UNIT 6 - ASSESSING GENETIC RISK

Precision Healthcare: Genomics-Informed Nursing by Andrea Gretchev

Please visit the web version of Precision Healthcare: Genomics-Informed Nursing (https://ecampusontario.pressbooks.pub/personalizedhealthnursing/) to access the complete book, interactive activities and ancillary resources.

Unit 6 Contents

Attribution

6.1 UNIT OVERVIEW

Learning Objectives

- Explain the importance and the process of taking a detailed three-generation family health history.
- Identify and use the symbols found in pedigree charts.
- Analyze pedigree charts to determine the genotypes and phenotypes of individuals in the chart and the probabilities of inheritance.
- Identify the patterns of inheritance of autosomal dominant and recessive, x-linked dominant and recessive, and y-linked traits in humans.
- Recognize the numerous interacting factors that contribute to polygenic risk.

Outline

Topics covered in this chapter include:

- Family history
- Constructing a pedigree chart
- Pedigree analysis and modes of inheritance
- Calculating probabilities using pedigree charts
- Polygenic risk scores

Competencies Nurses will Develop in this Chapter

ANA (2023):

Nursing assessment: Applying/integrating genomic knowledge:

- Collects, reviews, and updates personal and family health history to include any genomic testing and environmental and other risk factors.
- Conducts health and physical assessments that incorporate knowledge about known or potential environmental, genomic, and other risk factors (e.g., behavioral, lifestyle).
- Assesses clients' knowledge, perceptions, and responses to genomic information about themselves and their family members.

Identification:

- Evaluates assessment data to identify clients who may benefit from specific genomic information and services.
- Recognizes issues that undermine the rights of all clients for autonomous, informed genomic-related decision-making and voluntary action.

Referral activities:

- Facilitates referrals for specialized genomic services for clients as needed.

Provision of education, care, and support:

- Develops a plan of care in collaboration with the interdisciplinary team that incorporates genomic assessment information.
- Advocates for autonomous, informed genomic-related decision-making.
- Demonstrates in practice the importance of tailoring genomic information and services that are responsive to the unique attributes of every person.
- Uses health promotion and disease prevention practices that consider genomic influences as well as personal and environmental risk factors.
- Provides genomic health care in collaboration with interdisciplinary professionals and when possible clients and their families.

NHS (2023):

Identify individuals who might benefit from genomic services and/or information as part of assessing needs and planning care:

- recognizing the key indicators of a potential genetic condition, or clinical situation where genomics-

informed healthcare would be appropriate; and
- recognizing the importance of family history in assessing predisposition to a genetic condition.

Advocate for the rights of all individuals to make informed decisions and act voluntarily:

- promoting and supporting equitable access to genomic services.

Demonstrate a knowledge and understanding of genomics in human development, variation and health to underpin effective practice:

- relating it to the maintenance of health and manifestation of conditions;
- relating it to the prevention and management of a genomic condition or response to treatment; and
- underpinned by core genomic concepts that form a sufficient knowledge base for understanding the implications of different conditions and clinical situations that may be encountered.

Obtain and communicate reliable, current information about genomics, for self, patients, families and colleagues:

- using information technologies and other information sources effectively to do so;
- applying critical appraisal skills to assess the quality of information accessed; and
- ensuring the information is appropriate for the intended audience.

Provide ongoing nursing care and support to patients, carers, families and communities with genomic healthcare needs:

- being responsive to changing needs through the life-stages and during periods of uncertainty.

Key terminology

Absolute risk

The likelihood of a disease occurring which remains true without any comparison to any groups of people (NHGRI, 2020, para. 10).

Affected

An individual that is known to have symptoms of the disease (Singh, 2023a, para. 4).

Carrier

A carrier, as related to genetics, is an individual who "carries" and can pass on to its offspring a genomic variant (allele) associated with a disease (or trait) that is inherited in an autosomal recessive or sex-linked manner, and who does not show symptoms of that disease (or features of that trait). The carrier has inherited the variant allele from one parent and a normal allele from the other parent. Any offspring of carriers is at risk of inheriting a variant allele from their parents, which would result in that child having the disease (or trait).

Consanguinity

Generally defined as a union between two individuals related as second cousins or closer (GECKO, n.d., para. 7).

Consultand

A person receiving genetic counseling (Singh, 2023a).

Pedigree chart

A pedigree, as related to genetics, is a chart that diagrams the inheritance of a trait or health condition through generations of a family. The pedigree particularly shows the relationships among family members and, when the information is available, indicates which individuals have a trait(s) of interest.

Polygenic risk score

A polygenic risk score (abbreviated PRS) uses genomic information alone to assess a person's chances of having or developing a particular medical condition. A person's PRS is a statistical calculation based on the presence or absence of multiple genomic variants, without taking environmental or other factors into account.

Proband

A proband is an individual who is affected by a genetic condition or who is concerned they are at risk. Usually, the proband is the first person in a family who brings the concern of a genetic disorder to the attention of healthcare professionals (Singh, 2023b).

Relative risk

A polygenic risk score tells you how a person's risk compares to others with a different genetic constitution.

Risk, as related to genetics, refers to the probability that an individual will be affected by a particular heritable or genetic disorder. Both a person's genome and environmental exposures can influence risk. An individual's risk may be higher because they inherit a genetic variant (or allele) in one gene or a combination of many variants in different genes that increases susceptibility to or overtly causes a disorder. Other individuals may be at higher risk because they have been exposed to one or more environmental factors that promote the development of a certain disorder (NHGRI, 2020)

Sporadic

A disease not caused by a variant inherited from a parent (Singh, 2023a).

Attribution & References

Except where otherwise noted, this page is adapted from:

- Talking Glossary of Genomic and Genetic Terms, Courtesy of: National Human Genome Research institute (NGHRI), Public Domain with attribution.

References

American Nurses Association (ANA). (2023). *Essentials of genomic nursing: Competencies and outcome indicators* (3rd ed.). https://www.nursingworld.org/nurses-books/ana-books/ebook-essentials-of-genomic-nursing-competencies-/

Genetics Education Canada: Knowledge Organization (GECKO). (n.d.). *Family history red flags (general)*. https://www.geneticseducation.ca/resources-for-clinicians/family-history/point-of-care-tool-12

National Health Service (NHS). (2023). *The 2023 genomic competency framework for UK nurses*.

https://www.genomicseducation.hee.nhs.uk/wp-content/uploads/2023/12/2023-Genomic-Competency-Framework-for-UK-Nurses.pdf

National Human Genome Research Institute (NHGRI). (2020, August 11). *Polygenic risk scores*. https://www.genome.gov/Health/Genomics-and-Medicine/Polygenic-risk-scores

National Human Genome Research Institute (NHGRI). (n.d.). *Talking glossary of genetic and genomic terms.* www.genome.gov

Singh, N. R. (2023a, February 1). 4.2 Symbols used in Pedigree Charts. In *Introduction to Genetics*. Pressbooks. https://opengenetics.pressbooks.tru.ca/chapter/sporadic-and-non-heritable-diseases/

Singh, N. R. (2023b, February 1). 4.4 Sporadic and Non-Heritable Diseases. In *Introduction to Genetics*. Pressbooks. https://opengenetics.pressbooks.tru.ca/chapter/sporadic-and-non-heritable-diseases/

6.2 FAMILY HISTORY

Family Health History

Family health history-based risk assessment is still the **gold standard** in the initial assessment for heritable conditions. It is the least expensive genetic test available. The best way to identify red flags is by taking a family history (in addition to a personal health history).

A family health history records the health conditions of an individual and their biological relatives (alive and deceased), helping to identify genetic and heritable risks for certain diseases. It is often depicted through a family tree or pedigree.

Discussing genetic risk can be upsetting for some individuals. Nurses must consider the psychosocial aspects of risk assessment and use their training in relational practice and counseling during these conversations. Genetic counselors specialize in providing guidance and support to individuals and families about genetic conditions and their potential health implications. When genetic counselors are available, nurses should collaborate with them, ensuring that each professional works within their respective scope of practice. This collaborative approach ensures comprehensive care and support for patients.

Why take a family history?

1. All diseases have *some* genetic component, and the strength of the genetic component may be revealed by a family history.
   Family history, alone or in combination with other risk factors, increases the risk for common diseases, (i.e. heart disease, diabetes, and various cancers) much more than genetic variants, alone or in combination, can predict.
2. Even with advancing genomic technology, family history is still the gold standard to assess the likelihood of a genetic condition and to identify individuals who may benefit from referral to a specialist.
3. Pattern of inheritance can be demonstrated by a family history.
4. Family history can help to make or refine a diagnosis, particularly in conditions of variable expressivity (where not all individuals present with the same symptoms of a condition). For example, in hereditary hemochromatosis, a family history could reveal diabetes, liver failure, heart disease and/or early death in multiple family members.
5. Family history can affect testing, treatment, surveillance and management recommendations. For example, a woman's eligibility for the Ontario Breast Screening Program (OBSP) could be determined.
6. Taking the time to explore your patient's family history is an opportunity to build rapport, provide

patient education, and to correct misconceptions.

7. Drawing the family history in a pedigree format makes it easy to be read by other healthcare providers and easy to update.

