GENETICS: A BASIC HUMAN GENETICS PRIMER: PART II

Goal:
Understand the basic principles of medical genetics.

After completing this activity participants will be able to:
• Explain aneuploidy and common structural chromosome abnormalities
• Differentiate between disease-causing DNA mutations and polymorphisms
• Identify Mendelian inheritance patterns
• Describe nontraditional inheritance mechanisms

Professional Practice Gaps
There has been considerable discussion about the genetics revolution in healthcare, the insufficient numbers of genetics professionals to meet predicted demands, and the potential burden PCPs may experience. In an effort to define what healthcare providers need to know about medical genetics, several organizations developed core competencies (NCHPEG, 2000; ASHG, 2001). However, because clinical genetics is a relatively young and evolving field of medicine, many practitioners received insufficient formal genetics education. As a result, they express a lack of confidence in their clinical genetics knowledge and a lack of confidence in their ability to provide genetic counseling. Dr. Francis Collins, Director of the National Institutes of Health, has stated that it will be "critical to integrate genetics into continuing medical education so that current practitioners will have the knowledge and skills to effectively and responsibly incorporate new genetics knowledge and technologies into practice" (Collins, 1999, p.49).

ORIGIN OF GENETIC DISEASE

Note to Learner
For an optimal learning experience, it is recommended that A Basic Human Genetics Primer: Part I be completed prior to taking this course.

MECHANISMS OF GENETIC DISEASE
Traditionally, genetic disease referred to conditions inherited from a parent. Such diseases are caused by mutations in germline cells and are passed from parent to child. For example, a parent with neurofibromatosis, type 1

• Axillary and/or inguinal freckling
• Cafe au lait spots
• Lisch nodules
• Neurofibromas
• Bone lesions

For more information about neurofibromatosis, see the Related Resources to the right. has a 50% chance of transmitting the condition to each one of his or her children.
It is now understood that many more diseases, such as sporadic cancer, are also genetic disorders. These diseases are caused by mutations occurring in an individual's somatic cells and are not passed on from parent to child. This course will only discuss inherited genetic disease.

**Note**
Genetic disease can result from changes in the following:
- Chromosome number or structure
- DNA sequence

**NUMERICAL CHROMOSOMAL ABNORMALITIES**
People normally have 46 chromosomes. Twenty-three of them come from a person's mother and the other 23 from the person's father. Occasionally, however, either the egg or the sperm cell contributes a number other than 23 chromosomes at fertilization. The most common type of error resulting in abnormal chromosome distribution at fertilization is called nondisjunction. Nondisjunction results in aneuploidy. *Aneuploidy* refers to any number of chromosomes that is not a multiple of the usual 23 found in human egg and sperm.

At present, the cause or causes for nondisjunction are not well understood. One risk factor correlated with the incidence of nondisjunction in egg cells is maternal age. As women age, the chance for nondisjunction to occur increases. Male risk factors for nondisjunction have not been identified.

Most often, when a fertilized egg does not have the normal 46 chromosomes the pregnancy will not progress. However, there are a few forms of aneuploidy (trisomy and monosomy for select chromosomes) that can be found in live-born children.

**Zygote With Trisomy**

Abnormal human egg cell
24 chromosomes (n+1)

23

Normal human sperm cell
23 chromosomes (n)

Trisomic human fertilized egg (zygote)
47 chromosomes (2n+1)

**Zygote With Monosomy**

Normal human egg cell
23 chromosomes (n)

22

Abnormal human sperm cell
22 chromosomes

Monosomic human fertilized egg (zygote)
45 chromosomes (2n-1)

**TRISOMY**
The word trisomy means "3 bodies." Instead of having 2 members of each of the 23 pairs of chromosomes, a third chromosome has been added to one of the 23 pairs. Individuals with trisomy have a total of 47 chromosomes. The additional chromosome can be contributed by either the sperm
or the egg. The only complete trisomies found in live-born children involve an extra chromosome 13, 18, 21, X, or Y.

Information about specific trisomies is covered on the following pages.

**TRISOMY 21**

Trisomy 21, also known as Down syndrome, refers to the presence of an extra chromosome 21. Down syndrome is the most common trisomy in live births, occurring in approximately 1 in 800 live-born children (Jorde et al., 2000). Because of the genetic imbalance created by the presence of an extra chromosome, approximately 75% of pregnancies with trisomy 21 end in miscarriage (Jorde et al., 2000).

About 90% to 95% of the time, the extra 21st chromosome is contributed by the egg cell (Jorde et al., 2000). The incidence of trisomy 21 is positively correlated with maternal age. As a woman's age increases, her chance to have a child with Down syndrome also increases. For example, the chance for a 23-year-old woman to have a child with trisomy 21 is approximately 1 in 1450, the chance for a 35-year-old woman is approximately 1 in 355, and the chance for a 42-year-old is 1 in 50 (Gardner and Sutherland, 1996). Women who are 35 years of age or older at delivery are commonly offered additional prenatal diagnosis options because of the increased risk.

Karyotype of female with Trisomy 21

People with trisomy 21 are at greater risk than the general population for a host of medical complications. Some of the more common findings in individuals with Down syndrome include the following:

- Distinctive facial features
- Developmental delay/mental retardation (IQ average of 50, range 25-75)
- Congenital heart anomalies

While people with trisomy 21 and their families face many additional challenges in life, the loving and friendly personality of many individuals with trisomy 21 often greatly enriches their communities. To learn more about Down syndrome, visit Down Syndrome: Health Issues in the Related Resources to the right.
TRISOMY 13
Trisomy 13, also known as Patau syndrome, results from the presence of an additional chromosome 13. Trisomy 13 occurs in approximately 1 in 10,000 births (Jorde et al., 2000). The biological consequences of having an additional chromosome 13 are enormous. It is estimated that 95% or more of trisomy 13 conceptions result in miscarriage (Jorde et al., 2000). Of those babies that do survive the pregnancy, approximately 90% of infants will not survive the first year of life (Jorde et al., 2000).

The additional chromosome present in people with trisomy 13 is contributed most often by the egg cell; although in approximately 10% of cases, the chromosome is contributed by the sperm cell (Jorde et al., 2000). As with other trisomic conditions, the chance to have a child with trisomy 13 is correlated with maternal age. As women grow older, the chance to have a child with trisomy 13 also increases (Gardner and Sutherland, 1996). At 35 years of age, a woman's chance to have a child with trisomy 13 is 1 in 3,330. At 42 years of age, a woman's chance increases to 1 in 1,430. Women who are 35 years of age or older at delivery are commonly offered additional prenatal diagnosis options because of the increased risk.

Babies born with trisomy 13 frequently have some combination of the following findings:

- Central nervous system defects
- Severe mental retardation (IQ between 20 and 35)
- Posterior scalp lesions
- Oral-facial clefts
- Small, abnormally shaped eyes (microphthalmia)
- Heart defect
• An extra pinky finger (polydactyly)
• Additional organ anomalies

**TRISOMY 18**

Trisomy 18, or Edwards syndrome, is caused by the presence of a third chromosome 18. Approximately 1 in 6,000 babies are born with the condition (Jorde et al., 2000). The biological consequences of having an additional chromosome 18 are enormous. It is estimated that 95% or more of trisomy 18 conceptions result in miscarriage (Jorde et al., 2000). Of those babies that do survive the pregnancy, approximately 90% of infants will not survive the first year of life (Jorde et al., 2000).

