Single Gene Disorders

Some Definitions

Alleles – variants of a given DNA sequence at a particular location (locus) in the genome. Often used more narrowly to describe alternative forms of the same gene.

If there are at least two relatively common versions of a DNA sequence at a given locus in a population, the locus is said to exhibit **polymorphism**.

Allelic heterogeneity – the existence of many different disease causing alleles at a given locus

Autosome – any chromosome other than a sex chromosome

Homozygote – an individual having identical alleles at a particular locus

Heterozygote – an individual having two different alleles at a particular locus

Hemizygous – having only one copy of a gene or DNA sequence in diploid cells. Males are hemizygous for most genes on sex chromosomes, having only one X and one Y chromosome. A person having a deletion in a region of an autosome would be hemizygous for that region, having one remaining copy on the normal homologous chromosome

Compound Heterozygote – an individual with two different mutant alleles at a given locus. For example, and individual with two different mutant alleles for the hemoglobin beta-chain (e.g. HbS and HbC) in place of the two normal copies would be a compound heterozygote.

Dominant – in human genetics, any trait that is expressed in a heterozygote. **Incompletely dominant** is sometimes used to describe a phenotype or trait when its severity in a hemizygous individual is intermediate between that observed in individuals that are homozygous for either the normal or mutant allele

Dominant negative – a mutant gene whose product can inhibit the function of the wild-type gene product in heterozygotes

Haploinsufficiency – a locus shows haploinsufficiency when a single normal allele is unable to generate a sufficient amount of its gene product to produce a normal phenotype (when half of the normal amount of the gene product is not enough). When the heterozygous state manifests an abnormal phenotype, the disease trait is considered dominant.

Genotype – the set of alleles that make up an individual's genetic make-up either overall, or at a given locus.

Phenotype – The observable characteristics of a cell or organism resulting from its specific genotype.

Single gene disorder – one determined by the alleles at a single locus

Mutation – a rare difference in a DNA sequence or gene at a given locus (compare with polymorphism). In medical genetics it is often used to indicate a disease-causing allele

Consanguineous – used to describe couples who have one or more ancestors in common

Pedigree – a graphical representation of a family tree

Proband (synonyms **propositus** or **index case**) is the affected individual through whom the family with a genetic disorder is brought to the attention of others. The individual in a family that first consults a geneticist is referred to as the **consultand**, whether or not he or she is affected

Kindred – the entire family represented by the pedigree

Sibs - brothers or sisters. An entire family of sibs is referred to as a **Sibship**

Common symbols used in pedigrees
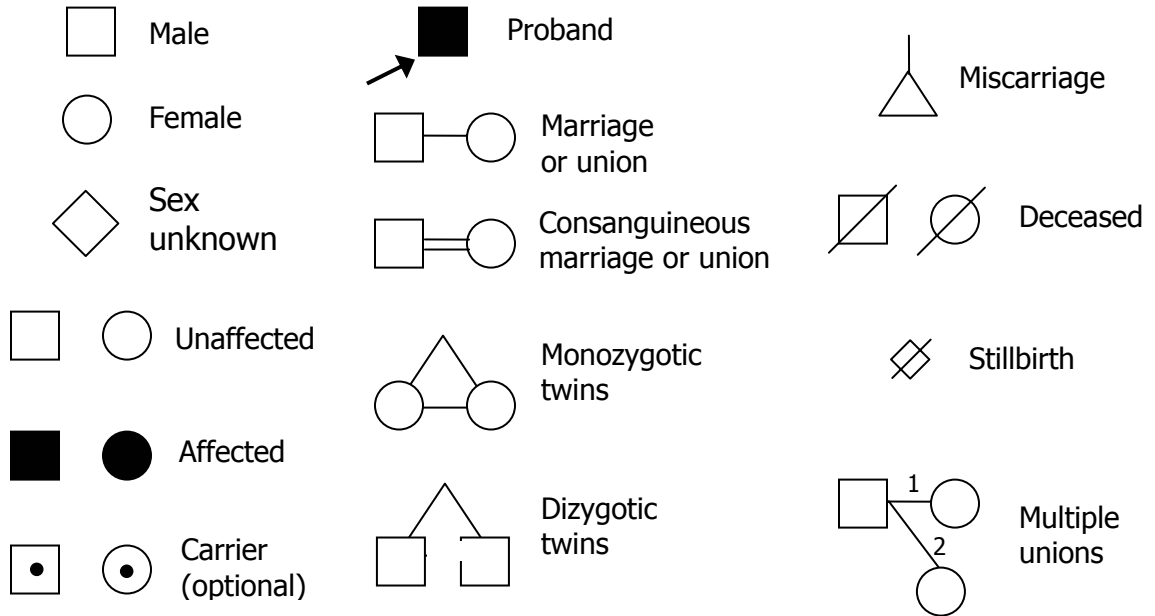
Basic Mendelian pedigree patterns (uncomplicated)