Read

Hickey, K.T., Katapodi, M.C., Coleman, B., Reuter-Rice, K. & Starkweather, A.R. (2017). Improving utilization of the family history in the electronic health record. *Journal of Nursing Scholarship, 49*, 80-86. https://doi.org/10.1111/jnu.12259

When should I take a family history?

A good place to start is at your first visit with a new patient. Risk assessment is an ongoing process, so the family history should be regularly updated. Take note of the life stage of your patient as questions may vary as patients age. For example, questions relevant for a pediatric patient will be different than those for a woman of childbearing age or a man in his late sixties.

How is a family history taken?

For each individual in the family:

- Ask about general health now and in earlier life
- Ask about development and intellectual functioning
- If deceased, ask about the age and cause

Start with your patient and ask about his/her children and his/her partner. Note:

- **Consanguinity** (*"Are you and your partner related by blood e.g. cousins?"*)
- Children from previous relationships
- Miscarriages and terminations of pregnancy (note if for medical reason and at what gestational age)

Ask about your patient's siblings and his/her children (nieces and nephews) and his/her partner's siblings and their children. Note full or half siblings *("Do your brothers and sisters have the same mother and*

father?"). Ask about your patient's parents and his/her partner's parents. If your patient does not have children, ask about grandparents on both sides of the family.

A three generation pedigree is generally accepted as the standard. Once this is complete, ask in general about other relatives, have your patient think of aunts, uncles and cousins, and ask:

- Are there any diseases that seem to run in the family?
- Is there a history of infertility, a couple that had more than three miscarriages, or a couple that had difficulty getting pregnant? If yes, do you know the reason?
- Are there any known genetic conditions in the family, for example cystic fibrosis or muscular dystrophy?
- Was anyone born with a physical difference, for example a hole in the heart or extra digits, or with congenital hearing loss?
- Did any children die at birth or at a young age?
- Is there a history of intellectual disability or developmental delay?
- Is there any cancer in the family? If so, what type and at what age?
- Is there any heart disease at an early age (under age 60)?

Example – Family History Risk Assessment Questionnaire

This risk assessment focuses on your close relatives including parents, children, brothers and sisters who are either living or dead.

Items	Yes	No
Have any of your close relatives had heart disease before the age of 60? 'Heart disease' includes cardiovascular disease, heart attack, angina and bypass surgery.	☐	☐
Have any of your close relatives had diabetes? 'Diabetes' is also known as type 2 diabetes or non-insulin dependent diabetes	☐	☐
Do you have any close relatives who have had melanoma?	☐	☐
Have any of your close relatives had bowel cancer before the age of 55?	☐	☐
Do you have more than one relative on the same side of the family who has had bowel cancer at any age? Please think about your parents, children, brothers, sisters, grandparents, aunts, uncles, nieces, nephews and grandchildren.	☐	☐
Have any of your close male relatives had prostate cancer before the age of 60?	☐	☐
Have any of your close female relatives had ovarian cancer?	☐	☐
Have any of your close relatives had breast cancer before the age of 50?	☐	☐
Do you have more than one relative on the same side of your family who has had breast cancer at any age? Please think about your parents, children, brothers, sisters, grandparents, aunts, uncles, nieces, nephews and grandchildren.	☐	☐

Figure 6.1 Source: Emery et al. (2014) © 2024 Annals of Family Medicine. Figure 3 republished here under CC-BY-NC-ND 4.0 with permission from Dr. Emery. Figure 6.1 Image Description. Full text available from Annals of Family Medicine.

Red Flags

Identifying Red Flags

Identifying Red Flags (text version)

GECKO: Genetics Education Canada: Knowledge Organization Point of Care Tool – Family History

Red flags that suggest that an individual (or his/her/their family) may be at increased risk for a genetic condition.

The best way to identify red flags is by taking a family history (in addition to a personal health history).

1. **Multiple affected family members (with the same or related disorder)**
    - breast and ovarian cancer (https://geneticseducation.ca/resources-for-clinicians/cancer-genomics/hereditary-breast-ovarian-cancer)
    - iron overload and diabetes (https://geneticseducation.ca/resources-for-clinicians/other-genomic-topics/hereditary-hemochromatosis/point-of-care-tool-13)
    - very high cholesterol (https://geneticseducation.ca/resources-for-clinicians/cardiogenomics/familial-hypercholesterolemia/point-of-care-tool-6)
2. **Earlier age of onset of disease (or symptom) than typically expected**
    - May demonstrate genetic predisposition in an individual who is more susceptible to environmental risk factors
        - e.g. pre-menopausal breast cancer (https://geneticseducation.ca/resources-for-clinicians/cancer-genomics/hereditary-breast-ovarian-cancer) (*BRCA1* or *BRCA2* variant); premature ovarian failure before age 40 (fragile X syndrome carrier (https://www.cdc.gov/ncbddd/fxs/index.html))
3. **Disease occurring in an individual of the less commonly affected sex**
    - e.g. breast cancer in a person assigned male at birth

4. **Presence of disease in the absence of other precipitating factors**
    - e.g. sudden unexplained death (https://geneticseducation.ca/resources-for-clinicians/cardiogenomics/long-qt-syndrome) in an athletic 20-year-old; diabetes mellitus (hereditary hemochromatosis (https://geneticseducation.ca/resources-for-clinicians/other-genomic-topics/hereditary-hemochromatosis) or myotonic dystrophy)
5. **Ethnicity**
    - Some genetic disorders (https://geneticseducation.ca/resources-for-clinicians/prenatal-and-preconception-genomics/carrier-screening-in-canada/point-of-care-tool-14) are more common in certain ethnic groups
    - e.g. Tay-Sachs disease Ashkenazi Jewish (https://geneticseducation.ca/resources-for-clinicians/prenatal-and-preconception-genomics/carrier-screening-in-canada/point-of-care-tool-14) individuals, Gaucher disease, Familial dysautonomia, Canavan disease in Ashkenazi Jewish individuals; Hemoglobinopathies (thalassemia, sickle cell anemia) in individuals of Mediterranean, African, Middle Eastern and South East Asian (https://geneticseducation.ca/resources-for-clinicians/prenatal-and-preconception-genomics/carrier-screening-in-canada/point-of-care-tool-14) ancestry
6. **Consanguinity**
    - Generally defined as a union between two individuals related as second cousins or closer
    - Higher than average chance for both members of a couple to be carriers of the same autosomal recessive condition
7. **History of congenital anomalies (e.g. heart defect, imperforate anus), still birth, childhood death, infertility, more than three unexplained miscarriages**
    - May be suggestive of underlying genetic etiology

Source: GECKO: Genetics Education Canada: Knowledge Organization Point of Care Tool – Family History, used with permission.

Disease specific tools:

After a general, three-generation family history is obtained, if there are red flags (e.g. multiple **affected** relatives, young age of diagnosis, see this point of care tool for more) you can use the tools below to complete

a more *targeted history* can help to identify those who may qualify for modified screening (e.g. starting earlier, more frequent, alternate modality), a genetic assessment and/or genetic testing.

- Cancer (https://www.geneticseducation.ca/resources-for-clinicians/family-history/family-history-poc-tools#cancergen) (general)
  - Hereditary breast/ovarian cancer (https://www.geneticseducation.ca/resources-for-clinicians/family-history/family-history-poc-tools#breastovary)
  - Hereditary Colorectal/Lynch syndrome (https://www.geneticseducation.ca/resources-for-clinicians/family-history/family-history-poc-tools#colon)
  - Prostate cancer (https://www.geneticseducation.ca/resources-for-clinicians/family-history/family-history-poc-tools#prostate)
  - Skin cancer (https://www.geneticseducation.ca/resources-for-clinicians/family-history/family-history-poc-tools#skin)
  - Renal cancer (https://www.geneticseducation.ca/resources-for-clinicians/family-history/family-history-poc-tools#renal)
- Cardiovascular disease (https://www.geneticseducation.ca/resources-for-clinicians/family-history/family-history-poc-tools#cardio)
  - Sudden unexplained death (https://www.geneticseducation.ca/resources-for-clinicians/family-history/family-history-poc-tools#sud)
- Diabetes

Image Descriptions

Fig 6.1 Example – Family History Risk Assessment Questionnaire

This risk assessment focuses on your close relatives including parents, children, brothers and sisters who are either living or dead.

- Have any of your close relatives had heart disease before the age of 60? 'Heart disease' includes cardiovascular disease, heart attack, angina and bypass surgery.
- Have any of your close relatives had diabetes? 'Diabetes' is also known as type 2 diabetes or non-insulin dependent diabetes.
- Do you have any close relatives have had melanoma?
- Have any of your close relatives had bowel cancer before the age of 55?
- Do you have more than one relative on the same side of the family who has had bowel cancer at any age? Please think about your parents, children, brothers, sisters, grandparents, aunts, uncles, nieces, nephews and grandchildren.