Most often, the extra chromosome is contributed by the egg cell at fertilization. However, about 10% of the time the additional chromosome comes from the sperm (Jorde et al., 2000). A woman’s chance to have a baby with trisomy 18 is correlated with her age (Gardner and Sutherland, 1996). Women who are 35 years old have a 1 in 3,330 chance to have a baby with trisomy 18. Woman who are 42 years old have a 1 in 630 chance to have a child with trisomy 18. Women who are 35 years of age or older at delivery are commonly offered additional prenatal diagnosis options because of the increased risk.

Individuals with trisomy 18 are usually recognizable at birth by the collection of features commonly associated with the condition. Not all infants with trisomy 18 will demonstrate all possible features. Common findings in infants with trisomy 18 include the following:

• Low birth weight
• Severe mental retardation (IQ commonly 20-35)
• Characteristic facial features
• Short sternum
• Heart defects
• Clenched hands with overlapping fingers
• Additional organ anomalies

Karyotype From a Female With Edwards Syndrome (47,XX,+18)

47,XXY
47,XXY is also called Klinefelter syndrome (KS). KS is caused by the presence of an extra X chromosome. Approximately 1 in 1,000 boys are born with KS (Jorde et al., 2000). The additional X chromosome is contributed by the child's mother in half of the cases and by the child's father in the other half of the cases (Jorde et al., 2000). For cases of KS caused by an extra maternal X chromosome, the incidence of KS is associated with the woman's age. For example, a 35-year-old woman has a 1 in 1,650 chance of having a son with KS, and a 42-year-old woman has a 1 in 370 chance (Gardner and Sutherland, 1996).

Unlike people with an additional autosome (Down syndrome, trisomy 13, and trisomy 18) individuals with KS do not have a significantly increased risk of major birth defects, characteristic facial features, or mental retardation. Males with KS are, however, more likely to have the following characteristics:

• Be taller than average
• Have longer arms and legs than usual
• Develop breast tissue during teen years
• Have smaller genitals than average
• Have learning disabilities
Because boys with KS are physically just like all other little boys, many are not diagnosed with KS until their teen years or in adulthood. Once puberty occurs, breast enlargement and/or hypogonadism may prompt teens to seek medical attention. However, not all males with KS will display significant physical differences from other males and may escape diagnosis until adulthood. Males with KS are almost always infertile. So those men remaining undiagnosed in adulthood may come to medical attention when they are unsuccessful in having children.

Karyotype From a Male With Klinefelter Syndrome (47,XXY)

47,XXY
About 1 in 1,000 males have 47,XXY (Jorde et al., 2000). The additional Y chromosome is contributed by the father. For the most part, boys and men with 47,XXY are not noticeably different than males with a normal karyotype, 46,XY. Males with 47,XXY are not at increased risk for anatomical birth defects or dysmorphic features. Males with 47, XYY, however, are more likely to have the following characteristics:

- Be taller than average
- Have a slightly lower IQ (10 to 15 points lower)
- Have behavioral disorders
- Have learning disabilities
MONOSOMY
The word monosomy means "one body." Instead of having 2 members of each of the 23 pairs of chromosomes, 1 chromosome is missing from one of the 23 pairs. A monosomic individual has a total of 45 chromosomes. Turner syndrome is the only example of a viable monosomy.

For more information about Turner syndrome, click on the link below.

45,X (Turner syndrome)
Monosomy X (45,X), or Turner syndrome, results when an individual inherits one X chromosome and no second sex chromosome. All individuals with Turner syndrome are female. This is because presence of the Y chromosome is required for male development; in its absence, all fertilized eggs default to becoming female. karyotype of female with Turner syndrome.

Most often, 45,X results when an egg containing 23 chromosomes is fertilized by a sperm containing only 22 chromosomes, lacking a sex chromosome. Of conceptions with a 45,X karyotype, 99% end in miscarriage (Jorde et al., 2000). Approximately 1 in 2,500 to 1 in 5,000 females are born with Turner syndrome (Jorde et al., 2000).

Most people with Turner syndrome have normal intelligence and are active members of their communities. To the majority of the community, the diagnosis of Turner syndrome is likely not apparent. Individuals with Turner syndrome commonly have the following characteristics:

- Short stature
- Absence of ovaries and failure to proceed through puberty
- Characteristic facial features and a webbed neck
- Congenital heart defects
Features associated with Turner syndrome are caused by the absence of the "second dose" of genetic information contained on the short arm of the X chromosome. To learn more about Turner syndrome, visit the Related Resource.

Karyotype From a Female With Turner syndrome (45,X)

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STRUCTURAL ABNORMALITIES

Structural Chromosome Abnormalities
In addition to those disorders caused by atypical numbers of whole chromosomes (trisomy and monosomy), many disorders exist that are caused by the gain, loss, or rearrangement of pieces of chromosomes. These types of chromosome changes are considered to be structural chromosomal abnormalities. Structural changes are described as balanced or unbalanced. Balanced chromosome rearrangements occur when none of the original piece(s) of the chromosome(s) are lost or gained. Unbalanced structural changes, however, result in either loss or gain of genetic information.

A zygote with an unbalanced rearrangement is at increased risk for miscarriage. Zygotes that survive pregnancy with an unbalanced rearrangement are very likely to have birth defects and/or cognitive impairments. In contrast, people with truly balanced chromosome rearrangements usually do not have any physical or cognitive problems as a result of their atypical karyotype. However, they do have an increased risk for producing sperm or egg cells with unbalanced rearrangements. Should an unbalanced gamete be involved in fertilization, there is an increased risk that the pregnancy will either end in miscarriage or that a child will be born with physical anomalies and/or mental retardation.

Examples of structural changes:
  - Complex rearrangements
Complex rearrangements involve 3 or more chromosomes. These rearrangements are not common in living individuals because they often result in a great deal of chromosomal damage. The greater the chromosomal damage, the greater the consequences to the organism. Frequently, complex rearrangements are unbalanced and are either not compatible with life or cause significant malformations and/or mental retardation. Infrequently, complex rearrangements are balanced. Individuals with truly balanced complex rearrangements are clinically unaffected but are at significant risk for an increased number of miscarriages and for having children with unbalanced rearrangements.

The illustration to the right depicts a complex chromosome rearrangement involving chromosomes 1, 14, and 16. Note that the blue and yellow derivative chromosome has 1 centromere. The blue and orange derivative chromosome does not have a centromere, and the yellow and orange derivative chromosome has 2 centromeres. This complex rearrangement is not stable. The blue and orange derivative chromosome will be lost because it does not have a centromere for spindle fibers to attach to during cell division. The yellow and orange derivative chromosome will likely encounter difficulty during cellular division as well because it has 2 centromeres.

- **Deletions**
  Deletions occur when a piece of a chromosome breaks off, does not reattach to any chromosome, and becomes lost to the cell. When a piece of chromosome is deleted, partial monosomy for the deleted region results. Deletions vary in size. Some deletions are large enough to be viewed on a routine karyotype. Other deletions are smaller (microdeletions) and need more elaborate laboratory techniques to demonstrate. The clinical impact of each deletion is dependent upon the amount and importance of the genetic information lost to the cell.

