

Primer in Genetics and Genomics, Article 4—Inheritance Patterns

Biological Research for Nursing
2017, Vol. 19(4) 465-472
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DOI: 10.1177/1099800417708616
journals.sagepub.com/home/brn



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Abstract

Since the completion of the Human Genome Project, much has been uncovered about inheritance of various illnesses and disorders. There are two main types of inheritance: Mendelian and non-Mendelian. Mendelian inheritance includes autosomal dominant, autosomal recessive, X-linked, and Y-linked inheritance. Non-Mendelian inheritance includes mitochondrial and multifactorial inheritance. Nurses must understand the types of inheritance in order to identify red flags that may indicate the possibility of a hereditary disorder in a patient or family.

Keywords

genotype, phenotype, allele, Mendelian inheritance, dominant, recessive, homozygous, heterozygous, Punnett square, mitochondrial inheritance, pedigree, non-Mendelian inheritance, multifactorial inheritance

The Human Genome Project (HGP) was an international research initiative that began in 1990 and was completed in 2003 with the successful sequencing of the entire human genome (National Human Genome Research Institute [NHGRI], 2012). The HGP identified the approximately 20,500 genes in each human (the complete set of human genes) as well as their locations. Finally, the project identified the blueprint for human health (NHGRI, 2012). Further information about the HGP can be found at <http://www.genome.gov>. Subsequent research has suggested that the focus of genetics (the study of single-gene disorders) should expand to include genomics, the study of how genes interact with each other and with environmental, psychosocial-behavioral, and cultural factors. Genetics and genomics provide the basis for health, illness, disease risk, and treatment response (Clark, Adamian, & Taylor, 2013). Genetics and genomics have already moved into mainstream health care. Presently, research in the field of genetics and genomics is focused on personalized medicine and precision medicine with the hope of improving health outcomes by developing customized therapies for individual patients.

Since knowledge in genetics and genomics is ever increasing, it is important for nurses to integrate genetics and genomics into their practice, regardless of academic preparation, role, practice setting, or clinical specialty (Consensus Panel on Genetic/Genomic Nursing Competencies, 2009). This process includes obtaining a complete family medical history, constructing a minimum of a three-generation pedigree, identifying “red flags” that may indicate the possibility of a hereditary syndrome or risk of disease, providing patient education, and referring the patient or family to a genetic specialist for a comprehensive evaluation, as indicated (Calzone et al., 2016;

Coleman et al., 2014). Thus, in order to integrate genetics and genomics into their practice, nurses must have a basic understanding of inheritance patterns. In this article, we discuss the basic concepts of inheritance, Mendelian and non-Mendelian inheritance, probabilities of inheritance, construction of a three-generation pedigree, and identification of red flags that indicate the need for a referral to a genetics specialist. Additional genetic and genomic educational resources for nurses are available in both print and electronic form (Tonkin, Calzone, Jenkins, Lea, & Prows, 2011; see resources in Table 1).

What Is Inheritance?

Each human nucleated cell contains 46 chromosomes arranged in 23 pairs. There are 22 pairs of autosomes and 1 pair of allosomes or sex chromosomes (XX or XY). An individual inherits one chromosome of each pair from each parent. The chromosomal complement of a normal female is 46, XX, while

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Series Information:

The “Primer in Genetics and Genomics” series is a collaboration between *Biological Research for Nursing* and the International Society of Nurses in Genetics (ISONG). Sheila A. Alexander, PhD, RN, FCCM, serves as guest editor for the series.

Table 1. List of Resources on Genetics and Genomics for Health Professionals.

Resource Name	Resource Website
American Medical Association, "Collecting a Family History"	https://www.ama-assn.org/delivering-care/collecting-family-history
Cincinnati Children's Genetic Education Program	https://www.cincinnatichildrens.org/education/clinical/nursing/genetics
Consensus Panel on Genetic/ Genomic Nursing Competencies (2009)	https://www.genome.gov/pages/careers/healthprofessionaleducation/geneticscompetency.pdf
DNA Learning Center	https://www.dnalc.org
GENE Tests International	https://www.genetests.org/clinics/
Genetics Clinic Directory	
Genetic Alliance	http://www.geneticalliance.org/
Genetics Home Reference	https://ghr.nlm.nih.gov/
Genetics in Primary Care Institute: A tool kit to improve care for pediatric patients with genetic conditions in primary care	https://geneticsinprimarycare.aap.org/Documents/GPCI_Toolkit.pdf
International Society of Nurses in Genetics	http://www.isong.org/
Jackson Laboratory (formerly, the National Coalition for Health Professional Education in Genetics)	https://www.jax.org/education-and-learning/clinical-and-continuing-education
Learn.Genetics	http://learn.genetics.utah.edu/
March of Dimes, "Your Family Health History"	http://www.marchofdimes.org/pregnancy/your-family-health-history.aspx
National Cancer Institute Cancer Genetics Services Directory	https://www.cancer.gov/about-cancer/causes-prevention/genetics/directory
National Human Genome Research Institute: Education	https://www.genome.gov/education/
Talking Glossary of Genetic Terms	https://www.genome.gov/glossary/
All About the Human Genome Project	https://www.genome.gov/10001772/all-about-the-human-genome-project-hgp/
Fact Sheets on Science, Research, Ethics, and the Institute	https://www.genome.gov/10000202/fact-sheets/
Online Genetics Education Resources	https://www.genome.gov/10000464/onlinegenetics-education-resources/
National Human Genome Research Institute Project	http://www.genome.gov
National Society of Genetic Counselors: About Genetic Counselors	www.nsgc.org
Find a Genetic Counselor (directory)	http://www.nsgc.org/page/find-a-gc-search