Autosomal Dominant Inheritance – The disease phenotype is usually seen in every generation, except in the case of a new mutation. A child of an affected parent has a 1 in 2 risk of inheriting the disease trait. Phenotypically normal family members are unlikely to transmit the disease to their offspring, and males and females are usually equally affected. A typical pedigree is shown below.
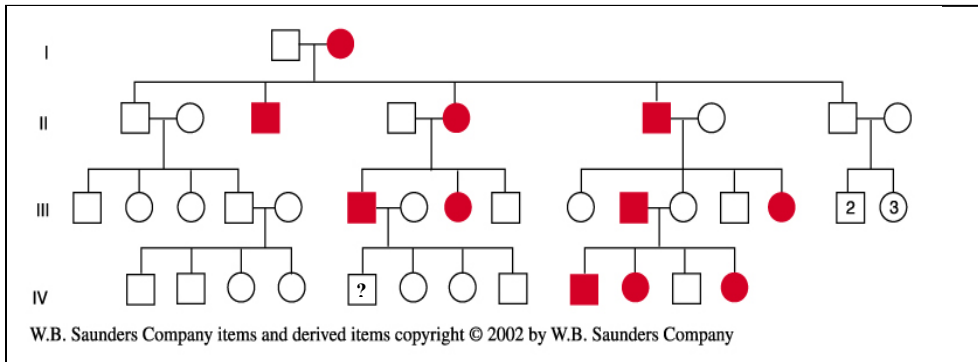
Figure 5-7. Pedigree showing typical inheritance of a form of progressive sensorineural deafness (DFNAI) inherited as an autosomal dominant trait. What is the risk for the individual marked with a **?**

Autosomal Recessive Inheritance – May be characterized by a clustering of the disease phenotype among siblings and its absence in prior and subsequent generations. Males and females are often equally affected and consanguinity may be present (see below). Parents are asymptomatic carriers and the risk of occurrence for each sib of the affected proband is 1 in 4.
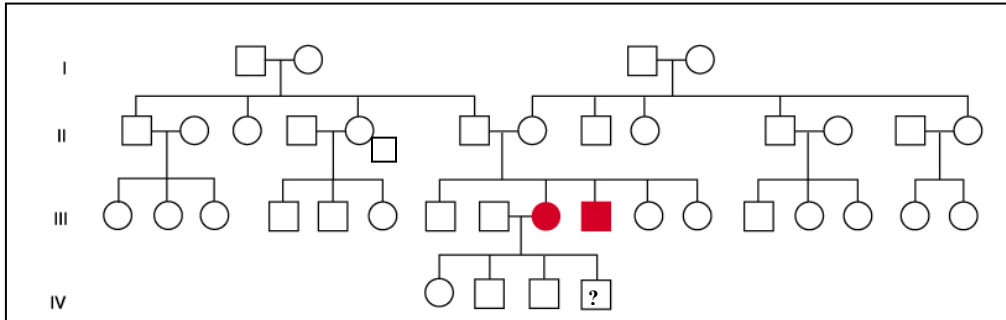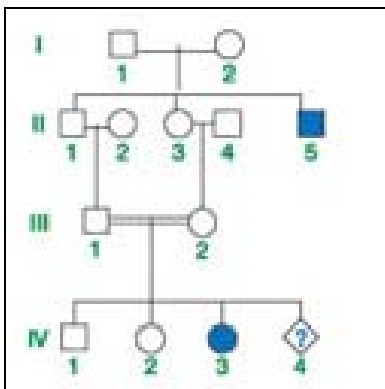

Figure 5-3. Typical pedigree showing autosomal recessive inheritance. From Thompson & Thompson, Genetics in Medicine


What is the risk for the individuals marked with a "**?**" in the two pedigrees?

Pedigree in which consanguinity increases the risk for reappearance of the disorder in a subsequent generation.

X-linked Inheritance

X-linked recessive inheritance – The incidence of the trait is much higher in males than in females, heterozygous females are usually unaffected. The gene (and trait) is usually transmitted from an affected male to his grandsons <u>through his daughters</u>; the grandsons have a 50% chance of inheriting the trait. Males never transmit the disease directly to their sons, so that affected males in a kindred are related to each other through females.
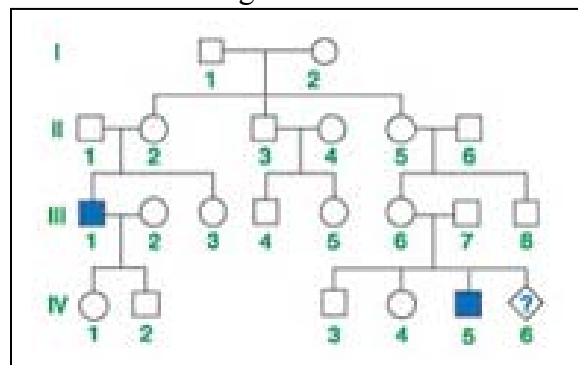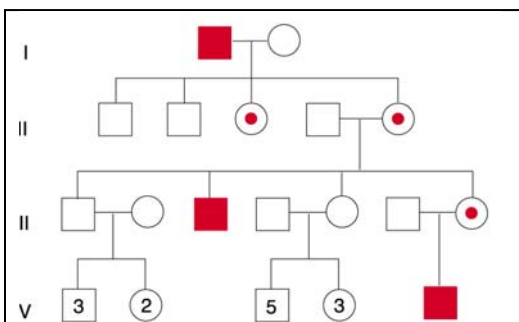
Pedigree pattern demonstrating an X-linked recessive disorder such as hemophilia A. In the example on the left, the disorder was transmitted from an affected male through females to an affected grandson and great-grandson. In the example on the right, the disorder was transmitted from a female carrier through her daughters to her affected grandson and great-grandson. **What is the risk to the fetus in generation IV?**