  The illustration to the right depicts a deletion of the tip of the p arm of chromosome 5. Deletions of the tip of chromosome 5p cause a genetic condition called cri du chat syndrome (cry of the cat). Approximately 1 infant in 50,000 is born with cri du

For information about family support for children with Cri du Chat syndrome, see the Related Resources section.

• Duplications
Duplications occur when a segment of a chromosome is copied and then inserted back into the same chromosome the genetic information was originally copied from. Duplications result in partial trisomy. The segment of chromosome that is duplicated has 2 copies on 1 chromosome plus a third copy on the homologous chromosome (unless the duplication occurs in males on a sex chromosome). Duplications are uncommon.

The illustration to the right depicts a duplication of a segment of the q arm of chromosome 10. Several cases of duplications of 10q have been reported in the literature (Chen and Lin 2003; Miglori et al. 2002; Devriendt et al. 1999). Clinical findings are dependent on the size and location of the duplication. Features commonly noted in patients include growth retardation, hypotonia, severe mental retardation, and congenital anomalies.

Families of children with duplicated portions of 10q have created an informational website, Distal Trisomy 10q Families. Several parents have included stories and photos of their children. The National Organization for Rare Disorders also has information about partial trisomy for 10q. For this information, please see the Related Resources section.

• Insertions
Insertions occur when a single chromosome breaks at 2 places and a piece of the chromosome is reinserted elsewhere. The piece of chromosome may be reinserted into a different location in the original chromosome (intrachromosomal insertion) or it may be reinserted into a
different chromosome (interchromosomal insertion). The piece of chromosome may be inserted right side up, or it may inserted upside down (inverted).

Insertions require a total of 3 chromosome breaks, two in the donor chromosome and one in the recipient chromosome. Because 3 breaks are required, insertions are not commonly found in humans. Clinical presentation and reproductive risk in an individual with an insertion is dependent upon the exact rearrangement.

In the illustration to the right, a balanced rearrangement is depicted. A piece of the long arm of chromosome 9 has broken off and become inserted in the short arm of chromosome 17. Because the insertion is balanced, it has no clinical relevance except to increase reproductive risks. Presence of the insertion carries with it an increased risk for miscarriage and for children with unbalanced chromosome rearrangements.

- **Inversions**
  
  Inversions occur when a piece of a chromosome breaks off, flips upside down relative to its original position, and reinserts itself into its parent chromosome. Two distinct categories of inversions exist, pericentric and paracentric inversions. Inversions are labeled pericentric when the breaks on the parent chromosome happen on opposite sides of the centromere (one on the p arm and one on the q arm). In contrast, the breaks in paracentric inversions occur on the same side of the centromere (either both on the p arm or both on the q arm).

  Inversions are relatively common in the general population. Approximately 1 in 1,000 people have an inversion (Jorde et al. 2000). Most inversions are balanced rearrangements and do not cause birth defects.

  The illustration (above, right) depicts a pericentric inversion of the Y chromosome. This inversion occurs fairly frequently among men. It is considered to be a normal variation because it has no impact on health or reproduction (Gardner and Sutherland, 1996).

**Mnemonic**

Pericentric inversions include the centromere.

Paracentric inversions do not include the centromere.

They only impact material from either the p or q arm.

- **Isochromosomes**
Isochromosomes are missing 1 arm (either p or q) and have a second copy of the remaining arm. Isochromosomes result in both partial monosomy (for the deleted region) and partial trisomy (for the duplicated region). Each copy of the remaining arm is attached to the other at the centromere, oriented as a mirror image. Isochromosomes are not common. Most of those documented contain 2 copies of the q arm. The impact an isochromosome has on an individual's health and reproduction is specific to the isochromosome involved. The illustration to the right demonstrates the most frequently observed isochromosome in live-born children, i(Xq). The isochromosome contains two X chromosome q arms and is present in approximately 15% to 20% of females with Turner syndrome (Nussbaum et al., 1996).

- Translocations
  
  Translocations occur when a piece of a chromosome breaks off and becomes attached to another chromosome. Two categories of translocations exist: reciprocal and Robertsonian translocations.

  **Reciprocal Translocations**
  
  Reciprocal translocations occur when 2 chromosomes exchange pieces. Portions of 2 different chromosomes break off from their chromosome of origin, swap places, and then reattach to the broken chromosome that the other chromosome piece originated from (see illustration below left). Most reciprocal translocations are balanced -- no genetic information is lost or gained. Individuals with truly balanced reciprocal translocations are usually healthy; however, they have an increased risk for miscarriages and children with unbalanced chromosome rearrangements.

  **Robertsonian Translocations**
  
  Robertsonian translocations are only found in chromosomes 13, 14, 15, 21, and 22 (the acrocentric chromosomes). Robertsonian translocations occur when the long arms of 2 acrocentric chromosomes become attached to each other at the centromere, while the short arms of the same 2 chromosomes are lost to the cell (see illustration below right). Robertsonian translocations are fairly common, occurring in 1 out of every 1,000 individuals (Gardner and Sutherland 1996). The Robertsonian translocation depicted below is the most common type of Robertsonian translocation, occurring in 1 out of every 1,300 individuals (Gardner and Sutherland 1996).

  People with balanced Robertsonian translocations are clinically unaffected but are at significant risk for an increased number of miscarriages and for having children with
Robertsonian translocations are considered to be balanced when the q arms of all of the acrocentric chromosomes are present.

CHROMOSOMAL MOSAICISM
Occasionally, people are born with an abnormal number of chromosomes or a structural chromosome abnormality that exists in only a percentage of their body cells. The remaining body cells have a normal chromosome complement. This phenomenon of having more than 1 karyotype present in the same individual is known as chromosomal mosaicism. For a clinical example, read about mosaicism
in Turner syndrome. Frequently the presence of cells with a normal chromosome complement helps to lessen the clinical impact of the chromosomally abnormal cells.

Confined Placental Mosaicism
In about 1% to 2% of pregnancies (Jorde et al. 2000), mosaicism occurs solely in the placenta. This clinical occurrence is known as **confined placental mosaicism**. Placental mosaicism can result in an abnormal placenta, increasing the likelihood of a miscarriage for a chromosomally normal fetus. In contrast, for fetuses with an abnormal karyotype, the presence of a chromosomally normal cell line in the placenta may help prevent fetal loss (Gardner and Sutherland 1996).

Etiology of Mosaicism

ALTERATIONS AT THE GENE LEVEL
The previously described disease-causing structural and numerical changes to chromosomes are often visible on a karyotype or through other specialized cytogenetic techniques. The majority of genetic diseases, however, are caused by changes in the DNA sequence of a chromosome that are not visible on a karyotype. Any disease-causing or disease-predisposing changes at the nucleotide level are considered mutations. Mutations can occur anywhere in the human genome. They can impact gene regulatory regions, exons, and introns.

Multiple types of mutations exist and, for convenience, are grouped in categories below. For additional information and diagrams about each type of mutation, see the Related Resources section.

