriving cells potentially evolving into various lineages and if germline cells are also affected then there is a risk of transferring the mutation to the next generation. In the epigenetic pattern (stable transmittable phenotype), lesions tend to follow the line of Blaschko, for example incontinentia pigmenti and CHILD syndrome.[5]

- Type 1 and Type 2 mosacism

Type 1 mosaicism

Autosomal dominant disorders of skin may present following the lines of embryological development of the ectoderm. In these cases, the surrounding skin is normal and molecular studies have shown that the causative mutation is confined to the affected ectodermal tissue.[7] For example, the first demonstration of clinical mosaicism in skin along Blaschko's lines correlates with keratinocyte genetic mosaicism involving keratin 10 gene localized to lesional skin in patients with a form of epidermal nevi which histologically shows epidermal lysis and marked stratum corneum thickening.[8] The molecular basis for somatic mosaicism in several other epidermal disorders which follow Blaschko's lines has been established, providing a further evidence that Blaschko's lines represent the prime pathways of ectodermal embryonic development.[9-13] Another example for the same is neurofibromatosis type 1.[14]

Type 2 mosaicism

An individual demonstrating skin lesions that follow a pattern similar to type 1 mosaicism, but the rest of the surrounding skin also shows a milder form of the disorder, is said to be having type 2 mosaicism. For example (a) patients with superficial actinic porokeratosis with streaks of thick linear porokeratosis;[15,16] (b)in those with tumor syndromes wherein large numbers of cutaneous tumors are confined to a segmental or linear distribution, (c) patients with Hailey-Hailey disease as reported by Poblete-Gutiérrez *et al* was characterized by segmental areas of severe crusting, oozing, and erythema in addition to the symmetrically distributed milder plaques of erythema and crusting.[17] In this patient, the loss of heterozygosity resulted from mutation and loss of the paternal allele. The localized genetic change from one normal allele and one abnormal allele gave the patient a double dose of the mutant gene in severely affected areas, leading to the patterned disease exacerbation along Blaschko's lines. They also demonstrated a loss of paternal allele with duplication in the mutated maternal allele, which could be due to postzygotic mitotic recombination.[7] This novel discovery on type 2 mosaicisms contributes to our understanding of gene mosaicism and the embryologic development of the ectoderm along the defined lines of Blaschko.

Keratinocyte mutations with an earlier time of onset during the postzygotic period are theorized to be associated with a lower risk of germline mutation, and more extensive skin involvement is thought to be associated with a higher risk of a germline mutation. In type 1 mosaicism, up to 50% of peripheral blood leukocytes may harbor the mutation; given the mesodermal origin of both blood cells and germline cells. One might speculate that a higher ratio of mutant to normal genomic DNA would be associated with a higher risk of germline involvement, but this possibility has not been assessed.

GENETIC HETEROGENECITY

It is attributed to settings in which exact clinical

phenotypes are associated with mutations in several genes. An example for this is lamellar ichthyosis which is a single disease entity that can be produced due to multiple mutations such as; mutations in keratinocyte transglutaminase (TGM1), ATP-binding cassette member A12 (ABCA12), cytochrome p450 protein CYP4F22. For a given genetic skin condition, mutations at a single loci are attributed in 84% of disorders whereas alterations at 2 or more genetic loci for single phenotypic expression are identified in 15% of disorders.[18]

CLINICAL HETEROGENICITY

It is defined by situations wherein mutations in a single gene loci results in a conglomerate of different phenotypes and thus diseases, for example, a mutation in connexin 26 or GJB2 (a single gene) causing Vohwinkel syndrome and keratitis-ichthyosis-deafness (KID) syndromes.[18]

PENETRANCE

It is defined as the proportion of individuals who carry a disease causing mutated gene and exhibit the clinical phenotype over a defined period. Some individuals may fail to exhibit the phenotype even though they carry the affected gene; this condition is termed as reduced penetrance or incomplete penetrance. Reduced penetrance often affects AD inherited disorders. It apparently results from a mixture of genetic, life style and environmental factors. This phenomenon poses a challenge even to the genetic experts at the time of counseling to predict the risk of passing the genetic condition. Common dermatological condition where reduced penetrance poses a problem is tuberous sclerosis.

MODES OF INHERITANCE

It is always good to be aware about the various modes of inheritance and transmission in a genetic disorder as it would aid us in the proper diagnosis and subsequently counseling of the family regarding the outcome of the disease and the risk of the subsequent siblings/progeny being affected. Inheriting a specific disease, condition, or trait depends on the type of chromosome affected (autosomal or sex chromosome), which may also depend on whether the trait is dominant or recessive. A mutation in a gene on one of the first 22 non-sex chromosomes can lead to an autosomal disorder.

AUTOSOMAL DOMINANT

Dominant inheritance means an abnormal gene from one parent is capable of causing disease, even though the matching gene from the other parent is normal. The abnormal gene "dominates" the pair of genes. If just one parent has a dominant gene defect, each child has a 50% chance of inheriting the disorder. For example, if four children are born to a couple and one parent has an abnormal gene for a dominant disease, statistically two children will inherit the abnormal gene and two children will not. Children who do not inherit the abnormal gene will not develop or pass on the disease [Figure 1]. If someone has an abnormal gene that is inherited in an autosomal dominant manner, then the parents should also be tested for the abnormal gene. The risk can be modified by the changes in environmental, mosaicism or age related penetrance.

Tuberous sclerosis (TS) and Neurofibromatosis (NF1) are common examples of AD inherited disorder. Often an affected individual is the first member of the family to manifest the condition which is the result of a denovo mutation in the affected individual.