X-linked dominant inheritance – Affected mothers have a 50% chance of transmitting the disorder to both sons and daughters (the same as in the case of an autosomal dominant disorder). In contrast, affected fathers have affected daughters (all) but no affected sons. Affected females may have milder (though variable) expression of the phenotype
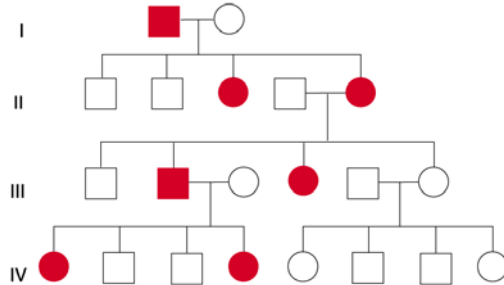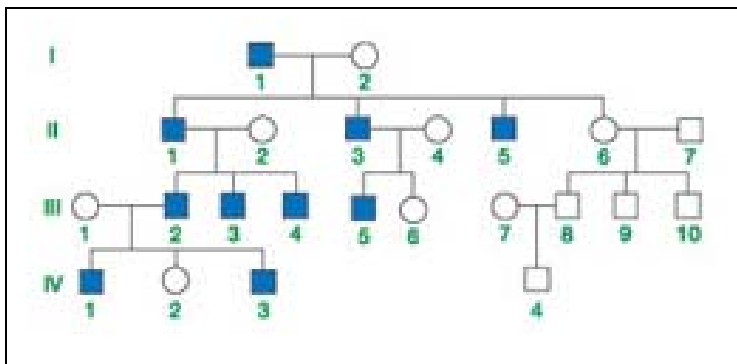

Figure 5-20. Pedigree pattern demonstrating X-linked dominant inheritance.

Y-linked Inheritance – Males are hemizygous for the Y chromosome (except in rare XYY males and for the small autosomal region of the Y chromosome). Consequently, in the uncomplicated case, a defect in a Y chromosome gene produces a dominant trait that is transmitted from male to male.

Additional Definitions
Heteroplasmy – the presence of two or more mitochondrial DNA variants in the mitochondria of an individual. Contrasted with **Homoplasty**, in which an individual's mitochondria contain only one form of mitochondrial DNA.
Penetrance – the fraction of individuals with a genotype known to cause a disease that actually have any signs or symptoms of the disease.
Expressivity – The extent to which a genetic defect is expressed. If a disease shows **variable expression**, the symptoms can vary from mild to severe, but are never completely unexpressed in individuals who have the appropriate genotype.
Mosaic – an individual or tissue containing at least two cell lines that differ in genotype or karyotype, derived from the same zygote.

Departures from basic Mendelian pedigree patterns
The mitochondrial genome is small, but highly mutable, and mutations in mitochondrial DNA are a significant cause of human disease. Mutations in mitochondrial genes show a distinctive **matrilineal inheritance** pattern (no affected male transmits the disease) and are often characterized by **heteroplasmy**. Because of the way mitochondria are transmitted between

mother and child, the proportion of normal and mutant mitochondrial DNA can vary greatly between them. Similarly, the distribution of mitochondria between daughter cells following mitosis is random, so that two daughter cells can have different proportions of normal and mutant mitochondrial DNA. Examples of two mitochondrial disease pedigrees is shown below. The second exhibits incomplete penetrance
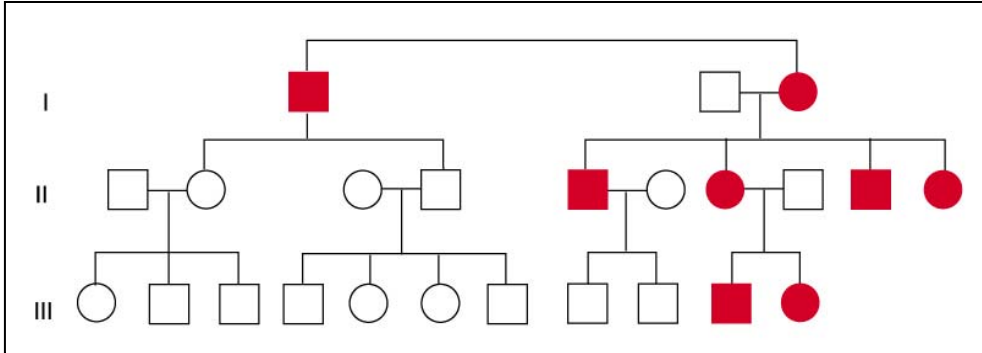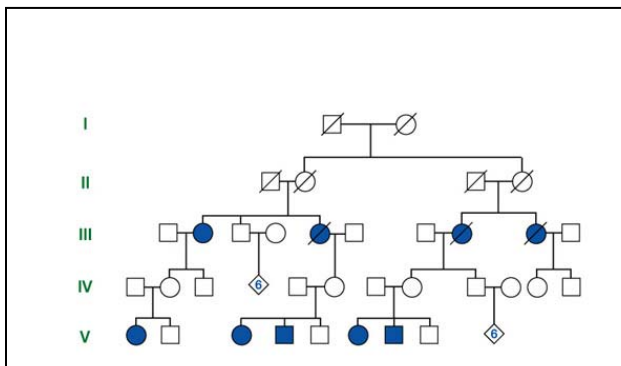

Figure 12-32. Pedigree of Leber's hereditary optic neuropathy, a disorder caused by a defect in mitochondrial DNA.   Inheritance is only through the maternal lineage, in agreement with the known maternal inheritance of mitochondrial DNA. No affected male transmits the disease.

Pedigree pattern showing mitochondrial inheritance with incomplete penetrance. Note – mothers in generation III do not appear to pass the disease on to their children in generation IV, but the disease reappears in their grandchildren in generation V through their mothers.