Mutations:
Point Mutations/single nucleotide changes Point mutations occur at the level of a single nucleotide and happen when any given nucleotide in a DNA sequence is replaced by another type of nucleotide. For example, the nucleotide A would be replaced by G, T, or C, altering the original sequence of nucleotides.

Not all types of point mutations have a clinical impact. For example, mutations that cause a change in nucleotide sequence but do not cause a change in amino acid sequence (recall the fact that there are 64 codons but only 20 amino acids) are called silent mutations.

Mutations that do have a clinical impact either alter the function of the gene product or result in a shorter-than-usual protein product. Mutations that alter protein function do so by changing the nucleotide sequence so that the resulting amino acid sequence is also altered. These types of mutations are known as missense mutations (see below left). Mutations that cause a shorter than usual protein product, a truncated product, do so by changing the nucleotide sequence so that a stop codon is introduced prematurely into the amino acid sequence. These types of mutations are called nonsense mutations (see below right).

Missense mutation

![Diagram of a missense mutation](image-url)
Nonsense mutation

Deletions and duplications can involve any number of nucleotides. Deletions occur when nucleotides are lost from the original nucleotide sequence, reducing the size of the DNA sequence (see illustration top right). Duplications occur when any number of nucleotides are copied and then inserted into the original nucleotide sequence, increasing the size of the DNA sequence. Deletions and duplications frequently have a clinical impact.

Deletions and duplications that occur in multiples of 3 nucleotides result in the subtraction or addition of codons to a gene's nucleotide sequence. However, they do not alter the codons in the gene that are not directly involved in the deletion or duplication. In contrast, any change in nucleotide number that is not a multiple of three alters all of the codons in the gene that come after the deletion or duplication. This type of mutation is known as a frameshift mutation. In the illustration at the top right, the deletion of a single nucleotide, A, causes a frameshift mutation.
Frameshift
Nonframeshift
Insertions Insertions occur when an additional nucleotide or nucleotides are added to an original sequence of DNA (excluding instances of duplicated DNA). Insertions can be small or large. Some pieces of DNA in the human genome are especially adept at inserting themselves into other places in the genome. These pieces of DNA are called transposons or mobile elements (Jorde et al. 2000).

Insertions of additional nucleotides that are not in multiples of three (the size of a codon) cause frameshift mutations. When additional nucleotides are inserted into a gene, the insertion frequently has a clinical impact.
Frameshift

Nonframeshift

Trinucleotide expansions Trinucleotide repeat expansions occur only in genes with stretches of DNA that repeat the same 3 nucleotides sequentially. Often the group of 3 nucleotides in a normally functioning gene is repeated 20 to 30 times in a row. When an expansion occurs, the same 3 nucleotides will be repeated many more times than is normal. Both small and large trinucleotide expansions are possible. The clinical impact of trinucleotide expansions depends both on the original number of repeats and the size of the expansion.

Repeat expansion mutation

GENE POLYMORPHISMS

Not all DNA nucleotide changes result in disease. Instead, some are considered benign, even when they occur in the middle of an important gene. Nonharmful genetic variations that occur in at least 1%
of the population are called polymorphisms (Jorde et al., 2000). The image below depicts a polymorphism in the beta-globin gene.

MENDELIAN INHERITANCE

There are numerous different types of genetic changes; thus, for diseases that are caused by different types of changes, there are also many different ways to inherit them. The majority of single-gene genetic conditions are inherited in a relatively straightforward manner (according to the principles originally described by Gregor Mendel). However, a number of conditions are inherited through much more complex mechanisms. Below is a table listing both Mendelian inheritance patterns and the more complicated, nontraditional modes of inheritance.

**Mendelian**
- Autosomal dominant
- Autosomal recessive
- X-linked dominant
- X-linked recessive

**Nontraditional**
- Imprinting
- Mitochondrial inheritance
- Uniparental disomy
- Trinucleotide repeat
- Germline mosaicism
• Multifactorial inheritance

MENDELIAN MODES OF INHERITANCE
The following pages discuss specific Mendelian modes of inheritance.

AUTOSOMAL DOMINANT

Mendelian Inheritance Patterns: Autosomal Dominant
Autosomal dominant patterns of inheritance are perhaps the easiest patterns to detect in a person’s family history. The term autosomal means that the disease-causing mutation is located on one of the 22 autosomes. The term dominant has classically meant any person with a mutation would manifest symptoms of disease. However, geneticists now recognize that people can have a mutation for a well-established autosomal dominant condition and not develop disease. Two explanations for this phenomenon exist, reduced penetrance and variable expressivity (both topics covered later in this course). An individual with an autosomal dominant mutation has a 50% chance with each pregnancy to pass the mutation onto his or her child, without regard to the sex of the child.

When constructing a pedigree, or a 3-generation medical family history, for a patient with an autosomal dominant condition, it is common to find relatives in many generations who also have the condition. For autosomal dominant conditions, only children of individuals with an autosomal dominant mutation will inherit the mutation. Children of parents without a mutation will not inherit a mutation.

View Punnett squares for autosomal dominant conditions in the Related Resources.

Classic Autosomal Dominant Inheritance

AUTOSOMAL RECESSIVE

Mendelian Inheritance Patterns: Autosomal Recessive
Autosomal recessive diseases, like autosomal dominant diseases, have distinct inheritance pattern characteristics. While autosomal dominant conditions are often passed from parent to child over several generations, autosomal recessive diseases usually impact the children of disease-free parents.
The term *autosomal* means that the disease-causing mutation is located on one of the 22 autosomes. The term *recessive* has traditionally meant that a person with 1 copy of a mutation would not be clinically affected with disease because the presence of a second copy of a normally functioning gene (on the homologous chromosome) would essentially compensate for the 1 nonfunctioning copy. A person with 1 copy of an autosomal recessive mutation was considered to be an unaffected carrier of the disease. Today, it is recognized that for some autosomal recessive conditions, people with one mutation may in fact experience some health complications.

Only when 2 parents who are carriers for the *same disease* have children are offspring at risk to have the disease. Two carrier parents have a 25% chance with each pregnancy (regardless of gender) for having a child who inherits the abnormal gene from both parents and is clinically affected with the disorder. In pedigrees of individuals with an autosomal recessive condition, there are often no other clinically affected family members (unless carrier frequency is high in the population). If there are other people with the same condition, those people are usually siblings of the clinically affected individual.

View Punnett squares for autosomal recessive conditions in the Related Resources.

**Classic Autosomal Recessive Inheritance**

X-LINKED DOMINANT

**Mendelian Inheritance Patterns: X-Linked Dominant**

In contrast to autosomal dominant diseases, X-linked dominant conditions are sex linked. The term *X-linked* indicates that the disease-causing mutation is located on the X chromosome. The term *dominant* has classically meant any person with a mutation would manifest symptoms of disease. However, geneticists now recognize that people can have a mutation for a well-established X-linked dominant condition and not develop disease. Several explanations for this phenomenon exist: reduced penetrance, variable expressivity, and lyonization (topics covered later in this course).

A woman with an X-linked dominant mutation has a 50% chance with each pregnancy to pass the mutation onto her child, regardless of the child's sex. X-linked dominant mutations are passed on from a clinically affected father to all of his daughters but to none of his sons.
Pedigrees of people with X-linked dominant conditions often demonstrate individuals in several generations with the same condition. As with autosomal dominant conditions, only children of people with the mutation will be affected. No children of clinically unaffected parents will have the condition.