In TS two thirds of the cases are secondary to denovo mutations. TS is caused by mutations in two tumor suppressor genes, hamartin (TSC1, 9q34)[19] and tuberin (TSC2, 16p13)[20] in which more than 300 different mutations have been identified till now.[21] Familial cases show approximately 50% linkages to TSC1 and TSC2. Sporadic cases are much more likely to have a mutation in TSC2 than TSC1 and the prevalence of mental retardation is more in carriers with TSC2 mutation.[21]

In NF 1, approximately half of the cases are inherited from an affected parent and the other arises from denovo mutations.[22] The bulk of the identified mutations are suggested to result in premature protein truncation. Molecular studies on neurofibromas and malignant peripheral nerve sheath tumors in NF1 patients have established a loss of heterozygosity which may account for the arbitrary appearance of clinical signs.[23]

AUTOSOMAL RECESSIVE

An autosomal recessive disorder means two copies of an abnormal gene (both genes in a pair must be defective) must be present to promote/cause the disease or trait. People with only one defective gene in the pair are considered carriers. However, they can pass the abnormal gene to their offspring.

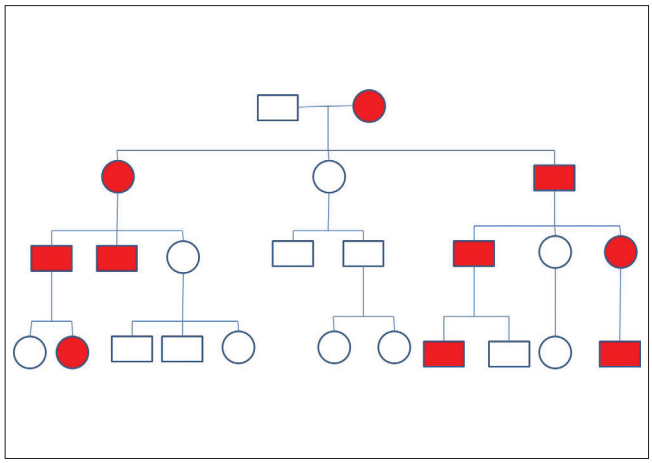

Figure 1: Prototype pedigree of an autosomal dominant disorder. Reds are affected while whites are normal

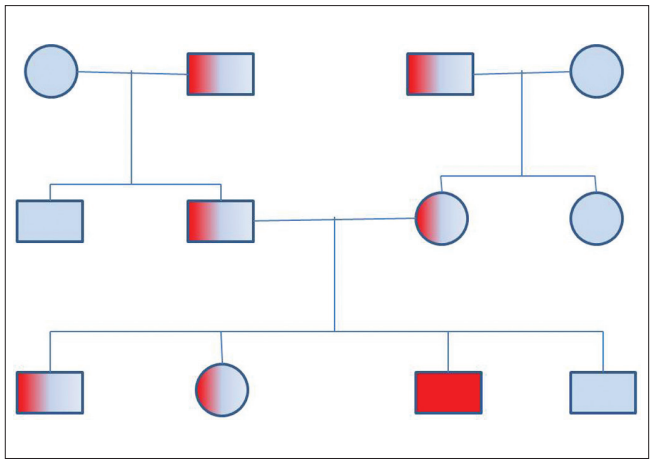

Figure 2: Prototype pedigree of an autosomal recessive disorder. Blues are unaffected, reds are affected, while others are carriers

If a baby is born to parents who both carry an autosomal recessive mutation, then the baby has 1 in 4 chances of getting the malfunctioning genes from both the parents and hence developing the disease [Figure 2]. If four children are born to parents who both carry the gene without the signs of the disease the statistical expectation is as follows:

- One child is born with two normal genes (normal)
- Two children are born with one normal and one abnormal gene (carriers, without disease)
- One child is born with two abnormal genes (at risk for the disease)

In the AR pedigree we see:

- Equal number of males and females are affected and the affected persons may or may not have a positive family history of the similar disorder.
- Parents will often be heterozygotes called carriers with about quarter of their children affected. The carriers are usually unaffected, but at times may show minor changes in the phenotype.
- If one parent is affected and the other a heterozygous carrier for the same gene, half of their children are affected, but if both the parents are affected and defective for the same gene then all children are affected.
- The risk of developing a trait can be altered by factors like environmental changes, mosaicism, mutations etc.

Albinism a well-known pigmentary disorder inherited in a recessive manner. The fact that it is hereditary condition may not be obvious if we look at someone born into a small family. On the contrary, when large families are screened and assessed, then chances of spotting someone with albinism increases. Carriers of albinism are usually unaware of their gene carrier status unless they come across a partner with the faulty gene and have children suffering from albinism. Other examples of AR cutaneous conditions are xeroderma pigmentosum, recessive dystrophic epidermolysis bullosa, Netherton's syndrome etc.