- Have any of your close male relatives had prostate cancer before the age of 60?
- Have any of your close female relatives had ovarian cancer?
- Have any of your close relatives had breast cancer before the age of 50?
- Do you have more than one relative on the same side of your family who has had breast cancer at any age? Please think about your parents, children, brothers, sisters, grandparents, aunts, uncles, nieces, nephews and grandchildren. [Back to Fig 6.1]

Attribution & References

Except where otherwise noted, this content is adapted from:

- Family history by Genetics Education Canada: Knowledge Organization (GECKO), Used with permission for educational purposes
- Identifying Red Flags reused from Family history red flags (general) by Genetics Education Canada: Knowledge Organization (GECKO), Used with permission for educational purposes
- Disease specific tools is reused from Family history tools for practice by Genetics Education Canada: Knowledge Organization (GECKO), Used with permission for educational purposes

References

Emery, J. D., Reid, G., Prevost, A. T., Ravine, D., & Walter, F. M. (2014). Development and validation of a family history screening questionnaire in Australian primary care. *The Annals of Family Medicine*, *12*(3), 241–249. https://doi.org/10.1370/afm.1617

6.3 CONSTRUCTING A PEDIGREE CHART

Taking and drawing a family history

Asking a patient about their family's medical history is a familiar scenario for most healthcare professionals. In nursing school, the formal process of recording this information is taught. The production of a family history diagram, sometimes referred to as a genogram, is an example of this.

Many traits which run in human families do not exhibit a simple pattern of Mendelian inheritance. This is usually because these traits are coded for by more than one gene. Conversely, traits that are governed by one gene are typically an abnormality that is life-threatening or debilitating (e.g., Huntington's Disease, caused by a dominant allele, and Cystic Fibrosis, caused by a recessive allele)]. From a methodical analysis of pedigree charts, we can determine if a particular trait is encoded for by different alleles of a particular (single) gene, as well as if the single-trait gene is recessive or dominant. We may also be able to determine if a trait is autosomal or sex-linked.

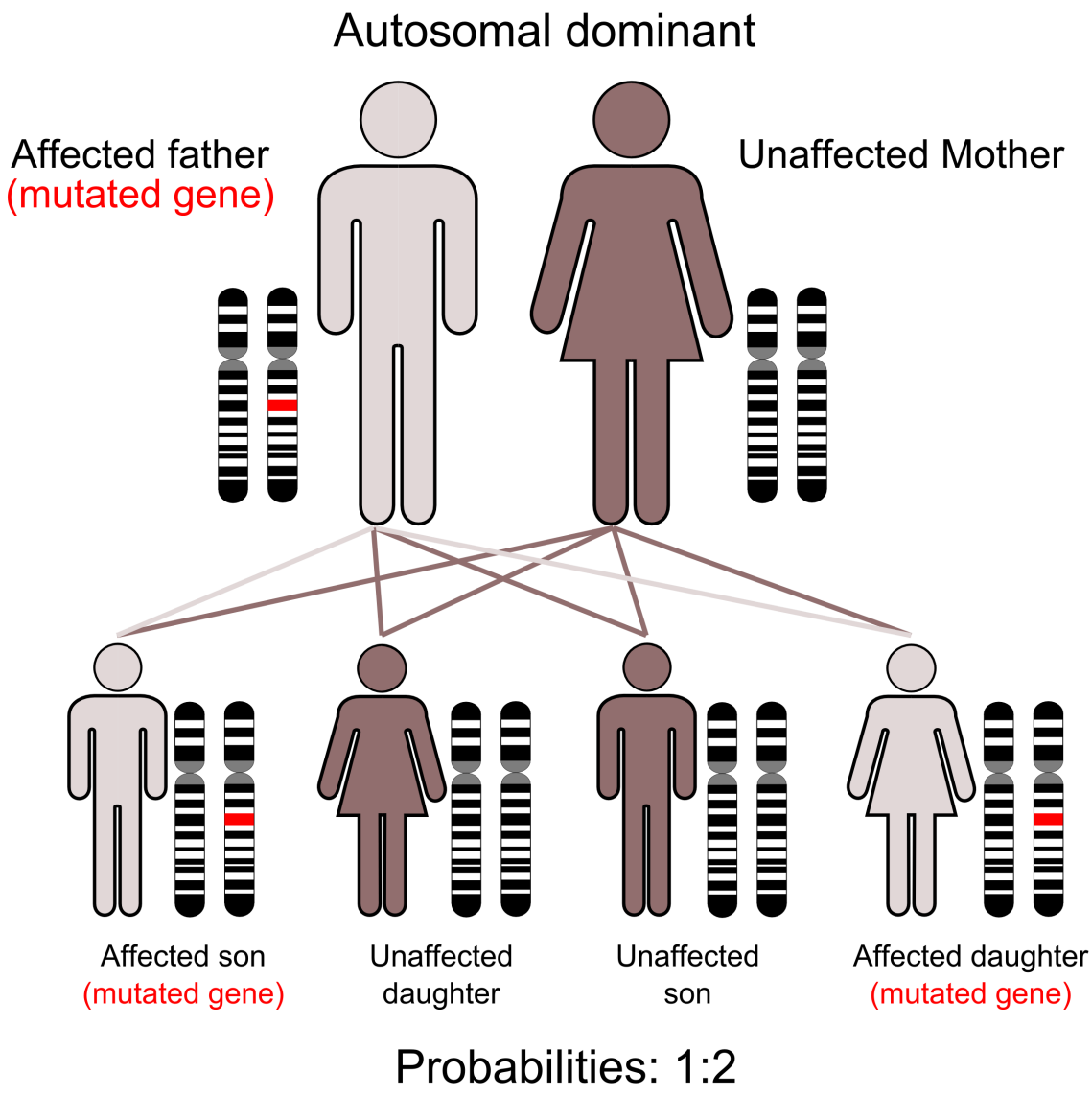


Figure 6.3 Inheritance of an autosomal dominant trait. Two parents are shown: male possesses the mutated gene, and female is unaffected. Their offspring are outlined, whereby they produce one affected son with the mutated gene, one unaffected son, an unaffected daughter, and finally, an affected daughter with the mutated gene. Alongside each individual is an image of the pair of homologous chromosomes which contains the gene loci for the trait under consideration. Affected individuals are shown via a red shading of the mutated gene locus on an otherwise black and white image of the homologous chromosomes. **Source:** Autodominant en 01 by Armin Kübelbeck, CC BY-SA 3.0.

What is a genetic pedigree?

A genetic **pedigree chart** is a family history diagram that differs from a genogram in that it does not include the psychosocial history that is collected when drawing a genogram and ecomap. A genetic pedigree captures details about the health of multiple generations. This information can be important in diagnosing

an inherited condition, revealing a pattern of inheritance, and informing clinical decisions regarding testing and management. Understanding the relationships between family members can also be useful when considering the communication of information and the clinical management of the whole family.

A genetic pedigree is a visual representation of several generations in a patient's family. It shows how family members are related to each other and notes any medical conditions they may have along with any other pertinent information. For example, a family's ethnic background may be relevant, as this could indicate whether certain tests should be considered based on the frequency of conditions in different populations.

The information needed to draw a pedigree is usually collected through a series of questions about each member of the family. Standardized symbols and lines are used to represent the family members and their relationships.

The example here shows a four-generation pedigree. The person giving the information is Julie Smith, as noted by the small arrow. Julie, her mother Mollie, her grandmother Alice, and her cousin Mary, have all been affected the same medical condition, indicated by the shaded circles.

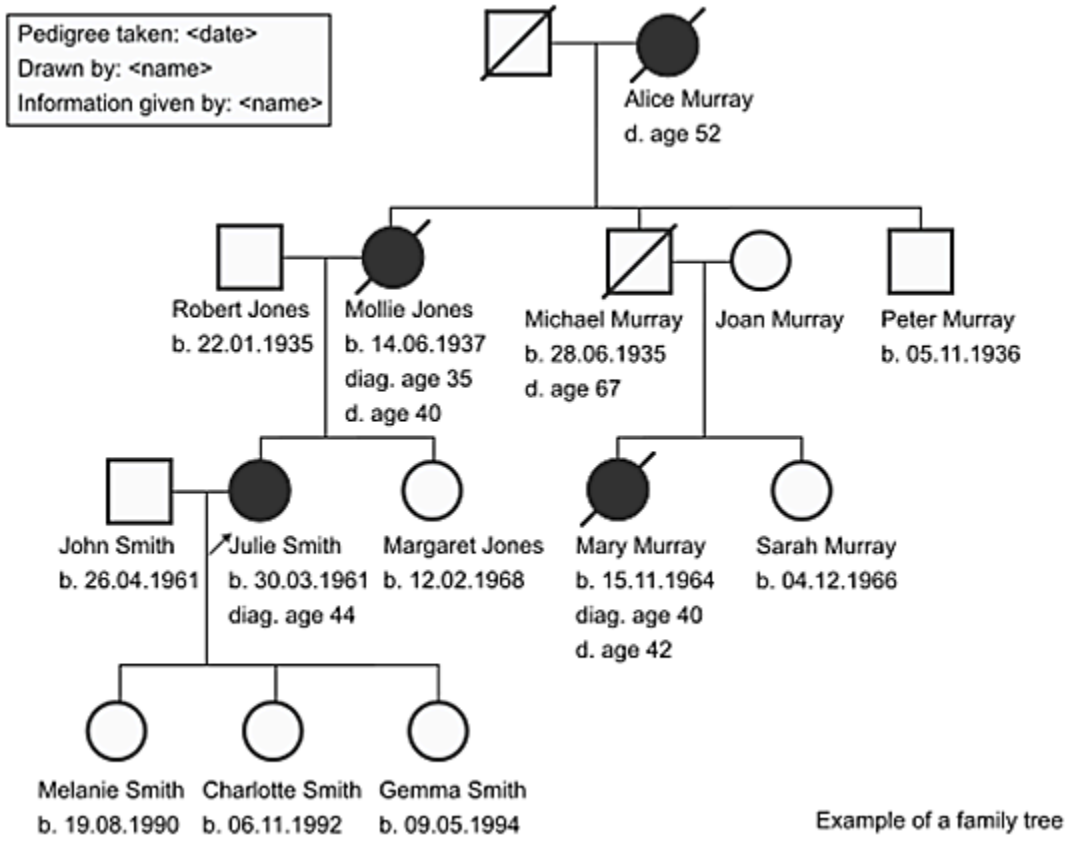
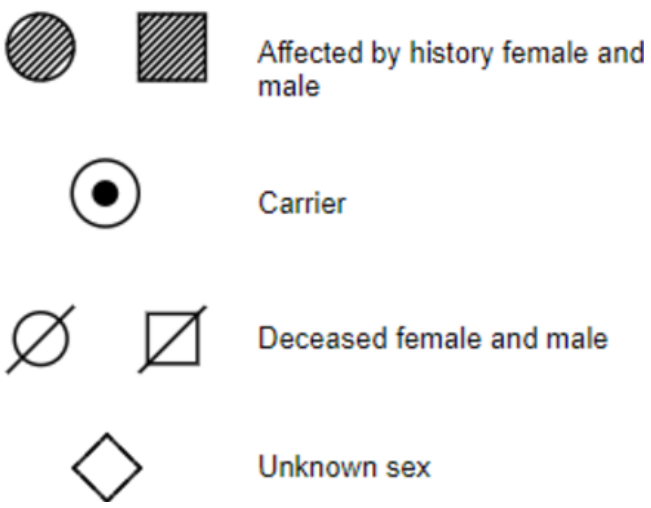