Nonpenetrance and variable expression are complications that are most frequently associated with dominant disorders.
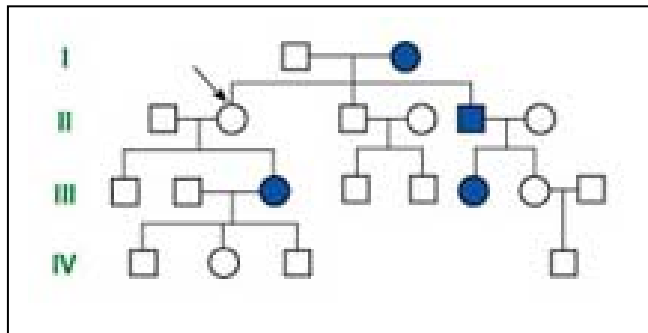
Autosomal dominant inheritance with nonpenetrance in the consultant in generation II.
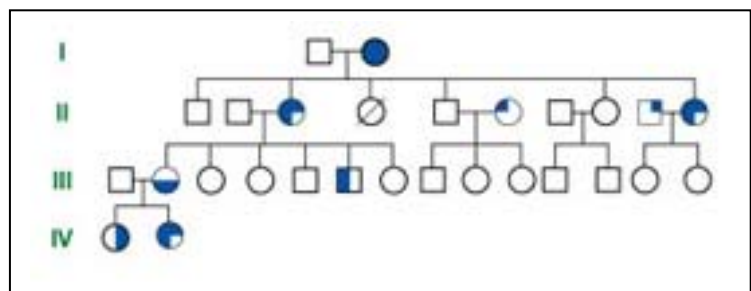
Autosomal dominant inheritance with variable expression in this family with Waardenburg syndrome, shading of first quadrant = hearing loss; second quadrant =different colored eyes; third quadrant = white forelock; fourth quadrant = premature graying of hair.

Triplet Repeat Disorders: Unstable Dynamic Mutations – Some genes contain a repeat of three nucleotides such as CAGCAGCAG……..CAG. In some instances, the number of triplet repeats in a given gene increases (expands) from generation to generation until some threshold is passed that results in disease. Because the number of triplet repeats can increase from generation to generation, an asymptomatic carrier can produce offspring that manifest symptoms later in life, and these in turn can produce offspring who manifest symptoms at birth. This phenomenon has been termed **anticipation**.
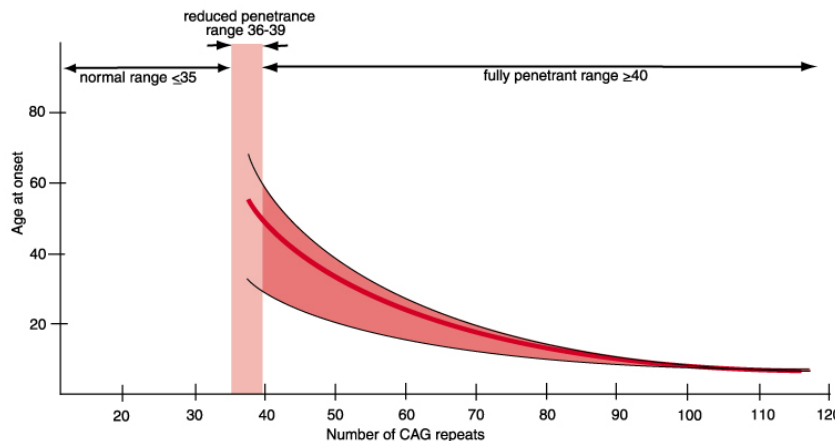

Figure 12-25. Graph correlating approximate age at onset of Huntington disease with the number of CAG repeats found in the *HD* gene. Solid line is the average age at onset, and the shaded area shows the range of age at onset for any given number of repeats. (Data courtesy of Dr. M. Macdonald, Massachusetts General Hospital, Boston, Massachusetts.)
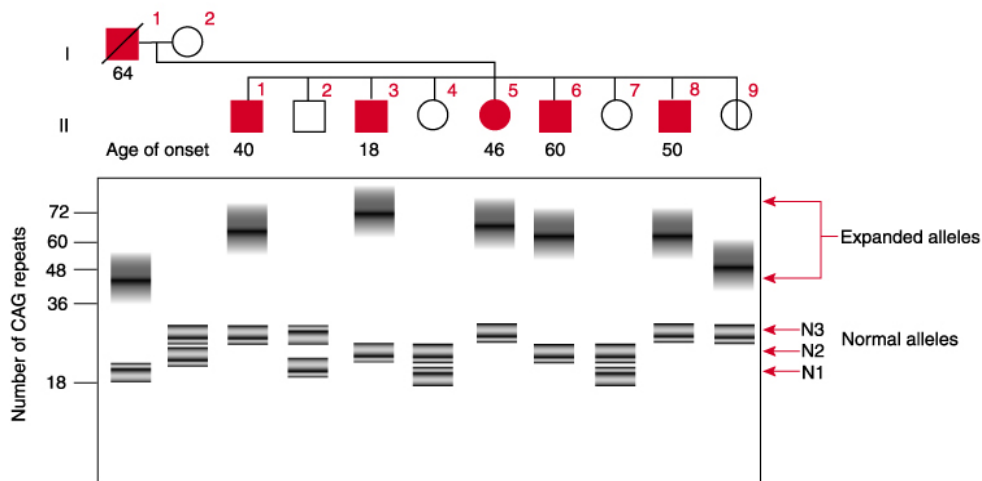
Figure 12-26. Pedigree of family with Huntington disease. Below is a schematic diagram of gel electrophoresis. Beneath each individual's symbol are the polymerase chain reaction (PCR) products containing the CAG repeat derived from the individual's two copies of the *HD* gene. Age at first symptoms is shown below each individual's pedigree symbol. Individual I-1 has an expanded repeat that undergoes further expansion when passed on to six of his children. Note that individual II-9 is an asymptomatic carrier of an expanded allele in whom the disease has not yet become penetrant. (The triple banding pattern of the normal alleles and the more diffuse appearance of the bands from expanded alleles result from technical difficulties in PCR amplifications of a triplet repeat as well as from somatic mosaicism in repeat length for the expanded alleles.)