the chromosomal complement of a normal male is 46, XY. *Genotype* refers to an individual's actual DNA sequence at a specific locus (location on a chromosome), and *phenotype* is

the observable ways in which that DNA sequence manifests in the individual, such as eye color, hair color, or susceptibility to a disease (Beery & Workman, 2012). An *allele* is an alternate form of a gene. For example, in the case of eye color, there is a gene responsible for the amount and quality of melanin. Different versions of this gene (i.e., different alleles) may lead to more or less melanin in the eye, thus affecting eye color (National Institute of Health, n.d.). There can be many different alleles for each gene. An allele in its most common form in a population is referred to as *wild type*. A *mutation* is an allele that has a permanent alteration in its DNA sequence (Kenner & Lewis, 2013). Mutations can be inherited or sporadic (not inherited). They can be disease causing or represent a normal variation. A *polymorphism* is a normal variation that does not have a deleterious effect. When an individual has two identical alleles for a particular gene, it is termed *homozygous*; when an individual has two different alleles for a gene, it is termed *heterozygous*.

Patterns of inheritance vary. The main types of genetic inheritance include traditional Mendelian inheritance and nontraditional, or non-Mendelian, inheritance (Kenner & Lewis, 2013).

Mendelian Inheritance

Mendelian inheritance is named after the Austrian monk and scientist Gregor Mendel who experimented with crossbreeding pea plants in the mid-19th century (refer to the first article in the Primer in Genetics and Genomics series for more information about Gregor Mendel; Dorman, Schmella, & Wesmiller, 2017). Mendel coined the terms *dominant* and *recessive* to explain the relationship between two versions of a gene (Leavitt, 2010). He identified the appearance of parental genes in offspring as dominant or recessive traits: If a pea plant was heterozygous for a gene, the gene would express the dominant allele, thus masking the recessive allele (National Institutes of Health, National Human Genome Research Institute, n.d.). Today, our knowledge has increased to understand that an allele does not have to be dominant or recessive. Rather, if two alleles of a gene are present, both can be expressed.

In a single-gene disorder, the individual inherits a single affected allele (the gene is mutated) or a pair of affected alleles (both copies of the gene are mutated). If the affected allele is on a nonsex chromosome, the disorder is referred to as an *autosomal disorder*, and if the affected allele is on a sex chromosome, it is referred to as an *X-linked* or *Y-linked disorder* (Kenner & Lewis, 2013). Common Mendelian inheritance patterns include autosomal dominant, autosomal recessive, X-linked recessive, X-linked dominant, and Y-linked.

Autosomal dominant inheritance. In an autosomal dominant disorder, only one copy of the affected (dominant) allele is required for the person to have the disorder or disease. An individual has a 50% chance of inheriting the affected allele from an affected parent. Males and females are equally at risk. Conversely, an affected individual with one mutated allele has a 50% chance of passing the mutated allele on to future

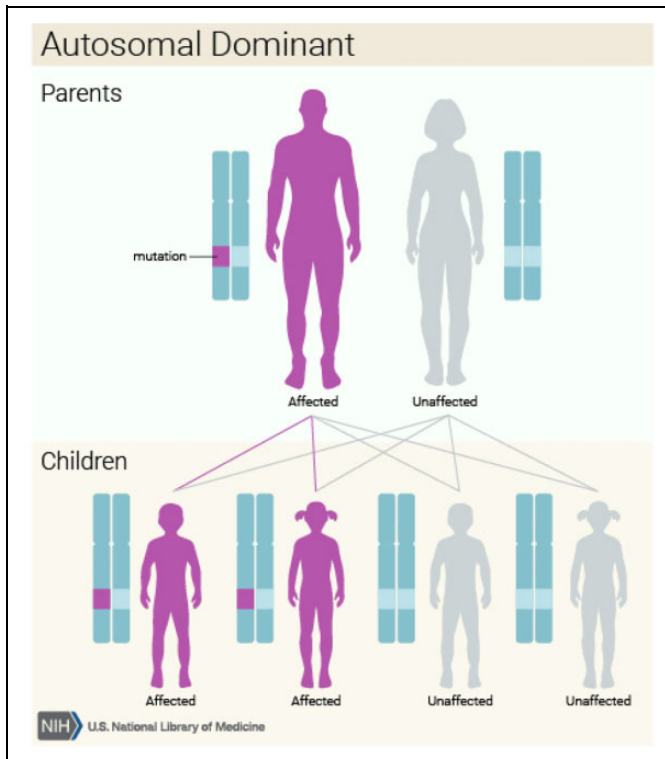


Figure 1. Autosomal dominant inheritance. *Source.* Illustration: National Library of Medicine (United States). Genetics Home Reference [Internet]. Bethesda (MD): The Library; April 11, 2017. [Illustration] Autosomal dominant; (cited April 13, 2017); (about one screen). Available from <https://ghr.nlm.nih.gov/primer/inheritance/inheritancepatterns>