Figure 6.4 Example of a family pedigree from the Genome Education Programme, NHS
Source: Genomics Education Programme, CC BY-NC 4.0

The symbols and lines

So that any health professional can read and understand a genetic pedigree, they use a set of internationally recognized symbols and lines, based on the proposed system by the National Society of Genetic Counselors (https://www.ncbi.nlm.nih.gov/pubmed/18792771).



Symbols used in constructing a pedigree chart by John Locke (2019), CC BY-NC-SA 3.0. / Cropped.

These diagrams are used to determine the mode of inheritance of a particular disease or trait, and to predict the probability of its appearance among offspring. Each pedigree chart represents all the available information about the inheritance of a single trait (most often a disease) within a family. The pedigree chart is therefore drawn using phenotypic information, but there is always some possibility of errors in this information, especially when relying on family members' recollections or even clinical diagnoses. In real pedigrees, further complications can arise due to incomplete penetrance (including age of onset) and variable expressivity of disease alleles, but for the examples presented in this book, we will presume complete accuracy of the pedigrees — that is, the phenotype accurately reflects the genotype. A pedigree may be drawn when trying to determine the nature of a newly discovered disease, or when an individual with a family history of a disease wants to know the probability of passing the disease on to their children.

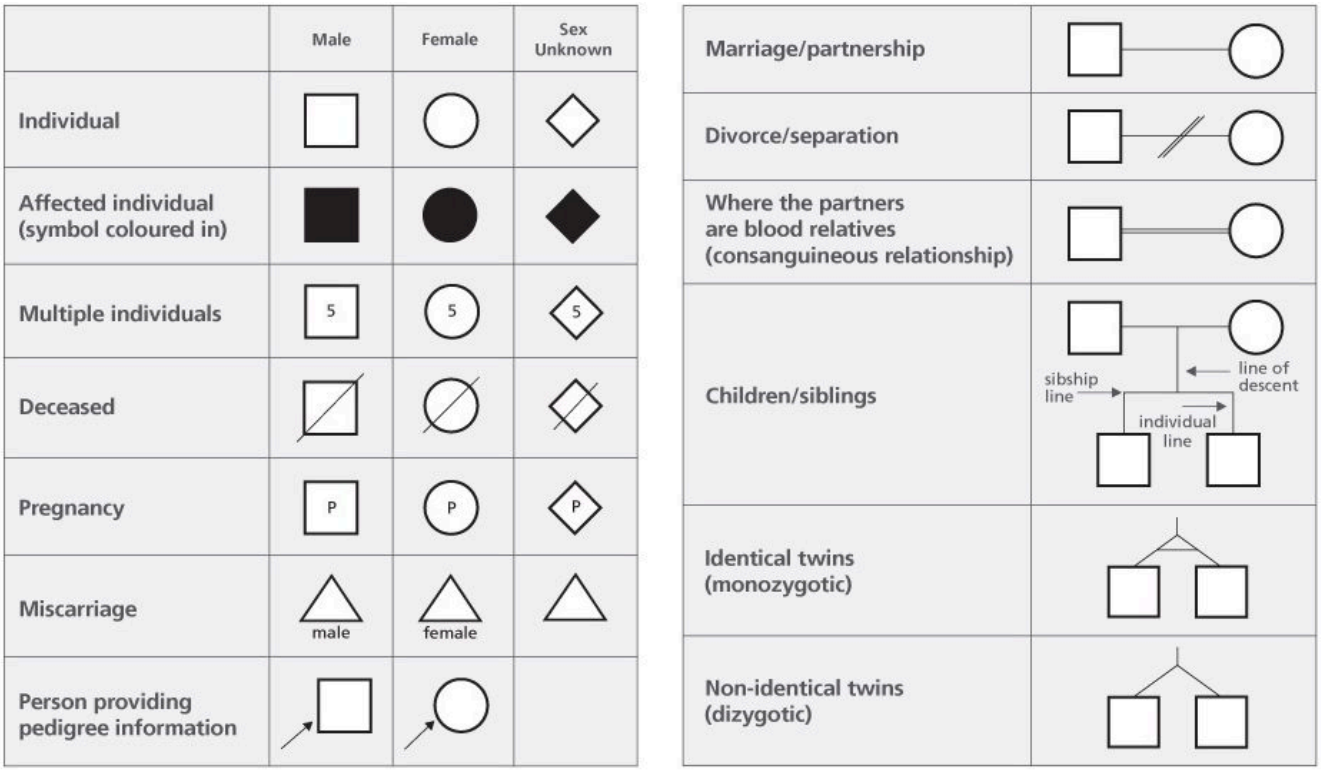


Figure 6.5 Genetic Pedigree Symbols and Lines. **Source:** Genomics Education Programme, CC BY-NC 4.0

Additional symbols

Symbols are used to construct pedigree charts. The major ones are as follows: male – square; female – circle; marriage – square and circle linked by a horizontal line. Males partners are usually to the left of the female partner; an individual affected by the trait has their symbol shaded; carrier – sex symbol with a dot inside; deceased – sex symbol with a diagonal line running through it; unknown sex – a diamond; Roman numerals symbolize generations, and Arabic numbers symbolize individuals within a given generation; birth order within each group of offspring is drawn left to right, from first-born to last-born.

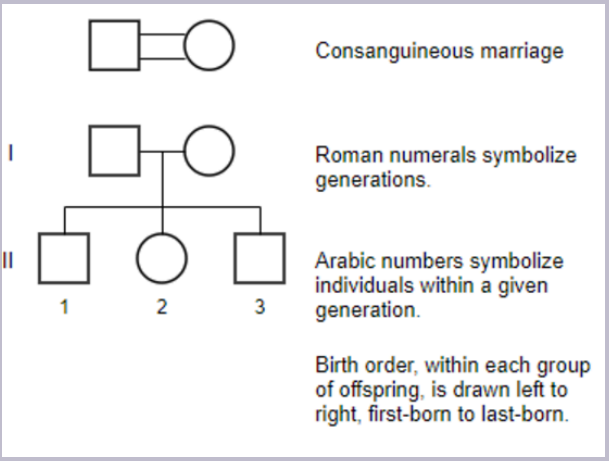


Figure 6.6 Additional symbols. **Source:** Introduction to Genetics, CC BY-NC SA 4.0. / Image cropped to focus on consanguineous marriage, generations notation, and birth order.

A note on how sex is depicted in pedigrees

Historically, circles have been used to represent females and squares males in pedigrees. As geneticists gain a better understanding of sex and gender, however, it becomes increasingly apparent that this is not always an accurate representation of either an individual's sex or gender. There are multiple ways to define "male" and "female". For example, an individual with chromosomes typically associated with males (XY) can have gonads and/or external anatomy that is typically associated with females. Likewise, an individual with chromosomes typically associated with females can have gonads and/or external anatomy that is typically associated with males. Depending on the purpose of the pedigree, different definitions of male and female may be more useful than others.

In this module, we will use pedigrees to determine mode of inheritance, including whether a gene is carried on the X- or Y- chromosome. Therefore, unless otherwise indicated, we will most often use the symbols to represent chromosomal sex, with circles to represent people with the most common female chromosomal genotype (XX) and squares to represent people with the most common male chromosomal genotype (XY). It should be understood that this is not a complete description of any individual's sex (sex assigned at birth, sex

determined by external genitalia, or gonadal sex may be different may be different from chromosomal sex) or gender (which may be cisgender or transgender).

Other symbols may offer a more complete or accurate representation of a person's sex or gender. While there is not currently a single standard for representation of transgender and gender diverse individuals or individuals with differences of sex development, there are a number of proposals from within the genetic counseling community (Sheehan et al., 2020; Tuite et al., 2020). One example, from Tuite et al (2020), is shown in Table 1.