Three generations of individuals with myotonic dystrophy demonstrating the concept of anticipation in triplet repeat expansion disorders.
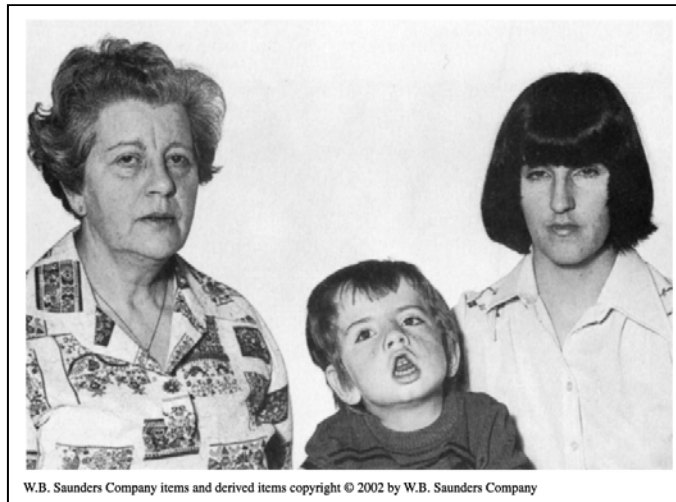

Figure 12-29. Myotonic dystrophy, an autosomal dominant condition with variable expression in clinical severity and age of onset.   The grandmother has bilateral cataracts but no facial weakness or muscle sumptoms. The daughter was thought unaffected until after the birth of her severely affected child, but she now has moderate facial weakness and ptosis (drooping of the upper eyelid. The child has congenital myotonic dystrophy)

Genomic Imprinting and Parent-of-Origin effects - For defects in imprinted genes, expression depends on parental origin, which can complicate pedigree interpretation.
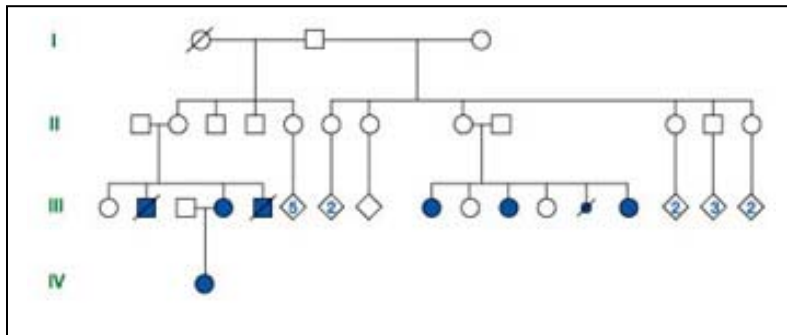
Pedigree of family with autosomal dominant Beckwith-Wiedemann syndrome. This rare disorder is characterized by abnormally enlarged organs, particularly the tongue and abdominal viscera. The affected gene located at 11p15 is imprinted (maternal allele expressed, paternal allele silenced). All the children in generation II are normal, whether or not their received the defective gene from their father in generation I, since their active maternal copy is normal. The silenced gene becomes activated in the germ cells of females in generation II and any female carrier has a 50% chance of transmitting the defective copy to their children. Since the maternal allele is expressed and is dominant, half the children, male or female, can be expected to have the disease.