offspring (see Figure 1). Over half of the 6,000 classified Mendelian disorders are autosomal dominant (Kenner & Lewis, 2013). Some examples of disorders that are transmitted in an autosomal-dominant pattern include achondroplasia (caused by one mutated allele in the *FGFR3* gene), Huntington's disease (caused by one mutated allele in the *HTT* gene), neurofibromatosis Type 1 (caused by one mutated allele in the *NF1* gene), neurofibromatosis Type 2 (caused by one mutated allele in the *NF2* gene), Marfan syndrome (caused by one mutated allele in the *FBN1* gene), and polycystic kidney disease (caused by one mutated allele in either the *PKD1* or *PKD2* gene; National Institute of Health, n.d.).

Autosomal recessive inheritance. Both copies of the affected (recessive) allele are required for a person to have an autosomal recessive disorder or disease. The affected offspring thus inherits two copies of the affected allele, one from each carrier parent. Individuals who inherit only one copy are *carriers* of the disorder but do not have the clinical manifestations of the disease. However, there are some exceptions to this rule. For example, if a person has only one copy of a mutation on the *HBB* gene (only one allele is affected), the person has sickle-cell trait (SCT), not sickle cell disease. Usually, a person with SCT does not have any symptoms, but in rare cases, people

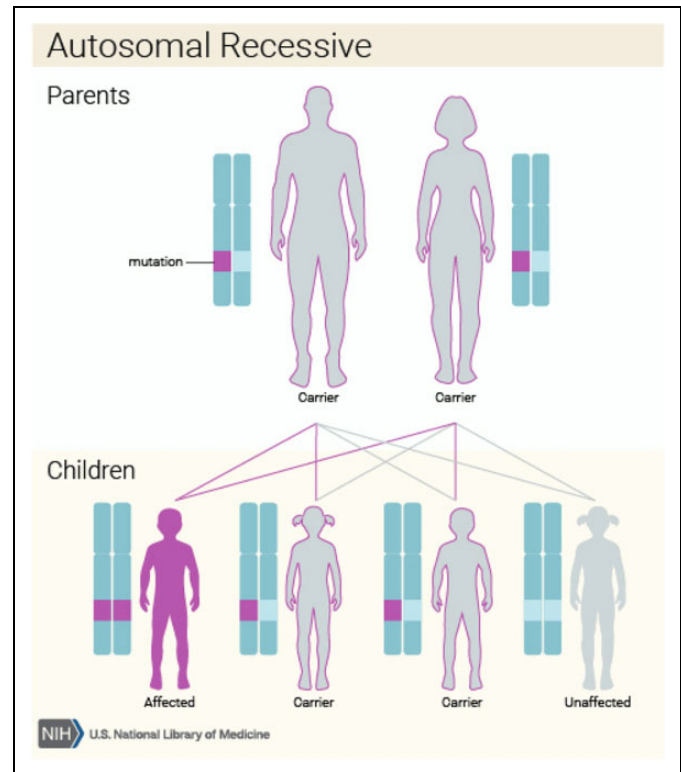


Figure 2. Autosomal recessive inheritance. *Source.* Illustration: National Library of Medicine (United States). Genetics Home Reference [Internet]. Bethesda (MD): The Library; April 11, 2017. [Illustration] Autosomal recessive; (cited April 13, 2017); (about one screen). Available from <https://ghr.nlm.nih.gov/primer/inheritance/inheritancepatterns>

with SCT may experience complications and/or symptoms (Centers for Disease Control and Prevention, 2016). When both parents are carriers of an autosomal recessive disorder, each child has a one-in-four chance (25%) of inheriting the disorder, a 50% chance of inheriting one copy of the affected gene and being a carrier, and a 25% chance of not inheriting the affected gene at all. Males and females are equally at risk (see Figure 2). If one parent is homozygous for an autosomal recessive disorder (has two copies of the affected gene and thus has the disorder) and the other parent is not a carrier and does not have the disorder (does not have an affected gene), each of their children has a 100% chance of being a carrier and a 0% chance of exhibiting the recessive disorder (affected; Kenner & Lewis, 2013). Examples of autosomal recessive disorders include cystic fibrosis (caused by two mutated copies of the *CFTR* gene), sickle cell disease (caused by two mutated copies of the *HBB* gene), phenylketonuria (caused by two mutated copies of the *PAH* gene), and Tay-Sachs disease (caused by two mutated copies of the *HEXA* gene; National Institute of Health, n.d.).