The affected individual that brings the family to the attention of a geneticist is called the **proband** (or propositus). If the individual is unaffected, they are called the consultand. If an individual is known to have symptoms of the disease (affected), the symbol is filled in. Sometimes, a *half filled-in symbol* is used to indicate a known **carrier** of a disease; this is someone who does not have any symptoms of the disease, but who passed the disease on to subsequent generations because they are a heterozygote. Note, that when a pedigree is constructed, it is often unknown whether a particular individual is a carrier or not, so not all carriers are always explicitly indicated in a pedigree. For simplicity, in this chapter we will assume that the pedigrees presented are accurate, and represent fully penetrant traits.

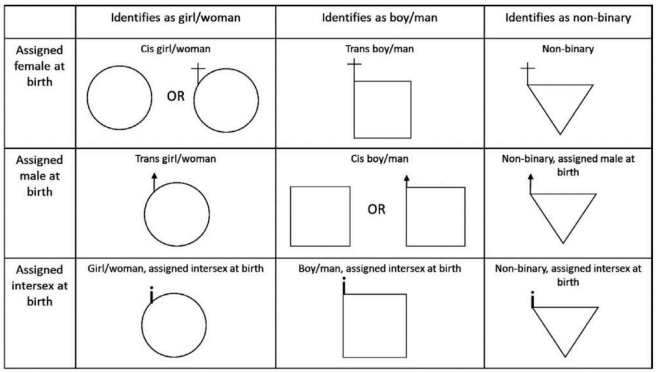


Table 1 Gender inclusive pedigree symbols. **Source:** National Society of Genetic Counselors from *Chromosomes, Genes, and Traits: An Introduction to Genetics*, CC BY-NC-SA 4.0.

Other conventions:

- Female carriers of X-linked traits are indicated by a circle with a dot in the centre.
- If possible, the male partner should be left of female partner on relationship line.
- Siblings should be listed from left to right in birth order, oldest to youngest.

Answers to frequently asked questions can be found here (https://www.genomicseducation.hee.nhs.uk/taking-and-drawing-a-family-history/#toggle-id-1). This page also contains a number of high quality video interview of a healthcare provider taking a family history and drawing a pedigree chart. These are excellent for further review or practice.

Attribution & References

Except where otherwise noted, this content is adapted from:

- Taking and drawing a family history: Constructing a Pedigree Chart by Genomics Education Programme, CC BY-NC 4.0
- 4.1 Introduction In *Introduction to Genetics* by Natasha Ramroop Singh, Thompson Rivers University, CC BY-NC SA 4.0
- 4.2 Symbols used in Pedigree Charts In *Introduction to Genetics* by Natasha Ramroop Singh, Thompson Rivers University, CC BY-NC SA 4.0
- Pedigree analysis In *Chromosomes, Genes, and Traits: An Introduction to Genetics* by Amanda Simons, Framingham State University, CC BY-NC SA 4.0

References

Mayo Clinic Staff. (n.d.). *Cystic Fibrosis*. MayoClinic.org. Retrieved January 18, 2022 from https://www.mayoclinic.org/diseases-conditions/cystic-fibrosis/symptoms-causes/syc-20353700

Mayo Clinic Staff. (n.d.). *Huntington's disease*. MayoClinic.org. Retrieved January 18, 2022 from https://www.mayoclinic.org/diseases-conditions/huntingtons-disease/symptoms-causes/syc-20356117

Sheehan, E., Bennett, R. L., Harris, M., & Chan-Smutko, G. (2020). Assessing transgender and gender non-conforming pedigree nomenclature in current genetic counselors' practice: The case for geometric inclusivity. *Journal of genetic counseling*, *29*(6), 1114–1125. https://doi.org/10.1002/jgc4.1256

Tuite, A., Dalla Piazza, M., Brandi, K., & Pletcher, B. A. (2020). Beyond circles and squares: A commentary on updating pedigree nomenclature to better represent patient diversity. *Journal of genetic counseling*, *29*(3), 435–439. https://doi.org/10.1002/jgc4.1234

6.4 PEDIGREE ANALYSIS AND MODES OF INHERITANCE

Analyzing Pedigree Charts to Determine Genotype

Usually, we are presented with a pedigree of an uncharacterized disease or trait, and one of the first tasks is to determine which modes of inheritance are possible, and then, which mode of inheritance is most likely. This information is essential in calculating the probability that the trait will be inherited in any future offspring. We will mostly consider five major types of inheritance: autosomal dominant (AD), autosomal recessive (AR), X-linked dominant (XD), X-linked recessive (XR), and Y-linked (Y) inheritance.

We generally make two assumptions in analyzing Pedigree Charts. These are as follows:

1. Complete Penetrance — an individual in the pedigree will be affected (express the phenotype associated with a trait) when the individual carries at least one dominant allele of a dominant trait, or two recessive alleles of a recessive a trait.
2. Rare-in-Population — generally, the trait in question is rare in the general population.

The following are some hints and clues to help us interpret Pedigree Charts:

1. An unaffected individual cannot have any alleles of a dominant trait (because a single allele of a dominant trait causes an individual to be affected).
2. Individuals marrying into the family are assumed to have no disease alleles – they will never be affected and can never be carriers of a recessive trait (because the trait is rare in the population).
3. An unaffected individual can be a carrier (have one allele) of a recessive trait (because two alleles of a recessive trait are required for an individual to be affected).
4. When a trait is X-linked, a single recessive allele is sufficient for a male to be affected (because the male is hemizygous – he only has one allele of an X-linked trait).
5. A father transmits his allele of X-linked genes to his daughters, but not his sons. A mother transmits an allele of X-linked genes to both her daughters and her sons.

Watch the video, *Pedigree Analysis*, by AK Lecture Series (2015) (15 mins) on YouTube

(https://youtu.be/Wgmgt_Ph6Ko), which discusses Pedigree Charts and how to analyze them.

Let us now take a look at the various modes of inheritance and typical pedigree charts which are characteristic of each mode.

Autosomal Dominant (AD)

When a disease is caused by a dominant allele of a gene, every person with that allele will show symptoms of the disease (assuming complete penetrance), and only one disease allele needs to be inherited for an individual to be affected. Thus, every affected individual must have an affected parent. A pedigree with affected individuals in every generation is typical of AD diseases. However, beware that other modes of inheritance can also show the disease in every generation, as described below. It is also possible for an affected individual with an AD disease to have a family without any affected children, if the affected parent is a heterozygote. This is particularly true in small families, where the probability of every child inheriting the normal, rather than disease allele is not extremely small. Note that AD diseases are usually rare in populations, therefore affected individuals with AD diseases tend to be heterozygotes (otherwise, both parents would have had to been affected with the same rare disease). Huntington Disease, Achondroplastic dwarfism, and Polydactyly are all examples of human conditions that may follow an AD mode of inheritance.