Prader-Willi and Angelman Syndromes are often the subjects of USMLE questions. These disorders result from a microdeletion in the long arm of chromosome 15. Different phenotypes are observed, depending on the parental source of the mutation.
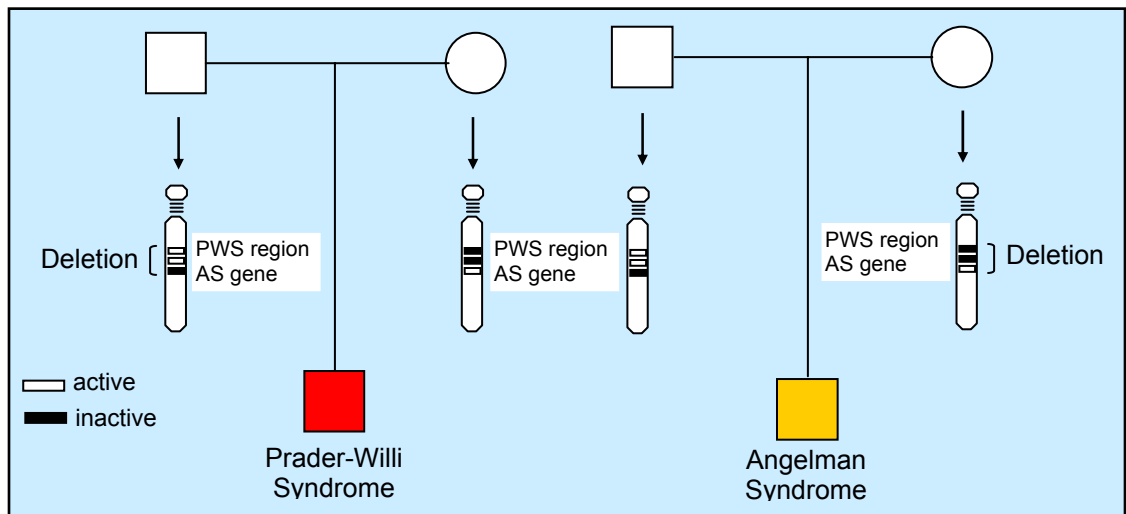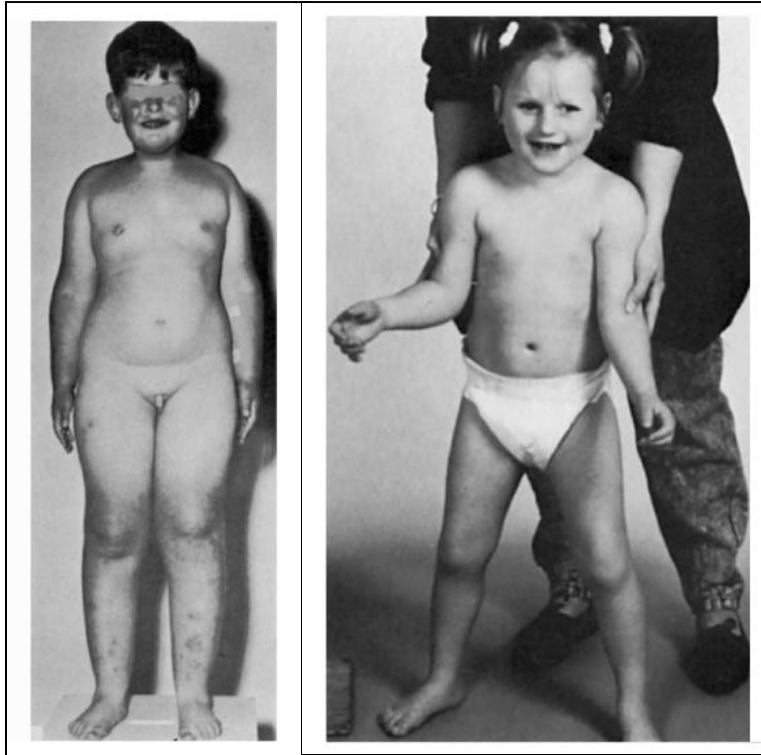
Prader-Willi and Angelman phenotypes

Fig. 5-25 (left) Prader-Willi Syndrome. Note the truncal obesity, hypogonadism, small hands in a 9.5-year-old affected boy. Short stature and mental retardation are also characteristic of this disorder.

Fig. 5-26 (right) Angelman Syndrome. Note the wide stance and position of the arms in this 4-year-old affected girl, which are characteristic of this syndrome. Short stature, mental retardation, spasticity and seizures are also characteristic of this disorder.

Both Prader-Willi and Angelman Syndromes can occur in either sex. The different phenotypes depend on the parental origin of the deletion in the long arm of chromosome 15.

Calculation of Risk based on simple Mendelian pedigrees and gene frequencies in populations

For a gene with two alleles, P and Q, one expects to find individuals in a population to have one of three genotypes, homozygous for allele P (PP), homozygous for allele Q (QQ) and heterozygous for P and Q (PQ). For a large population with random mating, the Hardy-Weinberg law allows one to calculate the frequency of each of the three genotypes from knowledge of the frequency of the individual alleles, and vice versa. If p is the frequency of the P allele in the population and q is the frequency of the Q allele, then the frequency of each of the genotypes can be determined from the binomial expansion below.

$$(p + q)^2 = p^2 + 2pq + q^2$$

From this equation, the frequency of the three genotypes are PP = p^2, PQ = $2 \times p \times q$, and QQ = q^2.

Note: Since we assume there are only two alleles for this gene, the sum of their frequencies $(p + q) = 1$, and the sum of the genotype frequencies, $p^2 + 2pq + q^2 = 1$.

For a locus having three alleles, there are six possible genotypes whose frequencies are given by the expansion of $(p + q + r)^2$, where p, q, and r are the frequencies of the P, Q and R alleles at that locus.

Knowledge of allele frequencies can be used to calculate genotype frequencies, make predictions about risk, and can form the basis of a recommendation for carrier screening.

Tay-Sachs disease is a recessive disorder resulting from a defective allele for the gene hexosaminidase A (*HEXA*). The allele frequency for the mutant *HEXA* (*ΔHEXA*) is 1/60 in Eastern European Jews and their descendents. Assuming random mating within that population (no genetic counseling and no selection of partners from outside the group) then we might expect the population of offspring to have the genotypic and pheonotypic frequencies shown in the Table below: homozygous normal = $(59/60)^2$ or 0.9669, heterozygous carriers = 2×(59/60)×(1/60) or 0.0328 (approximately 1/30), and homozygous affected = $(1/60)^2$ or 0.0003.