X-linked inheritance. X-linked disorders are due to mutations on the X chromosome. These mutations can be inherited from the mother (XX) or the father (XY). X-linked disorders can also be dominant or recessive.

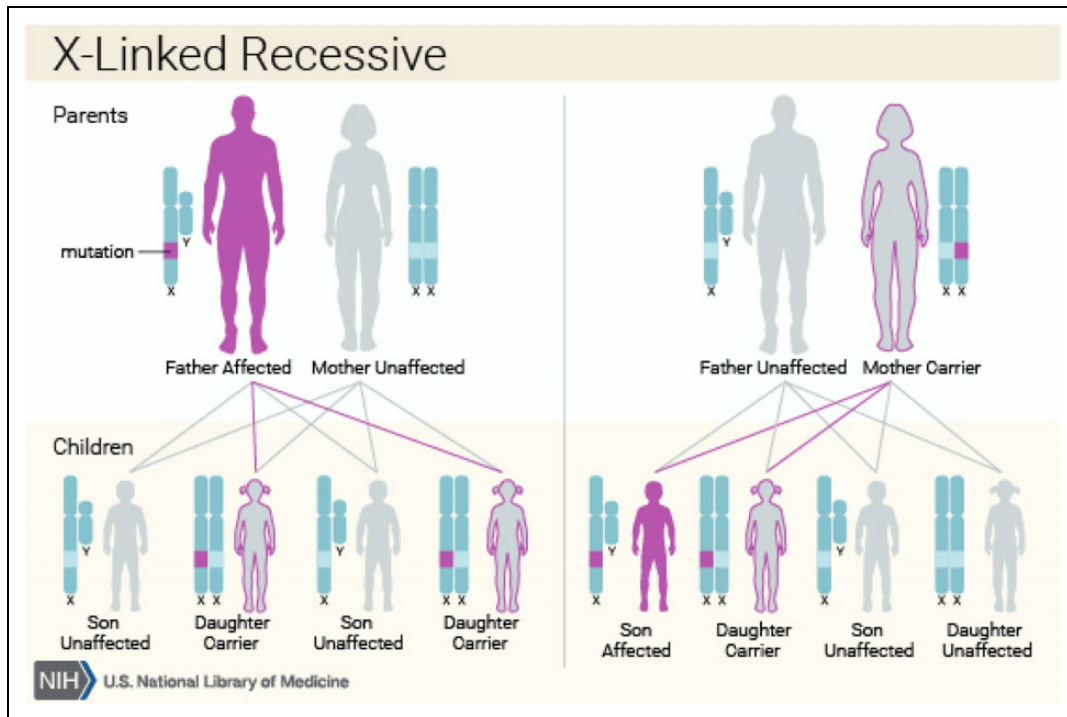


Figure 3. X-linked recessive inheritance. *Source.* Illustration: National Library of Medicine (United States). Genetics Home Reference [Internet]. Bethesda (MD): The Library; April 11, 2017. [Illustration] X-linked recessive; (cited April 13, 2017); (about 1 screen). Available from <https://ghr.nlm.nih.gov/primer/inheritance/inheritancepatterns>

For an X-linked recessive disorder to occur in females, the affected individual must have two copies of the affected gene, one in each of her X chromosomes. However, if a male's single X chromosome has an affected gene, leaving the individual with no healthy copy of the X chromosome, the male will have the disorder. Males only inherit X-linked recessive disorders from a mother who is either a carrier or affected since they inherit the Y chromosome from the father. Most X-linked disorders are recessive. If a female is a carrier of an X-linked recessive disorder, there is a 50% chance that each son will have the disorder (affected) and a 50% chance that each daughter will be a carrier. If a male is affected with an X-linked recessive disorder (which he had to have inherited from his mother), there is a 100% chance that each of his daughters will be at least a carrier. The daughters can only be affected with the recessive illness if they also inherit an affected allele from their mother. The male affected with an X-linked recessive disorder has a 0% chance of passing the disorder on to a son. As mentioned above, a son can only inherit an X-linked recessive disorder from his mother (Kenner & Lewis, 2013; see Figure 3). Some examples of X-linked recessive disorders include Duchenne muscular dystrophy, Fabry disease, hemophilia, red-green color blindness, and Lesch-Nyhan syndrome (National Institutes of Health, n.d.).

X-linked dominant disorders are rare, severe, and usually lethal. If a female has an X-linked dominant disorder, there is a 50% chance that each son will have the disorder and a 50% chance that each daughter will have the disorder. If a male is affected with an X-linked dominant disorder, there is a 100%

chance that each daughter will have the disorder and a 0% chance that he would pass on the disorder to any son (see Figure 4). X-linked dominant disorders include fragile X syndrome, Charcot-Marie-Tooth disease, hereditary hypophosphatemia rickets, and Rett syndrome (National Institutes of Health, n.d.).