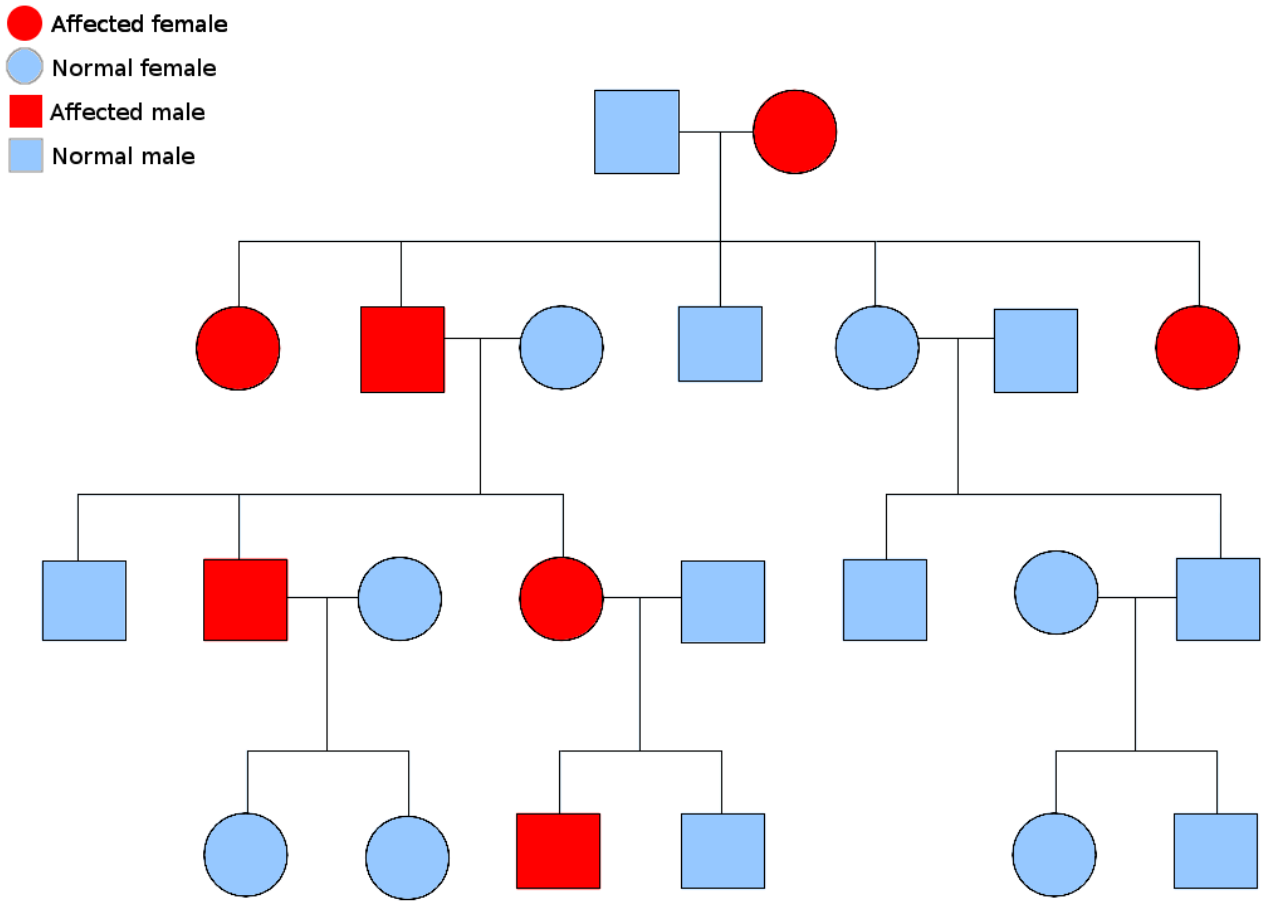


Figure 6.7 A Pedigree Chart Showing Autosomal Dominant Inheritance. Pedigree chart showing inheritance of an autosomal dominant trait over four generations. Affected females are shown as red-coloured circles; normal females are blue-coloured circles; affected males are red-coloured squares; normal males are blue-coloured squares. Generation I begins with a normal male and an affected female, mating to produce five offspring. Their offspring are: two affected and three unaffected. Two of these Generation II individuals mate, and their progeny is shown, along with a final Generation IV, with the characteristic pattern for autosomal dominant traits depicted. **Source:** Autosomal dominant by Simon Caulton, CC BY-SA 3.0

Example: Achondroplasia is a common form of dwarfism. *FGFR3* gene at 4p16 (chromosome 4, p arm, region 1, band 6) encodes a receptor protein that negatively regulates bone development. A specific base pair substitution in the gene makes an over-active protein and this results in shortened bones. Achondroplasia is considered autosomal dominant because the defective proteins made in A / a embryos halt bone growth prematurely. A / A embryos do not make enough limb bones to survive. Most, but not all dominant mutations are also recessive lethal. In achondroplasia, the A allele shows dominant visible phenotype (shortness) and recessive lethal phenotype.

X-Linked Dominant (XD)

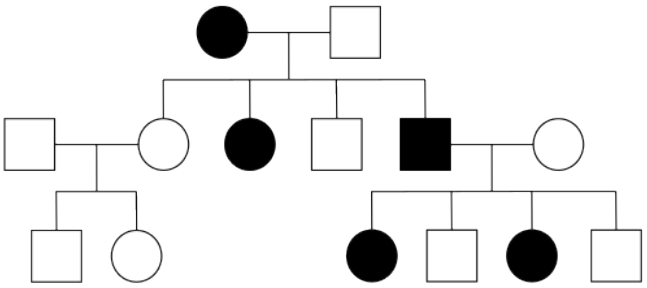


Figure 6.8 Pedigree chart showing the inheritance of a X-linked dominant trait over three generations. An affected female mates with a normal male in Generation I, to produce four offspring – one normal male, one affected male, one normal female and one affected female. The normal female mates with a normal male, and they produce two unaffected children. The affected male of Generation II mates with a normal female, and they produce four children – two affected females and two unaffected males. This pattern is characteristic for X-linked dominant inheritance. **Source:** Wiki Drawing – X-Linked Dominant (1) by Madibc68, CC BY-SA 4.0

In X-linked dominant inheritance, the gene responsible for the disease is located on the X-chromosome, and the allele that causes the disease is dominant to the normal allele in females. Because females have twice as many X-chromosomes as males, females tend to be more frequently affected than males in the population. However, not all pedigrees provide sufficient information to distinguish XD and AD. One definitive indication that a trait is inherited as AD, and not XD, is that an affected father passes the disease to a son; this type of transmission is not possible with XD, since males inherit their X chromosome from their mothers.

Example: fragile x syndrome — The *FMR1* gene at Xq21 (X chromosome, q arm, region 2, band 1) encodes a protein needed for neuron development. There is a (CGG)n repeat array in the 5'UTR (untranslated region). If there is expansion of the repeat in the germline cell the child will inherit a non-functional allele. X^A / Y males have fragile X mental retardation (IQ < 50) because none of their neurons can make FMR1 proteins. Fragile X syndrome is considered X-linked dominant because only some neurons in X^A / X^a females can make FMR1 proteins. The severity (IQ 50 – 70) in these females depends upon the number and location of these cells within in the brain.

Autosomal Recessive (AR)

Diseases that are inherited in an autosomal recessive pattern require that both parents of an affected individual carry at least one copy of the disease allele. With AR traits, many individuals in a pedigree can be carriers, probably without knowing it. Compared to pedigrees of dominant traits, AR pedigrees tend to show fewer affected individuals and are more likely than AD or XD to "skip a generation". Thus, the major feature that distinguishes AR from AD or XD is that unaffected individuals can have affected offspring. Attached earlobes is a human condition that may follow an AR mode of inheritance.

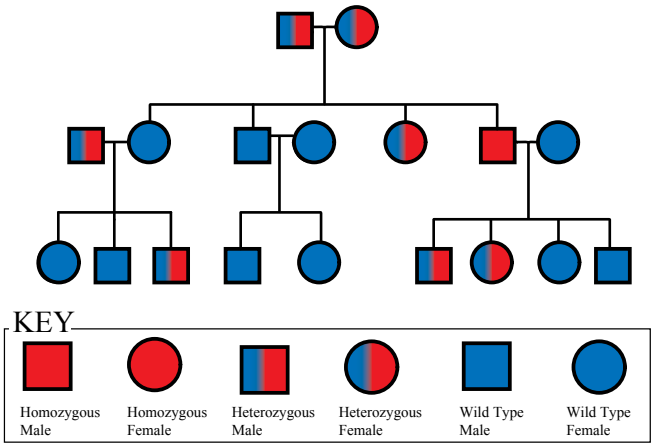


Figure 6.9 Pedigree chart showing the inheritance of an autosomal recessive trait, over three generations. Red and blue colours depict differences in the male and female. Both colours mean heterozygous, solid red colour means homozygous recessive, and solid blue color means wild type or homozygous dominant. Generation I begins with two carrier parents, who are therefore heterozygous. They produce four children, two are normal, one is a carrier and one is affected. This pattern is consistent with the inheritance of autosomal recessive traits. **Source:** Autosomal Recessive Pedigree Chart by Jerome Walker, CC BY-SA 3.0.

AR example: phenylketonuria (PKU) – Individuals with phenylketonuria (PKU) have a mutation in the *PAH* gene at 12q24 (chromosome 12, q arm, region 2, band 4), which encodes an enzyme that breaks down phenylalanine into tyrosine called phenylalanine hydrolase (PAH). Without PAH, the accumulation of phenylalanine and other metabolites, such as phenylpyruvic acid, disrupts brain development, typically within a year after birth, and can lead to intellectual disability. Fortunately, this condition is both easy to diagnose and can be successfully treated with a low phenylalanine diet. There are over 450 different mutant alleles of the PAH gene, so most people with PKU are **compound heterozygotes**. Compound heterozygotes have two different mutant alleles (different base pair changes) at a given locus, in this case the *PAH* gene.

X-Linked Recessive (XR)

Because males have only one X-chromosome, any male that inherits an X-linked recessive disease allele will be affected by it (assuming complete penetrance). Therefore, in XR modes of inheritance, males tend to be affected more frequently than females in a population. This contrasts with AR and AD, where both sexes tend to be affected equally, and XD, in which females are affected more frequently. Note, however, in the small sample sizes typical of human families, it is usually not possible to accurately determine whether one sex is affected more frequently than others. On the other hand, one feature of a pedigree that can be used to definitively establish that an inheritance pattern is not XR is the presence of an affected daughter from unaffected parents; because she would have had to inherit one X-chromosome from her father, he would also have been affected in XR.