Expected Incidence of Tay-Sachs Disease per 10,000 live births in Eastern European Jews				
Genotype	Phenotype	Relative Genotype Frequency	Number	Observed allele frequencies
HEXA/HEXA	Normal	0.9669	9,669	*HEXA = 59/60*
HEXA/*ΔHEXA*	Normal-carrier	0.0328	328	
ΔHEXA/ΔHEXA	Tay-Sachs	0.0003	3	*ΔHEXA = 1/60*

Knowledge of disease frequencies (phenotypes) can be used to calculate allele frequencies and carrier frequencies in a population, even when the nature of the gene defect is unknown.

In recessive disorders, the frequency of the disease (incidence) corresponds to the frequency of the homozygous state for the disease allele, which is q^2 according to the Hardy-Weinberg relationship.

The allele frequency is thus $q = \sqrt{incidence}$ $(=\sqrt{q^2}$).

Since $(p + q) =1$, p can also be determined as can the heterozygote or carrier frequency, $2pq$.

TABLE 7-7

Incidence, Gene Frequency, and Heterozygote Frequency for Selected Autosomal Recessive Disorders in Different Populations

Disorder	Population	Incidence (q^2)	Gene Frequency (q)	Heterozygote Frequency ($2pq$)	Heterozygotes Homozygotes ($2pq/q^2$)
Sickle cell anemia (*S/S* genotype)	African American	1 in 400	.05	1 in 11	38
	Hispanic American	1 in 40,000	.005	1 in 101	396
Alpha$_1$ antitrypsin deficiency (Z/Z genotype)	Denmark	1 in 2000	.023	1 in 22	90
	U.S. African American	1 in 100,000	.004	1 in 125	800
Cystic fibrosis	U.S. Caucasians	1 in 2000	.023	1 in 22	90
Phenylketonuria	Scotland	1 in 5300	.014	1 in 30	175
	Finland	1 in 200,000	.002	1 in 250	800
	Japan	1 in 109,000	.003	1 in 166	657
Tay-Sachs disease	U.S. Ashkenazic Jewish	1 in 3900	.016	1 in 30	130
	U.S. non–Ashkenazic Caucasian	1 in 112,000	.003	1 in 170	660

Figures are approximate. Data are from Online Mendelian Inheritance in Man (< *http://www3.ncbi.nlm.nih.gov/Omim/*>) and Scriver CR, Beaudet AL, Sly WS, Valle D (eds) (2000) The Metabolic and Molecular Basis of Inherited Disease, 8th ed. McGraw-Hill, New York.

In X-linked recessive disorders, males receive either the normal allele or the mutant allele in proportion to their frequency in the population. Because males are hemizygous for X-linked genes, the frequency of an X-linked disorder in males is directly equal to the frequency of the disease allele in the population. Table 7-5 below illustrates this for color-blindness.

TABLE 7-5
X-Linked Genes and Genotype Frequencies (Color-Blindness)

Sex	Genotype	Phenotype	Incidence (Approximate)
Male	X^+	Normal color vision	$p = 0.92$
	X^{cb}	Color blind	$q = 0.08$
Female	X^+/X^+	Normal (homozygote)	$p^2 = (0.92)^2 = 0.8464$
	X^+/X^{cb}	Normal (heterozygote)	$2pq = 2(0.92)(0.08) = 0.1472$
		Normal (total)	$p^2 + 2pq = 0.9936$
	X^{cb}/X^{cb}	Color blind	$q^2 = (0.08)^2 = 0.0064$

Examples of Risk Calculations from Past Problem Sets

(Submitted by Carolyn Jones, Pediatric Genetics). You are attempting to determine the carrier frequency of disease A. This disease is characterized by severe anemia beginning in childhood. In addition to anemia, affected patients suffer from severe pain in their joints. This disorder is recessive. It is particularly common in the African American population, where its incidence is about 0.25 percent (1/400).

   A. Using the Hardy-Weinberg formula, calculate the frequency of carriers in this population.

$q = \sqrt{0.0025}$ **= 0.05 (1/20), p = 0.95 (19/20), and the carrier frequency 2pq = 0.095 (~1/10)**

A family presents in the clinic. They have three children. Their son is affected with disease They have two daughters who are not affected. The couple is currently pregnant with their fourth child. An ultrasound examination indicated that the fetus is likely to be male.

   B. What is the chance this child will be affected with the same blood disorder as his brother?

In a recessive disorder when both parents are carriers, the risk to each child is 1/4

The eldest daughter is 20 years of age. She is concerned about her risk of having an affected child when she marries a nonrelated African American man.

   C. What is the risk she will have an affected child?

The daughter is an unaffected sibling of a child with a recessive disease. In such a pedigree, 3 out of 4 children are expected to unaffected, with 2 of the 3 being heterozygous carriers of the sickle cell trait, and the third being homozygous normal. Thus, a normal sibling has a ⅔ risk of being a carrier, and a ⅓ chance of having two normal genes. The daughter's probability of passing the HbS gene to a child is thus $^2/_3 \times {}^1/_2 = {}^1/_3$. An unrelated African-American male has the carrier frequency of the general population, 0.095 or about $^1/_{10}$, and a $^1/_2$ chance of passing that gene on to a child for a overall probability of about $^1/_{20}$. The probability of the daughter having an affected child is thus $^2/_3 \times {}^1/_2 \times {}^1/_{10} \times {}^1/_2 = {}^1/_{60}$.