View Punnett squares for X-linked dominant conditions.

**Classic X-Linked Dominant Inheritance**

![X-Linked Dominant Inheritance Diagram](Image)

**X-LINKED RECESSIVE**

**Mendelian Inheritance Patterns: X-Linked Recessive**

Like X-linked dominant conditions, X-linked recessive diseases are sex linked. The term **X-linked** indicates that the disease-causing mutation is located on the X chromosome. The term **recessive** has traditionally meant that if a female had 1 copy of a disease-causing mutation on an X chromosome that she would not have disease symptoms. The absence of disease symptoms was attributed to the presence of a second copy of a normally functioning gene (on the other X chromosome) that essentially compensated for the nonfunctioning copy. A woman with one X-linked recessive mutation was traditionally considered to be an unaffected carrier of the disease.

Today, it is recognized that for some X-linked recessive conditions, women with 1 mutation may in fact experience some health complications. Such women are described by geneticists as manifesting carriers. Symptom expression is impacted by lyonization (a topic covered on the next page).

Women with one X-linked recessive mutation have a 50% chance with each pregnancy of passing the mutation to her child, regardless of the sex of the child. Some of her daughters may experience health complications directly related to the mutation (i.e., manifesting carriers). In contrast, all of the sons who inherit the mutation from her will be clinically affected with the disease. None will be a carrier. This is because males have only one X chromosome. There is no second X chromosome to compensate for the one with the disease-causing mutation. Clinically affected males will pass the X-linked recessive mutation on to all of their daughters (all of whom will be carriers) and to none of their sons.

View Punnett squares for X-linked recessive conditions in the Related Resources.
For generations, people have noticed that occasionally genetic disease appears to skip generations. In other words, a parent with genetic disease has a child displaying no symptoms, who subsequently has a child with the disease. Physicians have also noticed that not all people with the same genetic disease have the exact same symptoms. Some people have few symptoms while other individuals
have many more. To help describe these nuances, the genetics community commonly uses 2 phrases: reduced penetrance and variable expressivity.

**Reduced penetrance:** There are healthy, disease-free individuals who have a disease-causing mutation but don't demonstrate any clinical symptoms. The reason that these individuals do not have symptoms is because the disease exhibits reduced penetrance.

Different penetrance rates exist for different diseases. Some diseases are highly penetrant, meaning that almost all who harbor a mutation will develop symptoms, while others have low penetrance. For example, of individuals who inherit a disease-causing mutation for Huntington disease, all are expected to become symptomatic. Thus, for Huntington disease penetrance approaches 100%. In contrast, for women who inherit a disease-causing mutation for hereditary breast and ovarian cancer in the BRCA1 gene, 85% or less (Ford et al. 1994; 1998) will develop breast cancer. Thus, mutations in the BRCA1 gene exhibit reduced penetrance.

**Variable expressivity:** This refers to the fact that not all people with the same genetic condition have the exact same symptoms. For example, while it is expected that all individuals with Huntington disease will demonstrate symptoms (loss of motor control, decreased cognitive skills, and/or mental illness), the disease does not present identically in all people with it. Some individuals may have great trouble with motor control for years and not experience mental illness until the end stages of disease. Other individuals may experience mental illness, decreased cognition, and loss of motor control in early stages of disease.

**Lyonization**
Named after Mary Lyon, the woman who first described this phenomenon, lyonization is the random inactivation of one X chromosome in all female body cells. The inactivation is thought to occur around the 32- to 64-cell stage of embryonic life. At that stage, all existing cells randomly inactivate one X chromosome. A portion of cells will inactivate one of the X chromosomes and the remainder will inactivate the other X chromosome. All cells derived from the original 32 or 64 cells will systematically inactivate the exact same X chromosome that the parent cell inactivated. Lyonization is thought to equalize the amount of X chromosome genetic material functionally active in both males and females (remembering that males only have one X chromosome).

**NONTRADITIONAL MODES OF INHERITANCE**
The following pages will discuss nontraditional modes of inheritance.

**IMPRINTED GENES**

**All Genes Are Not Equal**
In the 1980s, geneticists discovered an amazing fact: genes inherited from a person's mother are not equivalent to the same genes inherited from a person's father. This concept is most easily demonstrated by laboratory experiments in which mouse zygotes were created from the nucleus of either 2 sperm or 2 egg cells (Mange and Mange 1999). Zygotes with 46 maternal chromosomes developed into phenotypically normal embryos with vastly underdeveloped extraembryonic membranes. Zygotes with 46 paternal chromosomes developed the extraembryonic membranes but the embryos themselves were underdeveloped. No zygotes were formed exclusively from maternal nor paternal chromosomes were viable.
Findings supporting these results have been documented in pregnant women diagnosed with a hydatiform mole. A hydatiform mole is a uterine mass of extraembryonic tissues without a developing fetus. The genetic content of the tissue is always paternal in origin (complete absence of a maternal contribution).

**Imprinted Genes**
Maternal and paternal genes are not equivalent because of imprinting. The term *imprinting* simply means that a given gene has methyl groups attached to its cytosine nucleotides. In other words, the gene is methylated. Methylated genes are not actively transcribed and translated into protein, so these genes are essentially turned off. A specific set of genes inherited from a person's father is normally methylated. A different group of genes inherited from a person's mother is also normally methylated. Deviation from the normal methylation pattern can result in genetic disease.

Examples of diseases known to be caused by imprinting defects are listed below.

- Prader-Willi
- Angelman Syndrome
- Beckwith-Wiedemann Syndrome

**MITOCHONDRIAL DISEASE**

**Mitochondrial Genome**
Mitochondria are small organelles found in human cells. Each cell usually contains hundreds of mitochondria. They are responsible for producing cellular energy through a complicated process known as oxidative phosphorylation. Mitochondria are unique compared to other cellular organelles (excluding the nucleus) because they also contain DNA. Although the vast majority of genetic information necessary for cellular function is located within the cell's nucleus (in the 46 chromosomes), a few critical genes are located within the mitochondria.

The mitochondrial genome has a completely different structure than the nuclear genome does. Mitochondrial DNA is composed of the same 4 nucleotides as nuclear DNA; however, it exists as a circular strand that is 16,569 base pairs long. Each mitochondrion has approximately 10 identical copies of this circular DNA strand. In fact, the DNA strand in all of the mitochondria in a person's body...
should have this exact same sequence. Embedded within the mitochondrial DNA are genes for the following:

- 2 ribosomal RNAs
- 22 transfer RNAs
- 13 proteins needed for oxidative phosphorylation

As with nuclear DNA, mutations occurring in important mitochondrial genes can result in human disease. Some examples of mitochondrial diseases include Leber hereditary optic neuropathy, myoclonic epilepsy with ragged-red fibers, and Kearns-Sayre disease.

**Mitochondrial Disease Inheritance Pattern**

Mitochondrial mutations are inherited exclusively from a person's mother. This is because during fertilization the egg contributes all of its cellular contents, including its hundreds of mitochondria, to the developing zygote. In contrast, the sperm primarily contributes its nuclear content (the 23 chromosomes) but does not contribute mitochondria.