X LINKED INHERITANCE

X-linked inheritance is a pattern where the defective gene is located on the X chromosome. This faulty gene may be recessive or dominant. Changes in the genes on the X chromosome are commonly recessive. Females carry XX chromosomal type thus having an opportunity to subdue the expression of the defective recessive gene by the normal dominant gene. On contrary, males have XY type thus being unable to counter the defective expression. Consequently X linked diseases are more prevalent in men [Figure 3]. In X-linked dominant type of inheritance, if the mother alone is carrier of the mutated gene, she herself will manifest the disorder along with transmission of the affected gene to her off springs. This is because the expressions of genes on the X chromosome are influenced by epigenetics which involves switching off most of the X chromosomes in women. The chances that a child would inherit an X-linked recessive condition depend on whether the mother or father is affected and hence the rate of inheritance is different for sons and daughters.[24] If the mother is a carrier of the X linked faulty gene, 50% chances of her sons will be affected by the condition and 50% chance that her daughter will be a carrier. On the contrary when the father is affected then none of his sons will be affected because all sons will inherit the working X linked defective copy from

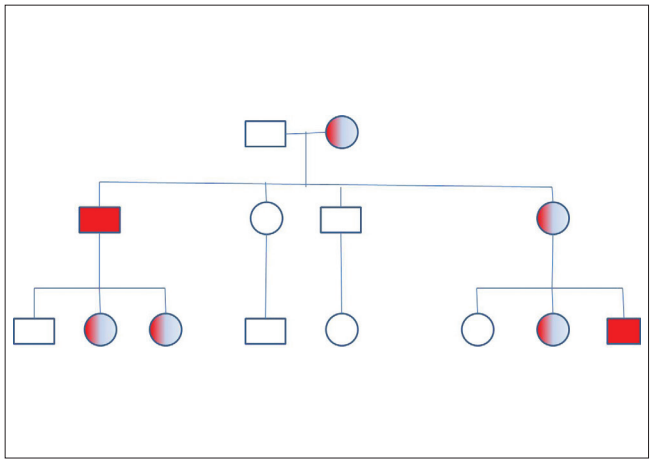

Figure 3: Prototype pedigree of an X- linked recessive disorder. Whites are unaffected, reds are affected, while others are carriers

their mother and all his daughters will become carriers but generally unaffected by the condition. Examples for X linked recessive condition are X linked recessive ichthyosis, dyskeratosis congenita, etc.

When the mother is affected by X linked dominant defective gene and father is healthy, the chances that both her sons and daughters will inherit the defective gene and manifest in every pregnancy is close to 50%. Examples of X linked dominant condition are X linked dominant ichthyosis, incontinentia pigmenti, etc. Some dermatological disorders with AR, AD and X-linked inheritance have been tabulated in Tables 1-3.

EPIGENETICS

It is the principle that regulates the phenotype variation in the absence of an underlying change in DNA. It is a stably transmittable phenotype resulting from changes in gene expression without any alterations in the DNA. DNA methylation is a major epigenetic modification of the genome that regulates crucial aspects of its function. Genomic methylation patterns in somatic differentiated cells are generally stable and heritable. However, in mammals there are at least two developmental periods in germ cells and in pre-implantation embryos, in which methylation patterns are reprogrammed genome wise, thus generating cells with a broad developmental potential.

Various epigenetic mechanisms have been described which includes histone modifications, cytosine modifications and non-protein coding RNA segments (ncRNA). Current data supports the fact that epigenetic aberrations contribute in pathogenesis of skin disease, autoimmune disease, malignancy, heart disease and metabolic diseases.

Table 1: Autosomal dominant disorders

Disease	Gene mutated
Neurofibromatosis	NF1/NF2
Tuberous sclerosis	TSC1/TSC2
Peutz–Jeghers Syndrome	STK11/LKB1
Gorlin syndrome	PTCH1
Muir–Torre syndrome	MLH1, MSH2, MSH6
Gardner syndrome	APC
Carney complex	PRKAR1A
Multiple mucosal neuroma syndrome (multiple endocrine neoplasia 2B, and 3)	RET protooncogene
Howel–Evans	TOC
Cowden syndrome	PTEN
Birt–Hogg–Dube/ Hornstein- Knickenberg syndrome	FLCN
Hereditary leiomyomatosis/ renal cell cancer syndrome	Fumarate hydratase
Melanoma/ pancreatic cancer syndrome	CDKN2A
Dyskeratosis congenita	TERC,TERT

Table 2: Autosomal recessive disorders

Disease	Gene mutated
Ataxia-telangiectasia syndrome	ATM
Xeroderma Pigmentosa	Nucleotide excision repair/ Post-replication repair
Bloom syndrome	RecQ2
Rothmund-Thomson syndrome	RecQ4
Werner syndrome	RecQ3
Fanconi anemia	FANCA, FANCC,FANCG
Chédiak–Higashi syndrome	LSYT
Griscelli syndrome	Myosin Va, Rab 27A, melanophilin
Dyskeratosis congenita	NOP10, NHP2, and TERT
Nijmegen breakage syndrome	NBS1
Seckel syndrome	SCKL1, ATR, SCKL2, SCKL3, Pericentrin

Table 3: X-linked recessive disorders

Disease	Gene mutated
Dyskeratosis congenita	DKC1
Wiskott-Aldrich	WASp

METHYLATION IN HUMAN DISEASE

Cytosine methylation is a big contributor to the generation of disease-causing germline mutations[25] and somatic mutations that cause cancer.[26] Recent work has shown that an abnormal methylation of the promoters of regulatory genes causes their silencing forming a substantial pathway to cancer development.[27,28]

Many conditions encountered in dermatology namely NF1, psoriasis, atopic eczema, hypomelanosis of Ito, vitiligo and systemic lupus erythematosus have been thought to occur secondary to the dysregulation of DNA methylation.[29] DNA methylation is a biochemical process in which a DNA base, usually cytosine, is enzymatically methylated at the 5-carbon position. DNA methylation is of paramount importance to biological health and disease, occurring more often at the region of promoter genes.[30] Many studies regarding tumorigenesis have shown that up to 50% of the genes are known to cause familial cancers which may undergo an epigenetic silencing in various forms of sporadic cancers. In a study of 56 patients with psoriasis, methylation of cytosine residue islands in p16INK4a gene was observed in basal keratinocytes of 17 patients.[31] This also correlated well with a higher psoriasis area severity index. Aberrant histone modification has been shown to contribute to the pathogenesis of melanoma and lupus erythematosus. The histone proteins are subjected to acetylation, methylation, phosphorylation and ubiquitination.