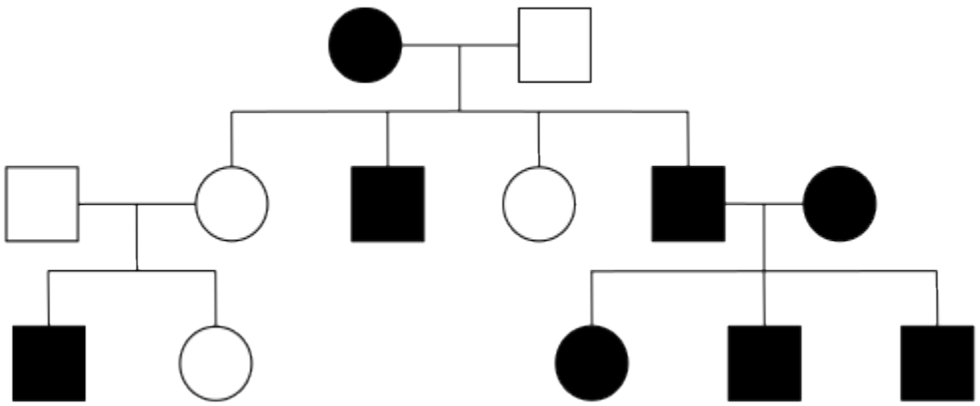


Figure 6.10 Pedigree chart showing the inheritance of a X-linked recessive trait over three generations. Generation I outlines one affected female and one affected male, mating to produce four children, two unaffected females and two affected males. One of the unaffected females mates with a normal man, and they produce two children: one affected male and an unaffected female. This indicates the unaffected mother was a carrier. This pattern of inheritance is typical of an X-linked recessive trait. **Source:** Wiki Drawing – X-Linked Recessive (1) by Madibc68, CC BY-SA 4.0

XR example: hemophilia A- *F8* gene at Xq28 (X chromosome, q arm, region 2, band 8) encodes blood clotting factor VIIIc. Without Factor VIIIc, internal and external bleeding can't be stopped. Back in the 1900s, Xa / Y male's average life expectancy was 1.4 years, but in the 2000s it has increased to 65 years with the advent of Recombinant Human Factor VIIIc. Hemophilia A is recessive because XA / Xa females have normal blood coagulation, while Xa / Xa females have hemophilia.

Y-Linked

Only males are affected in human Y-linked inheritance (and other species with the X/Y sex determining system). There is only father-to-son transmission. This is the easiest mode of inheritance to identify, but it is one of the rarest because there are so few genes located only on the Y-chromosome.

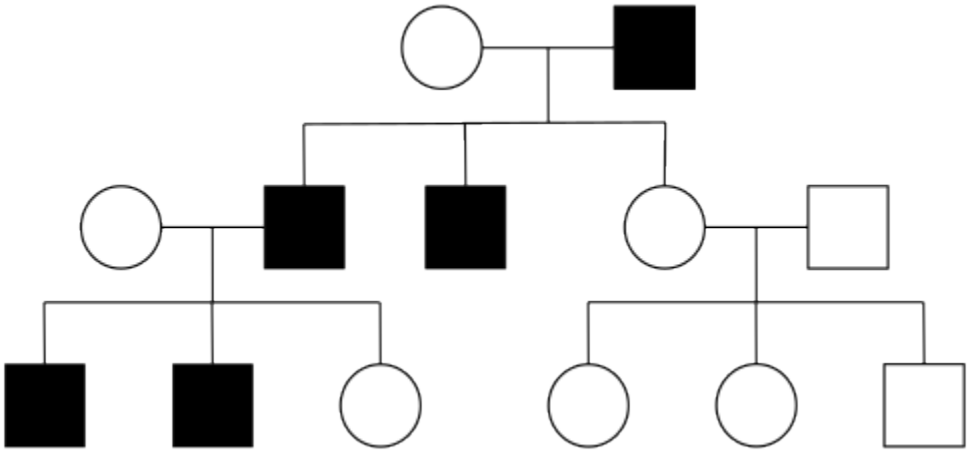


Figure 6.11 Pedigree chart showing the inheritance of a Y-linked trait. Three generations are shown, starting with a normal female and an affected male, who produce three offspring. Offspring are: one normal female and two affected males. One affected male mates with a normal female, and their offspring comprises one normal female and two affected males. This pattern of inheritance is typical of Y-linked traits. **Source:** Wiki Drawing – Y-Linked (1) by Madibc68, CC BY-SA 4.0

A common, but incorrect, example of Y-linked inheritance is the hairy-ear-rim phenotype seen in some Indian families. A better example are the Y-chromosome DNA polymorphisms that have been used to follow the male lineage in large families or through ancient ancestral lineages. For example, the Y-chromosome of Mongolian ruler Genghis Khan (1162-1227 CE), and his male relatives, accounts for ~8% of the Y-chromosome lineage of men in Asia (0.5% world wide).

Attribution & References

Except where otherwise noted, this section is adapted from 4.3 Modes of Inheritance In *Introduction to Genetics* by Natasha Ramroop Singh, Thompson Rivers University CC BY-NC-SA 4.0

6.5 CALCULATING PROBABILITIES USING PEDIGREE CHARTS

In practice, where available, model risk calculators are used. Examples include:

NCI (2024) **Breast Cancer Risk Assessment Tool: Online Calculator (The Gail Model)** (https://bcrisktool.cancer.gov/)

> "The Breast Cancer Risk Assessment Tool (BCRAT), also known as The Gail Model, allows health professionals to estimate a woman's risk of developing invasive breast cancer over the next five years and up to age 90 (lifetime risk)
>
> The tool uses a woman's personal medical and reproductive history and the history of breast cancer among her first-degree relatives (mother, sisters, daughters) to estimate absolute breast cancer risk-her chance or probability of developing invasive breast cancer in a defined age interval.
>
> This calculator takes about five minutes to complete" (para 1).

The University of Cambridge (2024) **CanRisk for Breast and Ovarian Cancer (https://www.canrisk.org/)**

> "CanRisk is an online tool that enables healthcare professionals to calculate an individual's future risks of developing *breast and ovarian cancer* using cancer family history, genetic and other risk factors. CanRisk also calculates variant carrier probabilities in breast and ovarian cancer susceptibility genes" (para 1).

MagView (2024). **Tyrer-Cuzick Risk Assessment Calculator** (https://ibis-risk-calculator.magview.com/)

> "This risk calculator asks questions about your personal and family history to determine the possibility of developing breast cancer. The results will display your lifetime risk score. The purpose of this tool is simply to inform you" (para 1).

Pedigree analysis can also be used to calculate risk. If the mode of inheritance of a trait is known, we can use information about others in the family to calculate the likelihood that another individual will develop the trait. This is useful in situations like genetic counseling: if a couple comes to a genetic counselor due to a family history of a genetic disorder, what is the risk that their child will also suffer from the disorder?

If the mode of inheritance is known, it's often possible to assign probable genotypes to some individuals in the pedigree, based on their phenotypes and relationships to others in the pedigree. For example, all individuals affected by an autosomal recessive trait have genotype "aa", and any of their offspring who are unaffected by the trait must have genotype "Aa". With this information, it's then possible to calculate the probability of other individuals either having the allele (being unaffected carriers) or having kids with the

trait. This makes pedigrees an important tool in genetic counseling if, for example, parents with a family history of a genetic disease would like to know the likelihood of passing the disease to their child.

Calculating risk from a pedigree chart

The rules of probability – and the laws of Mendelian inheritance – make these calculations possible. Remember from unit 2.5, we used two rules of probability: the product and sum rules. The product rule of probability states that the probability of two independent events occurring is the product of the probability of each event occurring independently. For example, in a cross between parents of genotypes Aa and Aa, the probability of having a child with phenotype A *and* a child with phenotype a is ¾ * ¼ = 3/8.

The sum rule of probability states that the probability of one event *or* another is the sum of their individual probabilities. In a cross between parents of genotypes Aa and Aa, the probability of having a child of genotype AA *or* Aa is ¼ + ½ = ¾.

In many of these complex family pedigrees, in order for a child to have a particular trait, the allele for the trait must be passed down from multiple individuals, often through several generations. But because all of these inheritance events must happen, we use the multiplication rule to calculate the combined probability.

When calculating the probabilities for a rare trait in the general population, unless there is evidence otherwise in the pedigree, we usually assume that unrelated individuals who are joining the family do not carry the same rare allele that "blood" relatives do, since this would be a pretty unlikely occurrence.

An example of this is shown using the pedigree shown in Figure 6.12. What is the probability that a child of III-1 and III-2 will be affected by the autosomal recessive trait?

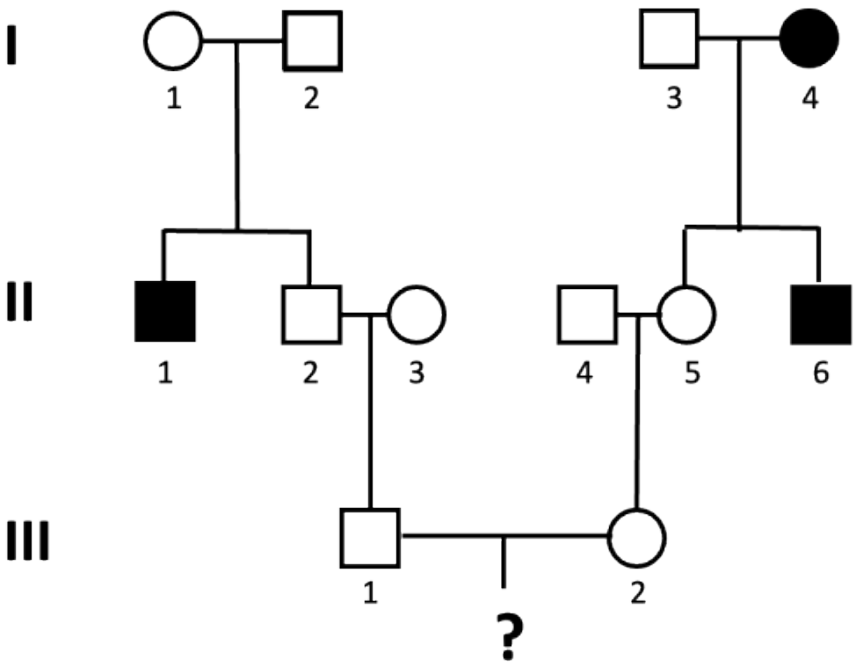


Figure 6.12 Pedigree tracking an autosomal recessive trait. Pedigree used to calculate the probability of a child in the 4th generation having the autosomal recessive trait tracked in this family. **Source:** *Chromosomes, Genes, and Traits: An Introduction to Genetics*, CC BY-SA 4.0.