Human body cells contain hundreds of mitochondria and occasionally a percentage of mitochondrial DNA will have a deleterious mutation while the remainder of mitochondrial DNA does not. This phenomenon of 2 distinct mitochondrial DNA populations coexisting within 1 person is known as heteroplasmy. Usually people can tolerate a small percentage of mutant mitochondria without manifesting clinical symptoms. However, the higher the percentage of mutant mitochondrial DNA, the more likely a person is to have symptoms of a mitochondrial disease. The point at which the mutant DNA load becomes great enough to cause clinical symptoms is known as the **threshold**. People
who have 100% of mutant mitochondrial DNA will have disease. Women with 100% of mutant mitochondrial DNA (i.e., homoplasm) will pass that mutation on to 100% of their children.

Mother With a Percentage of Mutant Mitochondria

Father With a Percentage of Mutant Mitochondria

**Uniparental Disomy**

The phrase uniparental disomy (UPD) accurately describes this rare inheritance pattern. *Uniparental* means "one parent." *Disomy* means "2 bodies." In other words, uniparental disomy occurs when 2 copies (instead of the usual 1 copy) of a chromosome are inherited from 1 parent at the same time that no copies of the homologous chromosome are inherited from the other parent. People with UPD have a total of 46 chromosomes. However, they inherited 24 of those chromosomes from 1 parent and 22 from the other.
Trisomy Rescue: There are several possible mechanisms to explain how uniparental disomy occurs. One explanation is that in an effort to correct a conception with trisomy, the embryo loses one of the 3 chromosomes for which it is trisomic. In discarding one chromosome of the three, should the cell happen to retain 2 chromosomes from the same parent, UPD occurs. This corrective measure of losing a trisomic chromosome is sometimes referred to as trisomy rescue (see illustration at right).

Few conditions are known to be inherited this way. Among them are:

- **Prader-Willi**

  Prader-Willi syndrome (PWS) is caused by abnormalities on the long arm (q arm) of the paternally contributed chromosome 15. The condition occurs in about 1 in 10,000 to 1 in 22,000 people (Cassidy and Schwartz 2004).

  Normally, a specific region of the long arm of the maternally inherited chromosome 15 is imprinted. In other words, the region on the maternal chromosome is turned off through methylation. An individual will not have PWS as long as he or she can transcribe and translate genes along that same portion of chromosome 15 from the paternally inherited chromosome. When an abnormality of the paternally inherited 15q occurs, causing loss of gene expression in that region, PWS results.

  Most often (70% of the time), PWS is caused by a deletion on the paternally contributed long arm of chromosome 15. Less often (less than 5% of the time), PWS results from changes at the DNA level or from another mechanism, uniparental disomy (about 25% of the time) (Cassidy and Schwartz, 2004).

  Individuals with PWS frequently demonstrate some combination of the following symptoms:
  - Low muscle tone
  - Small hands and feet
  - Small gonads in males
  - Failure to thrive followed by a voracious appetite
  - Mental retardation

- **Angelman Syndrome**

  Angelman syndrome (AS) is caused by abnormalities on the long arm (q arm) of the maternally contributed chromosome 15. The condition occurs in about 1 in 12,000 to 1 in 20,000 people (Williams et al. 2003).

  Normally, a specific region of the long arm of the paternally inherited chromosome 15 is imprinted. In other words, the region on the paternal chromosome is turned off through methylation. An individual will not have AS as long as he or she can transcribe and translate genes along that same portion of chromosome 15 from the maternally inherited chromosome. When an abnormality of the maternally inherited 15q occurs, causing loss of gene expression in that region, AS results.

  Most often (65%-75% of the time), AS is caused when a child inherits a deletion on the maternally contributed long arm of chromosome 15. Less often (approximately 18%-32% of the time), AS results from changes at the DNA level or from another mechanism, uniparental disomy (about 3%-7% of the time) (Williams et al. 2003).

  Individuals with AS frequently demonstrate some combination of the following symptoms:
• Severe mental retardation
• Microcephaly
• Seizures
• Happy demeanor
• Ataxia (loss of motor coordination)

• Beckwith-Wiedemann Syndrome

Beckwith-Wiedemann syndrome (BWS) is caused by abnormalities on the short arm (p arm) of the maternally contributed chromosome 11. The condition occurs in about 1 in 13,700 people (Shuman and Weksberg 2003).

Normally, a specific region of the short arm of the paternally inherited chromosome 11 is imprinted. In other words, the region on the paternal chromosome is turned off through methylation. An individual will not have BWS as long as he or she can transcribe and translate genes along that same portion of chromosome 11 from the maternally inherited chromosome. When an abnormality of the maternally inherited 11p occurs, causing loss of gene expression in that region, BWS results.

Most often (80%-90% of the time), BWS is caused when a child inherits mutations or methylation defects at the DNA level. The remainder of cases of BWS (about 10%-20% of the time) result from uniparental disomy (Shuman and Weksberg 2003).

Individuals with BWS frequently demonstrate some combination of the following symptoms:

• Large size at birth
• Large tongue
• Ear lobe creases/ear pits
• Asymmetric growth

All three of these conditions can result from UPD, since 1 member of the homologous chromosome pair has an imprinted region on it and UPD leads to an imbalance in gene expression (see illustration below).

UPD 15 Resulting in Prader-Willi Syndrome
TRINUCLEOTIDE EXPANSION

Similar to other nontraditional modes of inheritance, trinucleotide expansion is a relatively recent discovery. Trinucleotide repeat expansions (TREs) are a specific type of mutation and are inherited in a Mendelian pattern. Depending on the disease, TREs can be inherited as autosomal dominant, autosomal recessive, or X-linked traits.

Currently, there are about 20 distinct genetic diseases caused by TREs (Jorde et al., 2000). All of these conditions have in common the fact that a portion of each disease-causing gene contains an increased number of a repeating series of 3 nucleotides (thus the word trinucleotide). A certain number of these repeats are supposed to be present in select genes. However, if the number of those repeating trinucleotides greatly increases, normal function of the protein product is interrupted and causes genetic disease.

Anticipation

One unusual aspect of TREs is the fact that the number of repeats in a given gene can increase from one generation to the next. Such size increases are not common in the general population. In fact, for the most part the same number of repeats a parent has is passed down to the child. Occasionally however, an error occurs during meiosis. A few extra repeats are mistakenly inserted into a gene that is supposed to have a small number of trinucleotide repeats. Should that gene eventually be involved in fertilization, the child will have a larger number of repeats than its parent did.

Once one error has occurred that slightly increases the number of trinucleotide repeats in a gene, that same gene is more likely to continue slightly increasing in size, generation to generation. Eventually, the increase in repeat numbers becomes great enough to cause genetic disease. Genes with repeat sizes that are larger than normal, but still small enough to not cause clinical problems, are called intermediate alleles. The phenomenon of a slowly expanding trinucleotide repeat number from a normal size to an intermediate allele to a disease-causing mutation is known as anticipation. For some diseases, anticipation is more likely to occur when the gene is passed from mother to child (fragile X syndrome); while for others, it is more likely to occur when the gene is passed from father to child (Huntington disease).