Earlier ideas that most DNA sequences are not the protein coding regions has been validated by the completion of the human genome project. More importantly, this non coding region does not simply represent junk DNA but a role for non-coding RNA in regulating normal and pathologic states has emerged. Non coding RNAs (ncRNA) are defined as functional RNA molecules that are not translated into protein, e.g. tRNA, rRNA, miRNA. Thousands of ncRNAs regulate up to 50% of all human genes.[32]

POLYGENIC INHERITANCE

At the start of twentieth century a single major question which cropped up in genetics was: If Mendel's ideas were true, how can we explain the inheritance of quantitative traits? Statistical research has suggested that for quantitative traits the child of a cross between two parents tends to appear as an intermediate of the two parents. For example, if one parent is tall and the other is short, the child tends to be intermediate in height; in other words the child in a cross seems to be a blend of both the parents.[33]

Polygenic inheritance, also known as quantitative or multifactorial inheritance is an inheritance of a phenotypic characteristic which is accountable to two or more genes, or interaction with the environment, or both. Unlike monogenic traits, polygenic traits do not follow patterns of Mendelian inheritance. Multiple gene inheritance explains the vast variation in plant and animal traits between extremes of phenotypes, with most individuals having an intermediate phenotype. Few examples of polygenic inheritance in humans are: human skin color, color of the eyes; height, weight and intelligence in general population.

Human skin color is a very good example for polygenic inheritance. If we take three "dominant" P, Q and R genes controlling dark pigmentation because of excessive melanin pigmentation and the "recessive" alleles p, q and r controlling the light pigmentation due to decreased production of melanin, then a genotype with all "dominant" genes "PPQQRR" has very dark skin due to the maximum amount of melanin and a genotype with all "recessive" genes 'ppqqrr' has very light skin due to lowest amount of melanin. Each "dominant" gene produces one unit of color, so that a wide range of intermediate skin colors are produced, depending on the number of "dominant" genes available in the genotype. Hence an individual with three "dominant" and three "recessive" genes "PpQqRr", would have an intermediate amount of melanin, [Table 4]. Few dermatological disorders where polygenetic inheritance plays a part are psoriasis (PSORS1-6) and vitiligo.

GENETIC POLYMORPHISM

Genetic polymorphism is a specific term which describes frequent variations at a given loci which is later transmitted in the population through evolutionary forces (natural selection or drift). Polymorphism is defined as genetic modifications occurring in more than 1% of the population. Ford proposed that genetic polymorphisms occur at a frequency too high to be accounted for mutation alone.[34] Its well known that only a minute amount (<5%) of the human genome codes for DNA. Most of the genetic polymorphisms tend to occur in the non-coding region of the human genome. Hence most mutations are harmless and

Table 4: Polygenetic inheritance exemplified by range of pigmentation

Phenotypes	Genotypes	Color of skin
Extremely dark	PPQQRR	6
Very dark	PpQQRR	5
Dark	PpQqRR	4
Intermediate	PpQqRr	3
Light	ppQqRr	2
Very light	ppqqRr	1
Extremely light	ppqqrr	0

apparently lost from the population within which it arises. Only a few polymorphisms directly lead to genetic disorders.

In practice genetic polymorphisms are beneficial as a marker loci for genetic mapping, hence an extremely valuable tool to locate and identify genes that are responsible for single locus disorders. Another important application is its use in forensic medicine to determine identity and genetic relationships.

Population based studies have been used to investigate the functional significance of genetic polymorphisms. A particularly well known association is between HLA B 27 allele and ankylosing spondylitis wherein the data shows a convincing relation in upto 90% of the affected population. In dermatology, the common disorders where polymorphism plays a role are psoriasis vulgaris and ichthyosis vulgaris.

The association between susceptibility of psoriasis vulgaris (PV) and genetic polymorphisms in killer cell immunoglobulin like receptors was demonstrated by Suzuki *et al*.[35] They typed 14 KIR genes in 96 Japanese cases and 50 healthy controls using PCR with sequence-specific primers (PCR-SSP) and found that frequencies of KIR2DS1 and KIR2DL5 were significantly increased in PV cases compared with controls.

Kime *et al* studied genetic polymorphism of *FLG* in Korean ichthyosis vulgaris patients.[36] The analysis of base sequence revealed new nonsense mutation p.Y1767X in a Korean IV patient, and additional new single nucleotide polymorphisms.

Polymorphisms are responsible for many normal differences between people such as color of eyes, hair color, and blood groups. Although many polymorphisms have no negative effects on a person's health, some of these variations may influence the risk of developing certain disorders; for example, red hair is one of the risk factors for basal cell carcinoma. Failure to repair all mutations has led to the introduction of some mutations that have made organisms fitter and better able to adapt to their environments. Many mutations have detrimental effects on organisms and it is these mutations that are the basis for many human genetic disorders and diseases.