Y-linked inheritance. Y-linked disorders are due to mutations on the Y chromosome; therefore, these disorders only occur in males and are transmitted from father to son (see Figure 5). Y-linked genes are important in male sexual development and spermatogenesis. Y-linked disorders include Y-chromosome infertility and some cases of Swyer syndrome (National Institutes of Health, n.d.). Y-linked disorders have also been associated with skin abnormalities, hairy ears, webbed toes, height determination, and tooth enamel abnormalities (Kenner & Lewis, 2013).

Punnett squares. Punnett squares are a useful tool for evaluating the probability that an offspring will inherit a disorder via Mendelian inheritance mechanisms. It is important to note that a Punnett square determines probability rather than absolute certainty since there are other genetic and environmental factors that influence single-gene expression. Nonetheless, this tool can assist in determining risk for disease and help with reproductive decision-making. A Punnett square is drawn as a two-by-two grid. The dominant allele from either parent is represented by an upper case letter and the recessive allele by a lower case letter. Two upper case letters represent a

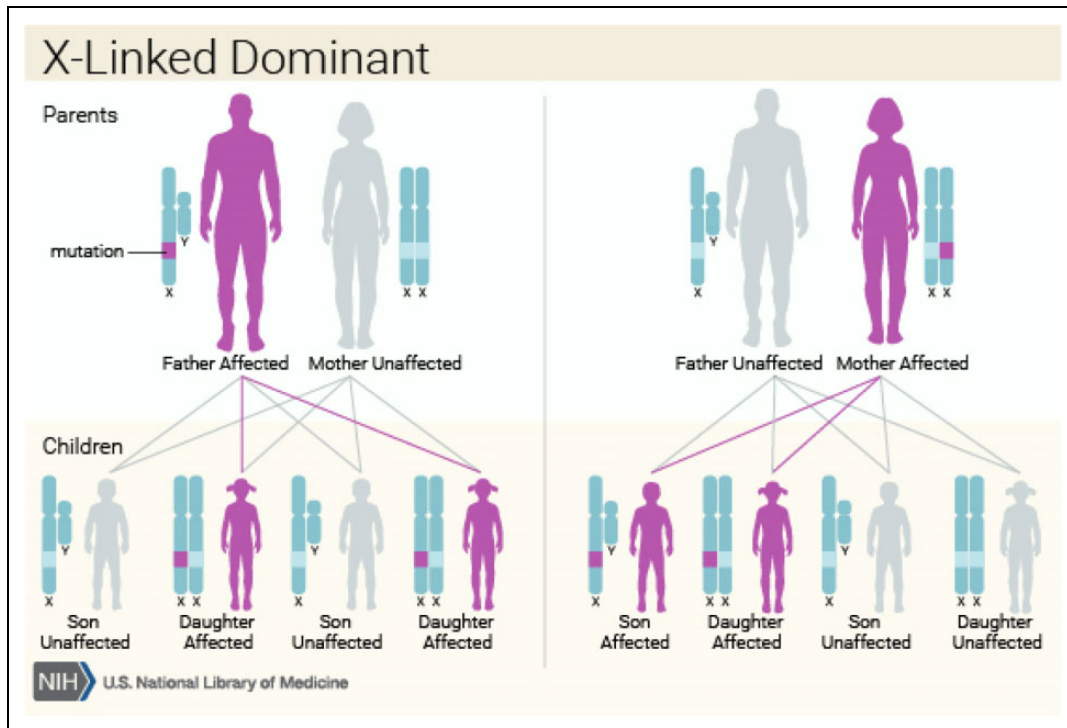


Figure 4. X-linked dominant inheritance. *Source.* Illustration: National Library of Medicine (United States). Genetics Home Reference [Internet]. Bethesda (MD): The Library; April 11, 2017. [Illustration] X-linked dominant; (cited April 13, 2017); (about 1 screen). Available from <https://ghr.nlm.nih.gov/primer/inheritance/inheritancepatterns>

homozygous dominant trait or disorder, and two lower case letters represent a homozygous recessive trait or disorder. The resulting diagram allows for the prediction of the probability (expressed as a percentage) of an offspring inheriting a Mendelian disorder (see Figures 6 and 7).

It is important to remember that the probability of inheritance of a Mendelian disorder is the same for each offspring of the same parents. Inheritance results of one offspring do not affect the probabilities of another offspring. Accordingly, if one offspring has a 50% chance of inheriting a dominant allele, each subsequent offspring has a 50% chance of inheriting the same dominant allele. The Punnett square thus reflects the probabilities for each offspring.

Non-Mendelian Inheritance

Additional patterns of inheritance, other than those described by Mendel, include complex, or multifactorial, inheritance and mitochondrial inheritance.