Below is a list of some diseases caused by trinucleotide repeat expansions, along with the mode of inheritance. To learn more about each disease, click on the links provided.

- Myotonic dystrophy, type I (autosomal dominant)

  Myotonic dystrophy, type I, occurs in about 1 in 20,000 people worldwide (Bird, 2004). The condition is autosomal dominant and is caused by a trinucleotide repeat expansion of CTGs in the DMPK gene. People without myotonic dystrophy have fewer than 36 CTG repeats. People with myotonic dystrophy will have 50 repeats or more. Repeat sizes between the normal 35 and disease-causing 50 are intermediate alleles and do not cause disease, although these repeats are more likely to expand in offspring.

  Depending upon the number of repeats present, symptoms in individuals with myotonic dystrophy can be relatively mild or can be life-threatening. Symptoms frequently observed include the following:

  - Muscle weakness
  - Low muscle tone
• Myotonia (delayed relaxation of muscle after a contraction)
• Cataracts

• Huntington disease (autosomal dominant)

About 1 in 12,500 to 1 in 25,000 people have Huntington disease (HD) (Haigh et al., 2004). HD is an autosomal dominant condition caused by an expansion of CAG trinucleotide repeats. People without HD usually have 26 or fewer CAG repeats. People with HD have 36 repeats or more. Repeat sizes between the normal 26 and disease-causing 36 are intermediate alleles and do not cause disease, although these repeats are more likely to expand in offspring.

Individuals with HD frequently demonstrate the following symptoms:
• Chorea (involuntary, jerky movements)
• Mental illness
• Decline in cognitive function

• Friedreich ataxia (autosomal recessive)

Friedreich ataxia occurs in about 1 in 25,000 to 1 in 50,000 people worldwide (Bidichandani and Ashizawa 2004). The condition is autosomal recessive and is most often caused by a trinucleotide repeat expansion of GAAs in the FRDA gene. People without FA have fewer than 34 GAA repeats. People with FA will have 66 repeats or more. Repeat sizes between the normal 33 and disease-causing 66 are intermediate alleles and do not cause disease, although these repeats are more likely to expand in offspring.

Symptoms frequently observed include the following:
• Ataxia
• Muscle weakness
• Absent reflexes in the legs

Some patients also experience additional health complications.

• Fragile X, type A (X-linked dominant)

Fragile X syndrome, type A, is found in about 1 in 5,000 males and in 1 in 10,000 females (Saul and Tarleton 2004). The condition is X-linked dominant and is caused by a trinucleotide repeat expansion of CGGs in the FMR1 gene. People without fragile X syndrome have fewer than 45 CGG repeats. People with fragile X will have 200 repeats or more. Repeat sizes between the normal 44 and the disease-causing 200 are intermediate alleles and do not cause classic fragile X syndrome, although these repeats are more likely to expand in offspring.

Depending upon the number of repeats present, symptoms in individuals with fragile X syndrome can be relatively mild or can be significant. Symptoms frequently observed include the following:
• Mental retardation
• Behavior problems
• Long, characteristic faces
• In males post-puberty, large gonads
Note: Although fragile X syndrome is caused by increased CGG repeats, phenotype is also impacted by methylation status of the FMR1 gene.

GERMLINE MOSAICISM
Germline mosaicism occurs when only a percentage of a person's germ cells have a disease-causing mutation in a gene. The somatic cells do not harbor the disease-causing mutation and, therefore, the individual has no symptoms of disease. However, the individual is at greater risk than the general population to have a child who inherits the mutation.

Germline mosaicism is a relatively rare event, although there are some diseases that are more frequently caused by germline mosaicism than others. Germline mosaicism should be considered when an individual is the first person in his or her family diagnosed with a genetic disease that is not autosomal recessive. Duchenne muscular dystrophy is an example of a disease that can be inherited from a mother with germline mosaicism.

Duchenne Muscular Dystrophy (DMD) is found in about 1 in 3,500 males (Mange and Mange 1999). The condition is X-linked recessive, so males are predominantly affected. Symptoms begin early in childhood for boys with DMD and usually include the following:

- Progressive muscle weakness
- Enlarged calves
- Cardiomyopathy

DMD frequently occurs in families without a previous history of the condition. Sometimes when the diagnosis is made in a child without a positive family history, the child is found to have a new mutation. However, more often it is discovered that the child inherited a mutation from his mother. Because DMD is X-linked recessive, it would have been unlikely that his mother demonstrated symptoms of DMD or was even aware that she carried the mutation. The mother may have the DMD mutation in all of her cells (somatic cells and germline cells) or may have the mutation in only some of her cells (somatic and/or germline mosaicism). For a mother whose blood sample tests negative for the DMD mutation present in her clinically affected son, there is a 12% to 15% chance that she has germline mosaicism (Korf et al., 2004). Although the mother will not experience any clinical symptoms, each of her children will be increased risk to inherit the mutation from her.

MULTIFACTORIAL CONDITIONS
Not all conditions with a genetic component follow a recognizable mode of inheritance (i.e., neither Mendelian nor nontraditional). Conditions that tend to occur more often in family members of an
affected person compared to the general population but that do not adhere to a recognized mode of inheritance usually have a multifactorial origin. Multifactorial conditions are caused by poorly understood interactions between genetic and environmental factors. Many common diseases, including diabetes, autism, and cardiovascular disease, are multifactorial.

To explain how the complex interaction between a person’s genes and the environment produces disease, the threshold model is frequently used. The threshold model assumes that there are multiple factors impacting disease status. Each factor by itself has a relatively small effect on disease development. An accumulation of multiple factors that predispose a person toward disease is required. The point at which enough factors add up to cause disease development is known as the **threshold**.

In the illustration to the right, a normal distribution of the population is shown. The X axis represents an individual's liability. Liability, as used here, means the total number of risk factors (genetic and environmental) that predispose an individual to disease. In the graph, liability increases, moving to the right along the X axis. People who are unaffected will have fewer risk factors and will fall under the bell curve to the left of the solid line labeled "Threshold." People to the right of the threshold line will have a greater number of risk factors and will be clinically affected.

Because multifactorial conditions do not follow predictable patterns of inheritance, recurrence risk calculations for family members of an affected individual are based on data derived from other families with similar circumstances. Recurrence risks for siblings of a single affected individual are often on the order of 2% to 5%.

**SUMMARY AND KEY POINTS**

- Genetic disease can result from mutations in vital DNA sequences. Not all DNA changes cause disease. Nondisease-causing DNA sequence variations that occur in 1% or more of the population are known as polymorphisms.
- Genetic disease can be inherited in many ways. Modes of inheritance are commonly grouped into 2 categories: traditional or Mendelian patterns and nontraditional modes of inheritance.

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<th>Mendelian</th>
<th>Nontraditional</th>
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<tr>
<td>• Autosomal dominant</td>
<td>• Imprinting</td>
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<td>• Autosomal recessive</td>
<td>• Mitochondrial</td>
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<td>• X-linked dominant</td>
<td>• Uniparental disomy</td>
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<td>• X-linked recessive</td>
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<td>• Germline mosaicism</td>
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• Many online genetic resources are available. GeneTests is a website containing helpful educational materials and a comprehensive listing of available genetic tests. OMIM contains a large repository of reviews of genetic conditions. Both the NSGC and ACMG websites allow clinicians to locate genetics professionals.