SINGLE NUCLEOTIDE POLYMORPHISM

Single nucleotide polymorphism, or SNP (pronounced as "snip"), is a small genetic change, or variation, which can occur within an individual's DNA sequence. The genetic code is specified by the four nucleotide "letters" A (adenine), C (cytosine), T (thymine), and G (guanine). SNP variation occurs when a single nucleotide, such as an A, replaces one of the other three nucleotide letters—C, G, or T.[37]

An example of a SNP is the alteration of the DNA segment AAGATTA to AGGATTA, where the second "A" in the first snippet is replaced with a "G". On an average, SNPs occur in more than 1 percent human population at a given time, because only about 3 to 5 percent of a person's DNA sequences code for the production of proteins, most of the SNPs are found outside the "coding sequences".

Even though many SNPs do not produce marked physical changes in population, scientists still believe that SNPs could predispose people to a certain disease and even influence the disease response to a particular drug regimen. Many common diseases in humans are not caused by a single genetic variation but are influenced by complex interactions among multiple genes, environmental and lifestyle factors. Although both environmental and lifestyle factors add enormously to the ambiguity of developing a disease, it is currently difficult to assess and evaluate their overall effect on a disease process. Thus, we refer here mainly to a person's genetic predisposition, or the potential of an individual to evolve a disease based on genes and hereditary factors. It will only be a matter of time before physicians can screen patients for susceptibility to a disease by analyzing their DNA for specific SNP profiles. Most SNPs are not responsible for a disease state. Instead, they serve as biological markers for pinpointing a disease on the human genome map.[38]

SINGLE NUCLEOTIDE POLYMORPHISM (SNP) IN PSORIASIS

The genetic basis of psoriasis has long been recognized, including the knowledge that family members of patients with psoriasis are at greater risk of developing the disease.[39] Several lines of evidence suggest that genes regulating IL-12 and IL-23 may be important in its pathogenesis. Part of the rationale stems from observations indicating that patients with psoriasis and those with Crohn's disease share common features: patients with Crohn's disease are five times more likely than the general population

to have psoriasis, and both diseases respond to anti–tumor necrosis factor-α therapy.[40] A recent genome wide association scan identified a highly significant association between Crohn's disease and a SNP in the coding region of the *IL23R* gene,[41] suggesting that this polymorphism might be present in patients with psoriasis. Additional studies from several diverse ethnic populations throughout the world have determined that psoriasis is associated with SNPs in IL-12 and IL-23 or their receptors.[42-46] These SNPs do not interact with known genetic risk factor for psoriasis, *HLA-Cw6*.

PUNNET'S SQUARE

The importance of studying genetics lies in the understanding of the likelihood of inheriting a particular trait, which can help many people explain and predict patterns of inheritance in different family lines. One of the easiest ways to calculate the mathematical probability of inheriting a specific trait was invented by early 20th century by an English geneticist named Reginald Punnett. His technique employs what we now call a Punnett square, which is a simple graphical way of discovering all of the potential combinations of genotypes that can occur in children, given the various genotypes of their parents [Figure 4]. It also shows us the odds of each of the offspring genotypes occurring.

In this example, 100% of the offspring will likely be heterozygous (YG). Since the Y (yellow) allele is dominant over the G (green) allele for pea plants, 100% of the YG offspring will have a yellow phenotype, as Mendel observed in his breeding experiments. It can be used as predictive tools when considering having children.

MAJOR STUDIES OR PROJECTS IN GENETICS WHICH ARE OF IMPORTANCE

- Human genome project was an international scientific project carried with a primary goal to determine the DNA sequence in all the genes of the human genome. It began in 1990 and the completed draft was published in 2003.[38]
- ENCODE was a research initiated by US national human research Institute in 2003 to identify all the functional elements in the human genome.[47]
- HapMap project that began in 2002 focuses on identifying common SNP.[48]

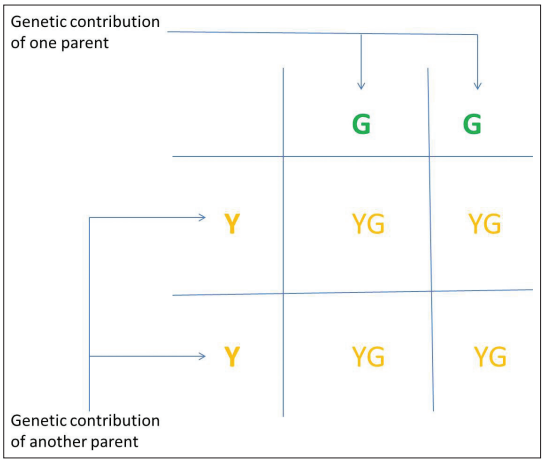

Figure 4: Punnet's square

PRENATAL DIAGNOSTIC TECHNIQUES

The impact of inherited disorders has reduced a lot in the recent past. Thanks to the advancement in the prenatal diagnostic techniques which helps the physician to pick up the suspicious disorder early and allows the parents to decide on the future of pregnancy. Patients who sought for prenatal diagnosis in the past were often presented with the single option of fetal skin biopsy. Fetal skin sample was obtained under fetoscopy or under ultrasound guidance at 15-27 weeks of gestation and subsequently analyzed with light microscopy, transmission electron microscopy with or without immunohistochemistry,[49] Bullous ichthyosiform erythroderma and junctional epidermolysis bullosa were among the initial conditions successfully diagnosed by this technique.[50-52] Fuchs and Rils initially analyzed fetal cells to determine the gender of the fetus thus giving an opening to a whole new way for the prenatal diagnosis of inherited conditions.[53] The preliminary article on the role of amniocentesis in prenatal diagnosis was published in 1970 and since then numerous centres have been established for diagnosis of X linked conditions, inborn errors of metabolism, chromosomal anomalies and neural tube defects.