Complex inheritance. While Mendelian inheritance involves a single gene, complex, or multifactorial, inheritance describes the process by which multiple genes in combination with lifestyle and/or environmental factors cause a trait or disorder. Researchers and clinicians thus understand less about the possible causes of complex disorders than they do about Mendelian disorders. Complex disorders are usually due to mutations in multiple genes that cause a predisposition to the disorder

combined with lifestyle and/or environmental factors that increase the risk. For example, an individual may have a predisposition to diabetes mellitus. If this individual is healthy, with an ideal body weight, and eats a healthy diet of fruits and vegetables, avoiding fast food and sugary food, she or he may never develop diabetes. Some examples of complex disorders include diabetes mellitus, epilepsy, glaucoma, hypertension, ischemic heart disease, manic depression, and schizophrenia.

Mitochondrial inheritance. Mitochondrial inheritance occurs through DNA found in the mitochondria of cells. Mitochondrial DNA is present in the egg cell at the time of conception; therefore, a person's mitochondrial DNA is inherited from the mother (Center for Genetics Education, 2015). Mitochondrial DNA differs from chromosomal DNA and contains 37 genes (National Institutes of Health, n.d.). These genes are responsible for mitochondrial function. Leber hereditary optic neuropathy is an example of a mitochondrial disorder.

Visualizing Inheritance Patterns via Pedigrees

In *Essentials of Genetic and Genomic Nursing: Competencies, Curricula Guidelines, and Outcome Indicators*, the Consensus Panel on Genetic/Genomic Nursing Competencies (2009) states that all nurses, regardless of academic preparation or practice setting, must possess the ability to provide competent genetic and genomic-based nursing care, which includes the

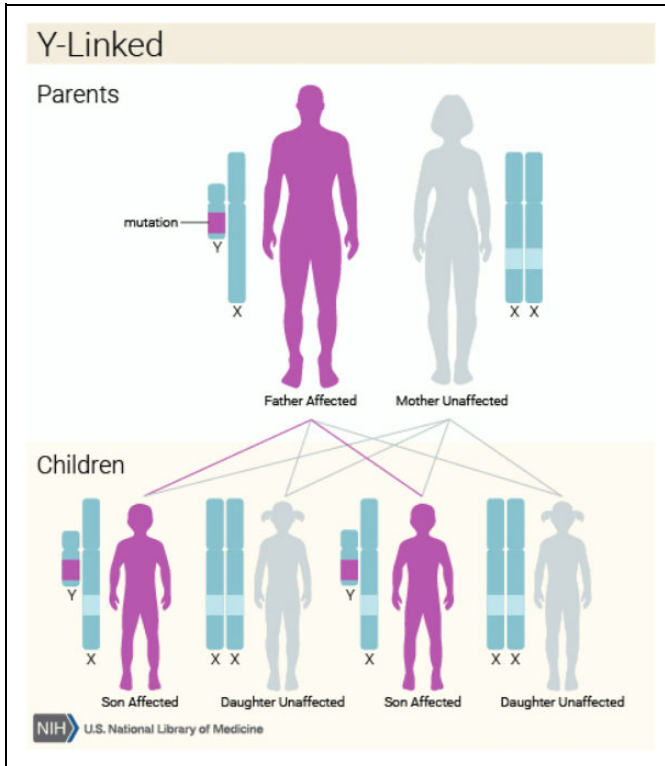


Figure 5. Y-linked inheritance. Source. Illustration: National Library of Medicine (United States). Genetics Home Reference [Internet]. Bethesda (MD): The Library; April 11, 2017. [Illustration] Y-linked; (cited April 13, 2017); (about 1 screen). Available from <https://ghr.nlm.nih.gov/primer/inheritance/inheritancepatterns>

	A	a
a	Aa	aa
a	Aa	aa

Figure 6. Punnett square illustrating the case of one parent with an autosomal dominant disease. A = autosomal dominant allele; a = autosomal recessive allele. Each offspring has a 50% chance (two of the four) of inheriting an autosomal dominant disorder and a 50% chance of not inheriting it.

ability to elicit a minimum of a three-generation family history, construct a minimum of a three-generation pedigree, identify red flags within the family history, and, when needed, refer patients to the appropriate genetics professional, such as a geneticist (MD), genetics counselor, or nurse credentialed as a genetics nurse (Advanced Genetics Nurse-Board Certified).

Pedigree

A pedigree is a pictorial representation of a family medical history (see, e.g., Figure 8). The purpose of a pedigree is to be able to visualize whether a disease is tracking through a

	A	a
A	AA	Aa
a	Aa	aa

Figure 7. Punnett square illustrating the case of both parents being carriers of an autosomal recessive disease. A = autosomal dominant allele; a = autosomal recessive allele. Each offspring has a 25% chance (one of the four) of having the autosomal recessive disease, a 50% chance (two of the four) of being a carrier, and a 25% chance (one of the four) of not being a carrier and not having the disease.