RESOURCES AVAILABLE THROUGH THIS MODULE:

• American College of Medical Genetics: Membership Directory
  The American College of Medical Genetics is composed primarily of doctoral (MD, PhD, DO) and master's level (genetic counselors) medical genetics professionals. This is a searchable database of all ACMG members by name or location.

• Angelman Syndrome
  This article provides information on the characteristics of Angelman syndrome, focusing on the genetic aspects such as genetic testing and genetic counseling.

• Beckwith-Wiedemann Syndrome
  This article provides information on the characteristics of Beckwith-Wiedemann Syndrome, focusing on the genetic aspects such as genetic testing and counseling.

• Beckwith-Wiedemann Syndrome Images
  This page provides images of children affected by Beckwith-Wiedemann syndrome.

• Distal Trisomy 10q Families
  The mission of this informational website is to bring families of children with Trisomy 10q together. The primary objectives are: provide a registry of children and families with 10q so families can contact each other, provide a place where families can submit information on their children and experiences, provide links to related web sites, and build a database for researchers on this syndrome (From their Website). Several parents have included stories and photos of their children.

• Down Syndrome: Health Issues
  This website is written and maintained by Len Leshin, MD, FAAP. Dr. Leshin is a pediatrician and father of a boy with Down syndrome. He has included many helpful resources, guidelines for healthcare, and photos of his son.

• Dystrophinopathies
  This article describes the disease characteristics of dystrophinopathies, which include Duchenne/Becker muscular dystrophy.

• Five P Minus Society: Family Support Group for Children with Cri du Chat Syndrome
  The mission of this website is to encourage and facilitate communication among families having a child with 5p-syndrome and to spread awareness and education of the syndrome to these families and their service providers (From their Website).

• FMR1-Related Disorders
  This article provides information on the disease characteristics of FMR1-related disorders including fragile X syndrome, fragile X-associated tremor/ataxia syndrome (FXTAS), and FMR1-related premature ovarian failure (POF).

• Friedreich Ataxia
  This article provides information on the disease characteristics of Friedreich Ataxia, with an emphasis on genetic testing.
• **Gene Mutations**
  This page provides information and diagrams on four main categories of gene mutations: Point Mutations, Deletions/duplications, Insertions, and Trinucleotide expansions.

• **Genetics Home Reference**
  The Genetics Home Reference website provides consumer-friendly information about the effects of genetic variations on human health, and is a guide to understanding genetic conditions (From their Website). It offers information about basic genetics, some genetic diseases and the underlying etiology of such diseases, and many helpful illustrations.

• **Growth Charts for Children With Down Syndrome**
  The site is maintained by the parent of a girl with Down syndrome and provides growth charts for the height, weight, and head circumference of females and males by age.

• **Huntington Disease**
  This web page provides a summary of the characteristics of Huntington Disease, as well as information on the genetic testing used to diagnose the disease.

• **Klinefelter Syndrome**
  This article discusses the prevalence, diagnosis, clinical features, and treatment of Klinefelter Syndrome. Images of the condition are also included.

• **Mitochondrial cytopathy in adults: What we know so far**
  This article discusses mitochondrial cytopathies in depth, including diagnosis and clinical features.

• **Mitochondrial DNA Deletion Syndromes**
  This article provides information on the characteristics of Mitochondrial DNA Deletion Syndromes, including Kearns-Sayre Syndrome (KSS), Pearson Syndrome, Progressive External Ophthalmoplegia (PEO).

• **Myoclonic Epilepsy Associated With Ragged-Red Fibers (MERRF)**
  This article describes the characteristics of MERRF and provides information on genetic testing and counseling.

• **Myotonic Dystrophy Type 1**
  This article describes the disease characteristics of myotonic dystrophy I, with emphasis on genetic testing.

• **National Society of Genetic Counselors, Inc. Search**
  The National Society of Genetic Counselors is the professional membership association for the genetic counseling profession. This Web page is a searchable database of genetic counselors by location, name, or specialty.

• **Neurofibromatosis**
  This article describes the characteristics of neurofibromatosis and includes images of the disease.

• **NHGRI: Chromosome Abnormalities**
  Chromosome Abnormalities informational page from NHGRI

• **Online Mendelian Inheritance In Man (OMIM)**
  OMIM is a comprehensive, authoritative, and timely compendium of human genes and genetic phenotypes. The full-text, referenced overviews in OMIM contain information on all known mendelian disorders and over 12,000 genes. OMIM focuses on the relationship between phenotype and genotype. It is updated daily, and the entries contain copious links to other
OMIM is intended for use primarily by physicians and other professionals concerned with genetic disorders, by genetics researchers, and by advanced students in science and medicine. While the OMIM database is open to the public, users seeking information about a personal medical or genetic condition are urged to consult with a qualified physician for diagnosis and for answers to personal questions (From their Website).

- **Patau Syndrome**
  This article provides information about the prevalence, diagnosis, clinical presentation, and treatment of Patau Syndrome (trisomy 13).

- **Prader-Willi Syndrome**
  This article provides information on the characteristics of Prader-Willi syndrome, focusing on the genetic aspects such as genetic testing and counseling.

- **Prader-Willi Syndrome (PWS)**
  This page provides an overview of Prader-Willi syndrome with links to many scientific resources about the disease.

- **Punnett Squares for Autosomal Dominant Conditions**
  Punnett squares are often used to predict reproductive outcomes for parents with an increased risk for having children with genetic disease. Along the top of the square are 2 egg cells from the mother. In each egg cell is 1 member of a homologous chromosome pair. The pair has previously separated from one another during meiosis. Along the left side of the square are 2 sperm cells from the father. In each sperm cell is 1 member of a homologous chromosome pair that also separated during meiosis.

- **Punnett Squares for Autosomal Recessive Conditions**
  Below are sample Punnett squares for autosomal recessive conditions. The disease-causing mutation is denoted by the lower case letter a. The normal gene is denoted by the capital letter A.

- **Punnett Squares for X-Linked Dominant Conditions**
  Below are sample Punnett squares for X-linked dominant conditions. The disease-causing mutation is denoted by the capital letter A. The normal gene is denoted by the lower case letter a.

- **Punnett Squares for X-Linked Recessive Conditions**
  Below are sample Punnett squares for X-linked recessive conditions. The disease-causing mutation is denoted by the lower case letter a. The normal gene is denoted by the capital letter A.

- **The Cruelest Disease: How Huntington’s destroyed the dreams of a Utah family**
  This article provides a personal account of the impact Huntington Disease can have on a family.

- **The United Mitochondrial Disease Foundation**
  This is the website of an organization dedicated to promoting research and education for the diagnosis, treatment and cure of mitochondrial disorders. It includes many helpful resources for affected individuals and their families.

- **Trisomy 18**
  This article provides a comprehensive information on the prevalence, diagnosis and clinical presentation of trisomy 18 (Edwards Syndrome) as well as photos of children with this condition.
• Turner Syndrome
The article provides a complete system review and photos of children with Turner syndrome.

REFERENCES USED IN THIS MODULE:


**PROFESSIONAL PRACTICE GAP REFERENCES**