DNA BASED PRENATAL DIAGNOSIS

The emergence of molecular basis of inherited cutaneous disorders has resulted in the practice of DNA-based prenatal diagnosis over non DNA-based methods. Indications include an affected family member/a previously affected offspring, wherein DNA samples from parents and affected members are required to characterize the given pathogenic mutation and to exclude situations like de novo mutations,

single parental disomy, and germline mosaicism.[54] Samples for genetic testing are often obtained via amniocentesis or chorionic villus sampling.

AMNIOCENTESIS

This is the most widely practised prenatal diagnostic method. It is usually performed at 15–20 weeks of gestation. In amniocentesis, a needle is inserted transabdominally through the uterus under ultrasound guidance to obtain amniotic fluid containing fetal-derived cells. Its main disadvantages are: fetal loss (0.5%), amniotic fluid leakage, vaginal spotting or bleeding and secondary infection of the amniotic fluid.

CHORIONIC VILLUS SAMPLING (CVS)

It is usually performed at 10–12 weeks of gestation in which a sample of placental tissue is obtained either transabdominally or transcervically under ultrasound guidance. The main advantage is that it is performed earlier in gestation and widely practiced procedure. However the disadvantages are: fetal loss (1%), limb defects, vaginal spotting or bleeding, secondary infection of the amniotic fluid, increased incidence of infantile hemangiomas and amniotic fluid leakage.[55-60]

PRE-IMPLANTATION GENETIC DIAGNOSIS

Despite many robust advances in DNA-based prenatal diagnosis, at present patients who have been found to carry an affected fetus, have minimal therapeutic options apart from the termination of pregnancy. However, abortion is often associated with significant psychological and physical morbidity in the mother. For parents at risk of transmitting a severe genetic disorder to their progeny, pre-implantation genetic diagnosis (PGD) presents as a back-up procedure in which embryos are evaluated for the suspected genetic disorder after in vitro fertilization (IVF), and those which are free from the suspected disorder are subsequently placed in the uterus, thereby eliminating the need for termination of pregnancy.

The disadvantages of this procedure are: technical challenges as to only one or two cells are available for analysis as compared to CVS. Furthermore, the diagnosis must be made within 12–48 h to allow proper re-implantation of embryos.[61] At present the risk of an affected fetus being mistakenly identified as normal is approximately 2% in autosomal recessive and 11% for autosomal dominant disorders.[62]

Some of the other methods of prenatal diagnosis which are time consuming and in infantile stages of development include: the detection of fetal DNA and RNA in maternal circulation. Various methods used to detect mutations in all the above methods include polymerase chain reaction (PCR) amplification, direct sequence analysis, linkage analysis, restriction enzyme digestion analysis, and denaturing high performance liquid chromatography.

CONCLUSION

An amalgamation of basic and novel principles of genetics in the context of rapidly evolving scientific technology and distinguishing the appropriate modes of functioning of the human genome is essential for an effectual clinical care in patients with inherited disorders or autoimmune disorders and those with malignancy. For many of the genetic disorders clinical judgement remains the backbone of diagnosis. It is anticipated that in near future the molecular genetics will not only aid is in clinching the diagnosis of genodermatoses but also usher us in the management of the same. This review summarizes the basics in understanding of medical genetics for a dermatologist.

REFERENCES

1. Agarwal BL, Agarwal SP. Basics in genetics. In: Agarwal BL, Agarwal SP, editors. Statistical analysis of quantitative genetics. 1st ed. New Delhi: New Age International; 2007. p.1-21.
2. Sturtevant AH. An experiment dealing with sex linkage in fowls. JEZ 1912;12:499-518.
3. Genetics home reference: Help me understand genetics, Your guide to understanding genetic conditions [Internet]. 2012 [Published 2012 Jan 30]. Available from http://ghr.nlm.nih.gov. [Last Accessed on 2012 July 20].
4. Chemke J, Rappaport S, Etrog R. Aberrant melanoblast migration associated with trisomy 18 mosaicism. J Med Genet 1983;2:135-7.
5. Has C. Mosaicism in the Skin: The importance of mild or minimal skin lesions. Arch Dermatol 2011;147:1094-6.
6. Frank J, Happle R. Cutaneous mosaicism: Right before our eyes. J Clin Invest 2007;117:1216-9.
7. Paller AS. Piecing together the puzzle of cutaneous mosaicism. J Clin Invest 2004;114:1407-9.
8. Paller AS. Genetic and clinical mosaicism in a type of epidermal nevus. N Engl J Med 1994;331:1408-15.
9. Colman SD, Rasmussen SA, Ho VT, Abernathy CR, Wallace MR. Somatic mosaicism in a patient with neurofibromatosis type 1. Am J Hum Genet 1996;58:484-90.
10. Munro CS, Wilkie AO. Epidermal mosaicism producing localised acne: Somatic mutation in FGFR2. Lancet 1998;352:704-5.
11. Sakuntabhai A, Dhitavat J, Burge S, Hovnanian A. Mosaicism for ATP2A2 mutations causes segmental Darier's disease. J Invest Dermatol 2000;115:1144-7.
12. Terrinoni A. A mutation in the V1 domain of K16 is responsible for unilateral palmoplantar verrucous nevus. J Invest Dermatol 2000;114:1136-40.
13. Messiaen L, Vogt J, Bengesser K, Fu C, Mikhail F, Serra E, *et al*.