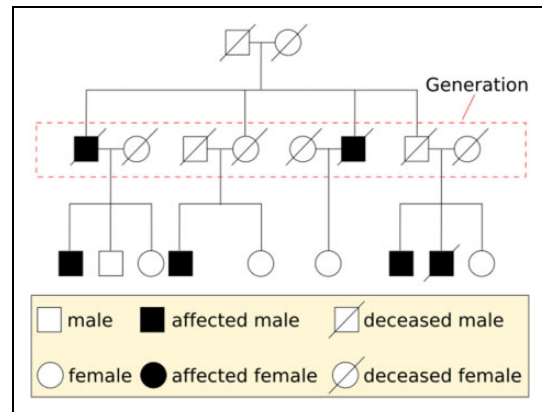


Figure 8. Example of a pedigree. This image, obtained from the Creative Commons, was downloaded from Wikipedia Commons on December 18, 2016. Author: Yassine Mrabet. <https://commons.wiki-media.org/wiki/File:Pedigree-chart-example.svg>

family and to identify inheritance patterns. Figure 9 illustrates the standard nomenclature clinicians use to construct a pedigree (Bennett, French, Resta, & Doyle, 2008). A pedigree should include all family members, including both maternal and paternal lineages; a minimum of three generations; illnesses of each family member; current age, age at diagnosis of an illness, and age at death; miscarriages or stillbirths; adoptions; ethnicity; birth defects; intellectual development disorders; and known genetic conditions (Genetics in Primary Care Institute, n.d.a). Specific features of Mendelian inheritance may be visualized on a pedigree. For instance, autosomal dominant disorders carry a 50% chance of inheritance, affect males and females equally, and do not skip a generation (see, e.g., Figure 10). Autosomal recessive disorders carry a 25% risk of inheritance, affect males and females equally, and appear to skip a generation (see, e.g., Figure 11). These disorders do not actually skip a generation; however, there may be a generation in which individuals are carriers only and not affected with the illness. X-linked disorders affect all males and 50% of females. Y-linked disorders affect only males and all male offspring.

Red Flags

Specific red flags in a family’s history may indicate the presence of a hereditary disorder. These red flags are easiest to

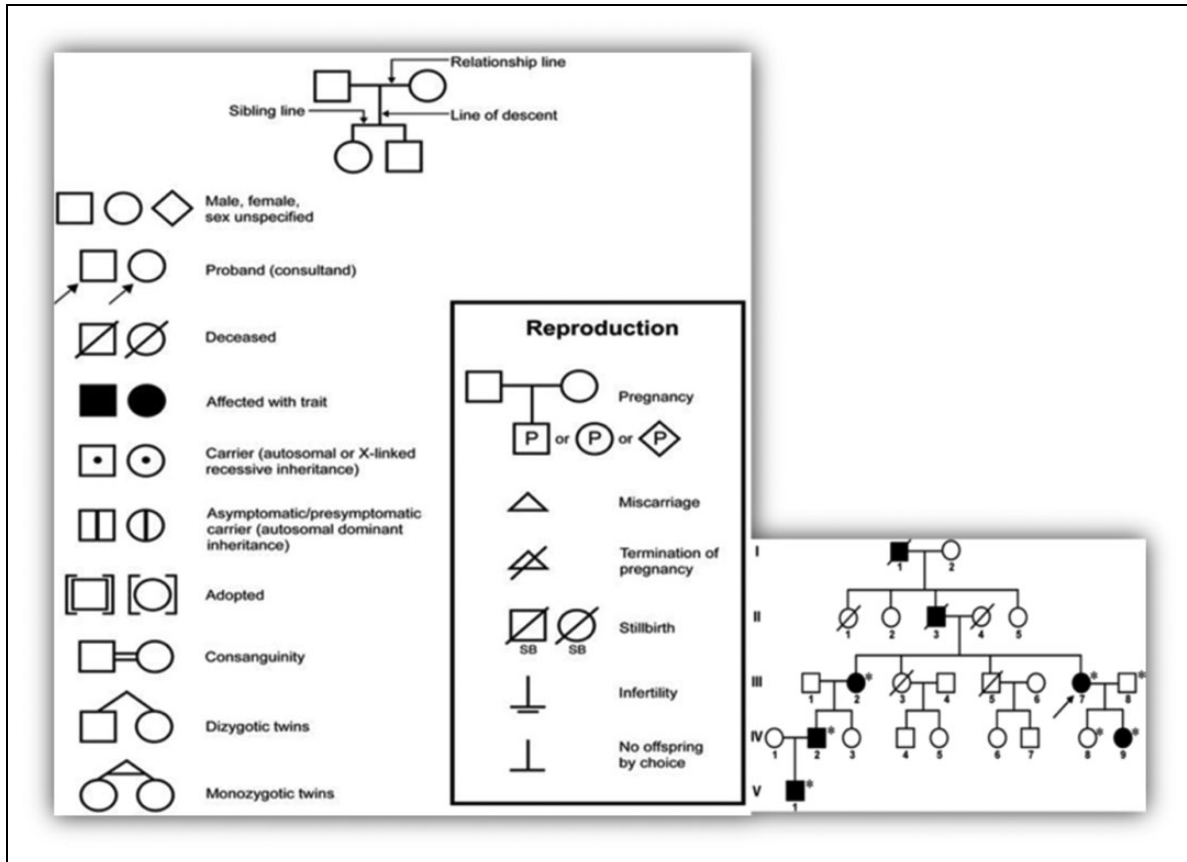


Figure 9. Standard pedigree nomenclature. This image was obtained from http://wiki.socr.umich.edu/index.php/SMHS_Epidemiology and is available under the GNU Free Documentation License 1.3.