2. (Adapted from a problem by Carolyn Jones). A couple, Mr. and Mrs. X, are pregnant and present for genetic counseling. The family history indicates the mother is 32 years of age, and this is her first pregnancy. She is of Polish and Irish descent. She has one living brother and one sister. She had a second brother who died at age 17 of Duchennes Muscular Dystrophy (DMD), which is an X-linked recessive disorder. Her sister has two daughters aged 1 and 4. Her brother has a son aged 2 and a daughter aged 6, and both are healthy. The mother of Mrs. X had one sister and one brother. The sister also had a son who died of DMD. There is no other family history of this disorder. Mr. X is 35 years of age. He is of German and Italian descent. He has two healthy brothers, and his mother and father are both well. His mother's sister died of cystic fibrosis.

A. Draw a pedigree using the family history
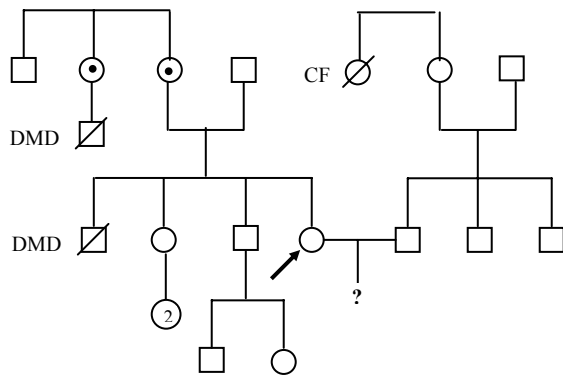
B. What is the risk that the baby Mr. and Mrs. X are carrying has Duschennes Muscular Dystrophy?

Mrs. X's brother died of Duschennes Muscular Dystrophy so that Mrs. X's mother must be a carrier. Mrs. X has a $^1/_2$ chance of inheriting the gene from her mother, a $^1/_2$ chance of passing the gene to her child, and a $^1/_2$ chance of having a son. Thus, there is a $^1/_8$ chance she will have a child with the disease.

C. What is the risk that the mother of Mr. X is a carrier of cystic fibrosis (CF)

Mr. X's mother is the normal sibling of an affected child, so she has a $^2/_3$ chance of being a carrier, and a $^1/_2$ chance of passing the gene on to Mr. X.

D. What is the risk Mr. X is a carrier of cystic fibrosis. **His risk of being a carrier is $^1/_3$.**

E. What is the risk the unborn child of Mr. and Mrs. X will have cystic fibrosis. (Hint: the frequency of cystic fibrosis in the Caucasian population, q^2, is about $^1/_{2000}$)

q, the frequency of the cystic fibrosis gene in the Caucasian population is equal to $\sqrt{1/2000} \approx {}^1/_{45}$. The chance that Mrs. X is a carrier is $2pq$ or approximately $^1/_{23}$. Her chance of passing on the gene is about $^1/_2 \times {}^1/_{23}$ or about $^1/_{46}$. Mr. X's chance of passing on the gene is $^1/_2$ his risk of being a carrier or $^1/_6$. The risk to Mr. and Mrs. X of having a CF child is $^1/_6 \times {}^1/_{46} = {}^1/_{276}$, which is about 7 times greater than the incidence of CF in the general population ($^1/_{2000}$).

3. Disease *B* is characterized by excessive bleeding. Disease B overwhelmingly affects males with an incidence of approximately 1 out of 4900 births.

    A. Calculate the frequency of the Disease *B* causing allele in the general population.

        Disease B seems to be an X-linked recessive disorder. In that case, q = the incidence of the disease ($^1/_{4900}$)

    B. Estimate the frequency of carriers of Disease *B* in the population. **The frequency of carriers is 2pq. Since q is small, $p \approx 1$, and the carrier frequency is $2 \times 1 \times {}^1/_{4900}$ or about $^2/_{4900}$.**

4. Disease *C* is a recessive disorder. It is prevalent in the Eastern European Jewish population, among whom it has a carrier frequency of about 1/30. It is characterized by a progressive neurological deterioration leading to death between the ages of 2 and 4 years. An early indication of the disease in infants is the appearance of a cherry red spot on the retina as determined by a funduscopic examination of the eye. Mr. and Mrs. Y, who are pregnant with their second child, are of Eastern European Jewish ancestry, but have never gone for genetic testing.

    A. Estimate the risk of Mr. and Mrs. Y are carrying a baby with Disease *C*.

        When q is small, $p \approx 1$. Therefore, as a first approximation, the frequency of carriers in the given population is $2pq = {}^1/_{30}$ and the gene frequency $q = {}^1/_{60}$. Thus, the likelihood that Mr. and Mrs. Y are carriers is about $^1/_{30}$ for each. They each have about a 1/60 chance of passing on the gene ($^1/_2 \times {}^1/_{30}$), so the risk to the baby is about $^1/_{3600}$ (actual value $^1/_{3480}$), which corresponds to the frequency of the disease in the population.

    B. Mrs. Y has just learned that her brother's child has just been diagnosed with Disease *C*. Based on this new information, estimate the risk of Mr. and Mrs. Y are carrying a baby with this disease. **Mrs. Y's brother must be a carrier, so that at least one of Mrs. Y's parents is also a carrier. Mrs. Y thus has a $^1/_2$ chance of also being a carrier. (Note Mrs. Y and her brother are 1st degree relatives and therefore share half their genes in common). Mrs. Y in turn has a $^1/_2$ chance of passing the gene on to her child, so the risk of her child getting a defective gene from her is $^1/_2 \times {}^1/_2 = {}^1/_4$. Mr. Y has a $^1/_{60}$ chance of passing the gene on to his child (see above). Thus, the probability that Mr. and Mrs. Y will have a child with the disease increases to $^1/_4 \times {}^1/_{60} = {}^1/_{240}$.**