Mosaic type-1 NF1 microdeletions as a cause of both generalized and segmental neurofibromatosis type-1 (NF1). Hum Mutat 2011;32:213-9.
14. Happle R. Somatic recombination may explain linear porokeratosis associated with disseminated superficial actinic porokeratosis. Am J Med Genet 1991;39:237.
15. Happle R. Segmental forms of autosomal dominant skin disorders: Different types of severity reflect different states of zygosity. Am J Med Genet 1996;66:241-2.
16. Vakilzadeh F, Kolde G. Relapsing linear acantholytic dermatosis. Br J Dermatol 1985;112:349-55
17. Poblete-Gutiérrez P, Wiederholt T, König A, Jugert FK, Marquardt Y, Rübben A, *et al*. Allelic loss underlies type 2 segmental Hailey-Hailey disease, providing molecular confirmation of a novel genetic concept. J Clin Invest 2004;114:1467-74.
18. Feramisco JD, Tsao H, Siegel DH. Genetics for the Practicing Dermatologist. Semin Cut Med Surg 2010;29:127-36.
19. van Slegtenhorst M, de Hoogt R, Hermans C, Nellist M, Janssen B, Verhoef S, *et al*. Identification of the tuberous sclerosis gene TSC1 on chromosome 9q34. Science 1997;277:805-8.
20. European chromosome 19 Tuberous Sclerosis Consortium. Identification and characterization of tuberous sclerosis gene on chromosome 16. Cell 1993;75:1305-15.
21. Parisi MA, Sybert VP. Molecular Genetics in pediatric dermatology. Curr Opin Pediatr 2000;12:347-53.
22. Friedman JM. Epidemiology of neurofibromatosis type 1. Am J Med Genet 1999;89:1-6.
23. Shen MH, Harper PS, Upadhyaya M. Molecular genetics of neurofibromatosis type1 (NF1). J Med Genet 1996;33:2-17.
24. Barlow-Stewart K. (2007) X-linked inheritance- traditional patterns of inheritance 3 Available from: http://www.genetics.edu.au [Last accessed on 2011Nov].
25. Cooper DN, Youssoufian H. The CpG dinucleotide and human genetic disease. Hum Genet 1988;7:151-5.
26. Rideout WM, Coetzee GA, Olumi AF, Jones PA. 5-Methylcytosine as an endogenous mutagen in the human LDL receptor and p53 genes. Science 1990;249:1288-90.
27. Baylin SB, Herman JG, Graff JR, Vertino PM, Issa JP. Alterations in DNA methylation: A fundamental aspect of neoplasia. Adv Cancer Res 1998;72:141-96.
28. Jones PA, Laird PW. Cancer epigenetics comes of age. Nat Genet 1999;21:163-7.
29. Li Y, Sawalha AH, Lu Q. Aberrant DNA methylation in skin diseases. J Dermatol Sci 2009;54:143-9.
30. Feramisco JD, Tsao H, Siegel DH. Genetics for the Practicing Dermatologist. Semin Cutan Med Surg 2010;29:127-36.
31. Chen M, Chen ZQ, Cui PG, Yao X, Li YM, Li AS, *et al*. The methylation pattern of p161INK4a gene promoter in psoriatic epidermis and its significance. Br J Dermatol 2008;158:987-93.
32. Lewis BP, Burge CB, Bartel DP. Conserved seed pairing, often flanked by adenosines, indicates that thousands of human genes are microRNA targets. Cell 2005;120:15-20.
33. Polygenetic inheritance: Available from: http://staff.jccc.net/pdecell/evolution/polygen.html#polygen [Last Accessed on 2010 Feb 23].
34. Ford EB. Polymorphisms and Taxonomy, in The New Systematics. In: Huxley J, editors. Oxford: Clarendon Press;1940. p. 493-513.
35. Suzuki Y, Hamamoto Y, Ogasawara Y, Ishikawa K, Yoshikawa Y, Sasazuki T. Genetic polymorphisms of killer cell immunoglobulin-like receptors are associated with susceptibility to psoriasis vulgaris. J Invest Dermatol 2004;122:1133-6.
36. Kim EJ, Jeong MK, Li MS, Park MK, Lee MK, Yoon Y, *et al*. Genetic polymorphism of *FLG* in Korean ichthyosis vulgaris patients. Ann Dermatol 2011;23:170-6.
37. Single nucleotide polymorphisms: Available from: http://www.ncbi.nlm.nih.gov/About/primer/snps.html [Last Accessed on 2012 Feb 24].
38. International Human Genome sequencing consortium. Finishing the euchromatic sequence of the Human Genome. Nature 2004;431:931-45.
39. Henselers T, Christophers E. Disease concomitance in psoriasis. J Am Acad Dermatol 1995;32:982-6.
40. Lee FI, Bellary SV, Francis C. Increased occurrence of psoriasis in patients with Crohn's disease and their relatives [comments]. Am J Gastroenterol 1990;85:962-3.
41. Duerr RH, Taylor KD, Brant SR, Rioux JD, Silverberg MS, Daly MJ, *et al.* A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. Science 2006;314:1461-3.
42. Capon F, Di Meglio P, Szaub J, Prescott NJ, Dunster C, Baumber L, *et al.* Sequence variants in the genes for the interleukin-23 receptor (IL23R) and its ligand (IL12B) confer protection against psoriasis. Hum Genet 2007;122:201-6.
43. Cargill M, Schrodi SJ, Chang M, Garcia VE, Brandon R, Callis KP, *et al.* A large-scale genetic association study confirms IL12B and leads to the identification of IL23R as psoriasis-risk genes. Am J Hum Genet 2007;80:273-90.
44. Chang YT, Chou CT, Yu CW, Lin MW, Shiao YM, Chen CC, *et al.* Cytokine gene polymorphisms in Chinese patients with psoriasis. Br J Dermatol 2007;156:899-905.
45. Nair RP, Ruether A, Stuart PE, Jenisch S, Tejasvi T, Hiremagalore R, *et al.* Polymorphisms of the *IL12B* and *IL23R* genes are associated with psoriasis. J Invest Dermatol 2008;128:1653-61.
46. Tsunemi Y, Saeki H, Nakamura K, Sekiya T, Hirai K, Fujita H, *et al*. Interleukin-12 p40 gene (IL12B) 3′-untranslated region polymorphism is associated with susceptibility to atopic dermatitis and psoriasis vulgaris. J Dermatol Sci 2002;30:161-6.
47. ENCODE Project Consortum: Identification and analysis of functional elements in 1% of human genome by the F pilot project. Nature 2007;447:799-816.
48. International HapMap Consortum: A haplotype map of the human genome. Nature 2005;437:1299-320.
49. Fassihi H, Eady RA, Mellerio JE, Ashton GH, Dopping- Hepenstal PJ, Denyer JE, *et al*. Prenatal diagnosis for severe inherited skin disorders: 25 years' experience. Br J Dermatol 2006;154:106-13.
50. Golbus MS, Sagebiel RW, Filly RA, Gindhart TD, Hall JG. Prenatal diagnosis of congenital bullous ichthyosiform erythroderma (epidermolytic hyperkeratosis) by fetal skin biopsy. N Engl J Med 1980;302:93-5.
51. Rodeck CH, Eady RA, Gosden CM. Prenatal diagnosis of epidermolysis bullosa letalis. Lancet 1980;1:949-52.
52. Holbrook KA, Smith LT, Elias S. Prenatal diagnosis of genetic skin disease using fetal skin biopsy samples. Arch Dermatol 1993;129:1437-54.
53. Fuchs F, Riis P. Antenatal sex determination. Nature 1956;177: 330.
54. Fassihi H, Eady RA, Mellerio JE, Ashton GH, Dopping- Hepenstal PJ, Denyer JE, *et al*. Prenatal diagnosis for severe inherited skin disorders: 25 years' experience. Br J Dermatol 2006;154:106-13.
55. Cunniff C. Prenatal screening and diagnosis for pediatricians. Pediatrics 2004;114:889-94.
56. Caughey AB, Hopkins LM, Norton ME. Chorionic villus sampling compared with amniocentesis and the difference in the rate of pregnancy loss. Obstet Gynecol 2006;1:612-6.
57. Burton BK, Schulz CJ, Angle B, Burd LI. An increased incidence of haemangiomas in infants born following chorionic villus sampling (CVS). Prenat Diagn 1995;15:209-14.
58. Bruce S, Duffy JO, Wolf JE Jr. Skin dimpling associated with midtrimester amniocentesis. Pediatr Dermatol 1984;2:140-42.
59. Raimer SS, Raimer BG. Needle puncture scars from midtrimester amniocentesis. Arch Dermatol 1984;120:1360-2.
60. Ahluwalia J, Lowenstein E. Skin dimpling as a delayed manifestation of traumatic amniocentesis. Skinmed 2005;4:323-4.
61. Braude P, Pickering S, Flinter F, Ogilvie CM. Preimplantation genetic diagnosis. Nat Rev Genet 2002;3:941-53.
62. Lewis CM, Pinel T, Whittaker JC, Handyside AH. Controlling misdiagnosis errors in preimplantation genetic diagnosis: A comprehensive model encompassing extrinsic and intrinsic sources of error. Hum Reprod 2001;16:43-50.