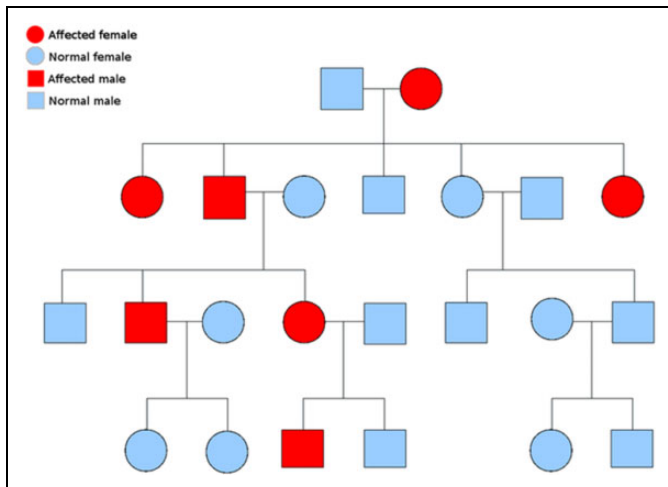


Figure 10. Pedigree chart showing the inheritance pattern of an autosomal dominant disorder. This image was obtained from the Creative Commons and downloaded from Wikimedia Commons on December 18, 2016. Author: Simon Caulton. https://commons.wikimedia.org/wiki/File:Autosomal_dominant.png

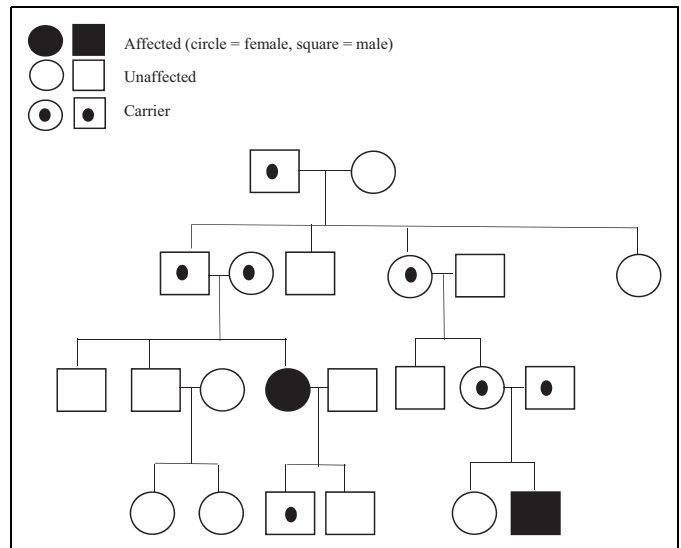


Figure 11. Pedigree chart showing the inheritance pattern of an autosomal recessive disorder.

visualize once a pedigree is constructed. The Genetics in Primary Care Institute (n.d.b) lists these red flags as follows.

- Family history of multiple affected family members with the same or related disorders, which may or may not follow an identifiable pattern in the family;
- Earlier age at onset of disease than expected;
- Condition in the less-often-affected sex;
- Disease in the absence of known risk factors;
- Ethnic predisposition to certain genetic disorders;
- Close biological relationship between parents (i.e., consanguinity);
- Evidence of a Mendelian pattern of inheritance (see, Figures 10 and 11).

If a nurse identifies any of these red flags in a patient's history, she or he should refer the patient to a genetics professional. This professional will elicit a thorough family history; construct a pedigree; educate the patient about his or her risks for disease as well as the risks to the family; discuss genetic testing, if appropriate; and educate the patient about the ethical, legal, and social implications as well as the risks and benefits of genetic testing. Patients who pursue genetic testing will also receive both pre- and posttest counseling. Nurses who do not have access to a genetics professional in their facility, health system, or community can use web-based directories to identify appropriate providers (see Table 1).

Summary

Genetics and genomics have moved into mainstream health care. In order to provide competent care, nurses must integrate genetic and genomic care into their practice. Accordingly, they must be able to elicit a family history, construct a pedigree, assess the pedigree for red flags indicating the possibility of the presence of a hereditary disorder, and refer patients to genetics professionals, as appropriate. In order to meet these expectations, a nurse must first have a good understanding of inheritance patterns.

Authors' Contribution

Lisa B. Aiello contributed to conception, design, acquisition, analysis, and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; and agrees to be accountable for all aspects of work ensuring integrity and accuracy. Beth Desaretz Chiatti contributed to conception, design, acquisition, analysis, and interpretation; drafted the manuscript; gave final approval; and agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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