Multiple Choice Questions

1. Father of genetics is
   a. Gregor Johann Mendel
   b. William Bateson
   c. Rosalind Franklin
   d. Barbara Mc clintoch

2. Phenotype is
   a. Blue print of the organism
   b. Individuals who carry 2 different alleles
   c. Appearance of the organism
   d. None of the above

3. Mutations occurring in the ovum is termed as
   a. Somatic mutations
   b. Type 1 mosacism
   c. De-novo mutations
   d. All of the above

4. Genetic modification in polymorphism occurs in
   a. < 1% population
   b. >1 % population
   c. <0.5% population
   d. None of the above

5. New genetic concepts in skin mosaicism was given by
   a. Irwin Mc lean
   b. Rudolf
   c. Gregor Mendel
   d. Watson and Crick

6. Linear porokeratosis is an example for
   a. Type 1 mosaicism
   b. Germline mosaicism
   c. Type 2 mosaicism
   d. None of the above

7. Mother carrying faulty X gene
   a. 50% chances that her sons will be carriers
   b. 50% chances that her daughters will manifest the disease
   c. 50% chances that the sons will manifest the disease
   d. None of the above

8. Epigenetic mechanisms includes:
   a. Histone modification
   b. Cytosine modifications
   c. Non protein coding RNA
   d. All of the above

9. Polygenetic inheritance is known as
   a. Qualitative inheritance
   b. Quantitative inheritance
   c. Sporadic inheritance
   d. All of the above

10. Most SNPs are found in
   a. Within the coding sequence
   b. <1% population
   c. Outside coding sequences
   d. None of the above

Answers
1. a, 2. c, 3. c, 4. b, 5. b, 6. c, 7. c, 8. d, 9. b, 10. c