We solve this type of problem by determining the genotypes of the direct ancestors to the individual for whom we will calculate the probability. The next figures walk through this process, step by step. Let's assume the allele associated with the recessive trait is "a".

Steps to determining the genotypes of direct ancestors

1. We can assign genotypes to all of the individuals in generation I.
   Individuals I-1 and I-2 must both have genotype Aa, since they have an affected child (II-1) who is presumed to have genotype aa. This is also true for individual I-3, who has a child with the trait as well. I-4 has the genotype aa, since they have the trait.

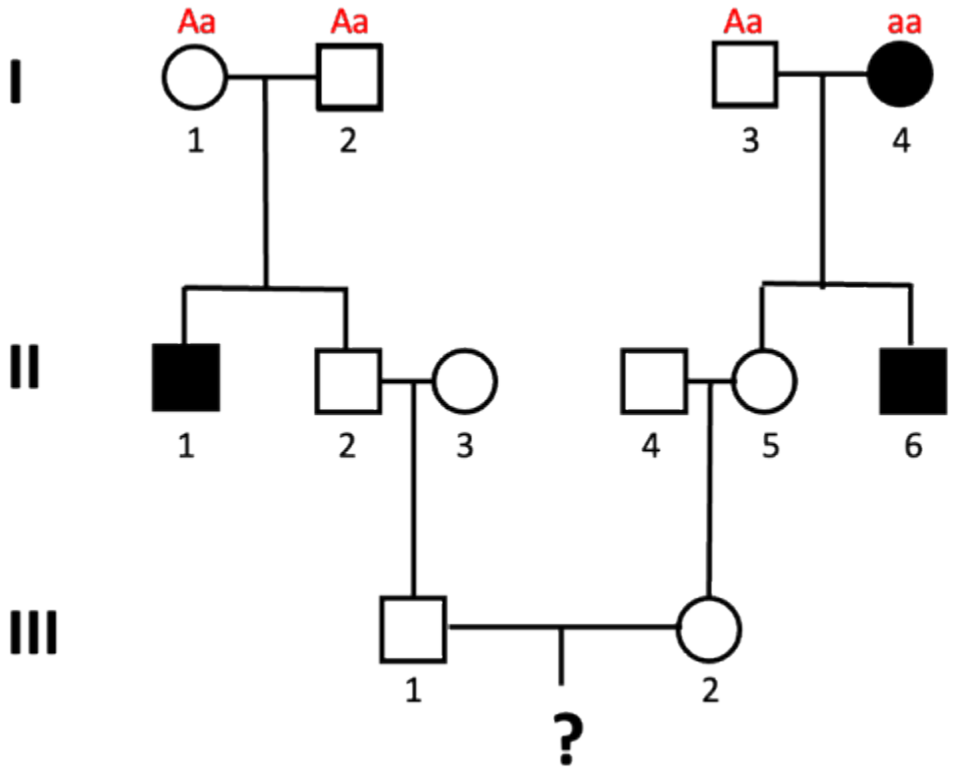


Figure 6.13 Pedigree used to calculate the probability of a child in the 4th generation having the autosomal recessive trait tracked in this family. Genotypes of all individuals in generation I are indicated: Aa, Aa, Aa, and aa. **Source:** *Chromosomes, Genes, and Traits: An Introduction to Genetics*, CC BY-SA 4.0.

2. Since this is a rare trait in the population, in Generation II we assume that individuals II-3 and II-4 do not carry the allele (they have genotype AA).

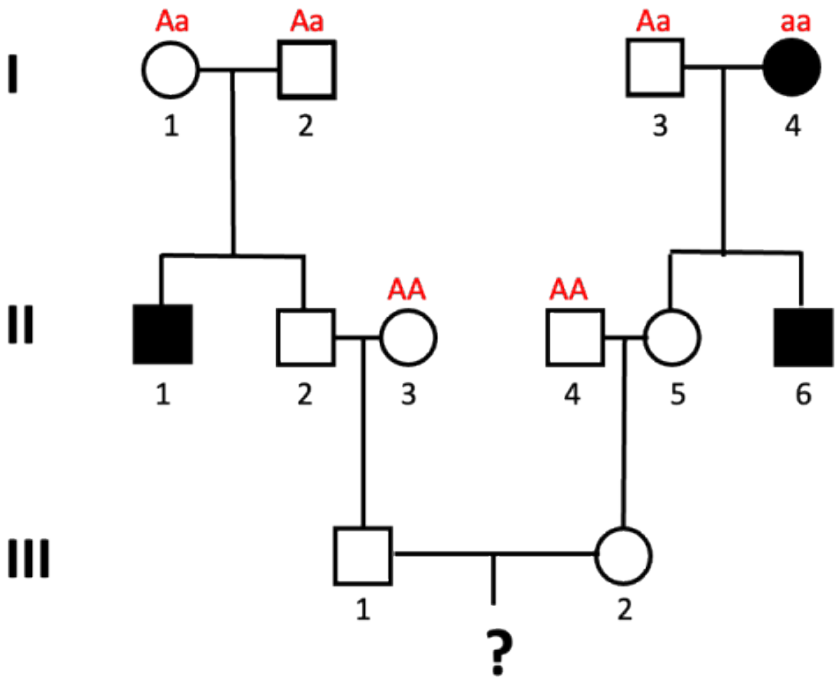


Figure 6.14 Pedigree used to calculate the probability of a child in the 4th generation having the autosomal recessive trait tracked in this family. Genotypes of all individuals in generation I are indicated: Aa, Aa, Aa, and aa. In generation II, II-3 and II-4 are also labeled with genotypes AA. **Source:** *Chromosomes, Genes, and Traits: An Introduction to Genetics*, CC BY-SA 4.0.

3. Individual II-5 must have genotype Aa, since she inherits a dominant (unaffected) allele from her dad, but must inherit the recessive allele from mom.

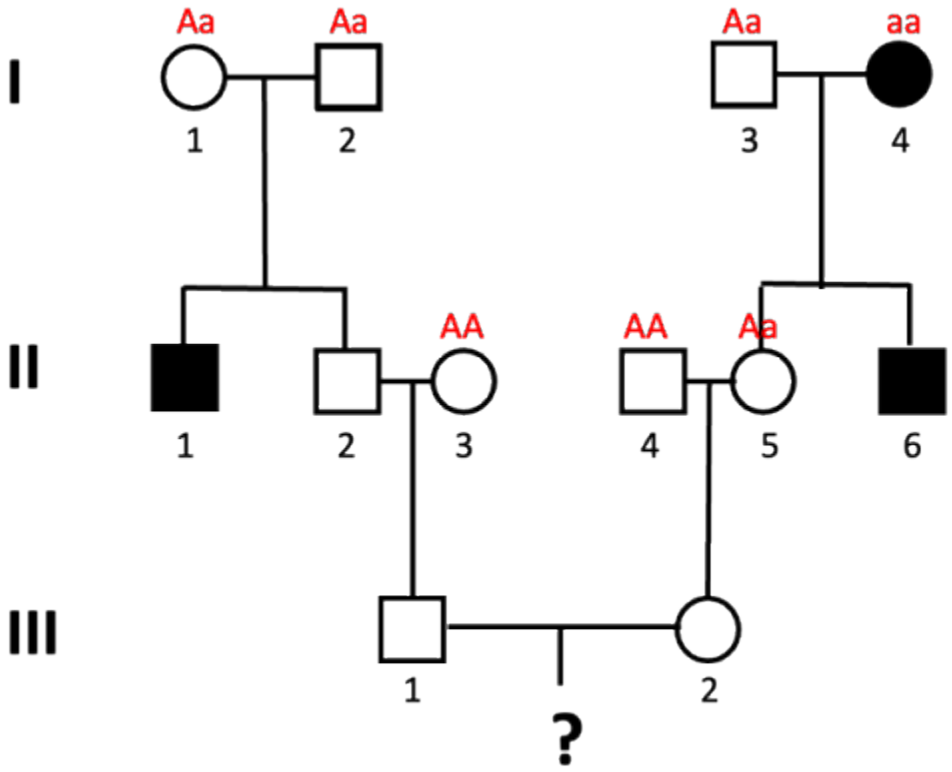


Figure 6.15 Pedigree used to calculate the probability of a child in the 4th generation having the autosomal recessive trait tracked in this family. Genotypes of all individuals in generation I are indicated as well as II-3 and II-4. Individual II-5 is labeled Aa. **Source:** *Chromosomes, Genes, and Traits: An Introduction to Genetics*, CC BY-SA 4.0.

4. What about individual II-2? In order for our final offspring to show the trait, individual II-2 must be a carrier of the "a" allele.
   What's the probability that they inherited the "a" allele? Well, let's look at the Punnett Square expected from Aa x Aa parents (which is what individual II-2 has). This requires a bit of tricky reasoning: it might be tempting to say that ½ are Aa, but that is incorrect. We know that II-2 does not have an aa genotype because II-2 does not show the trait. Of the remaining possibilities, 2/3 are Aa.

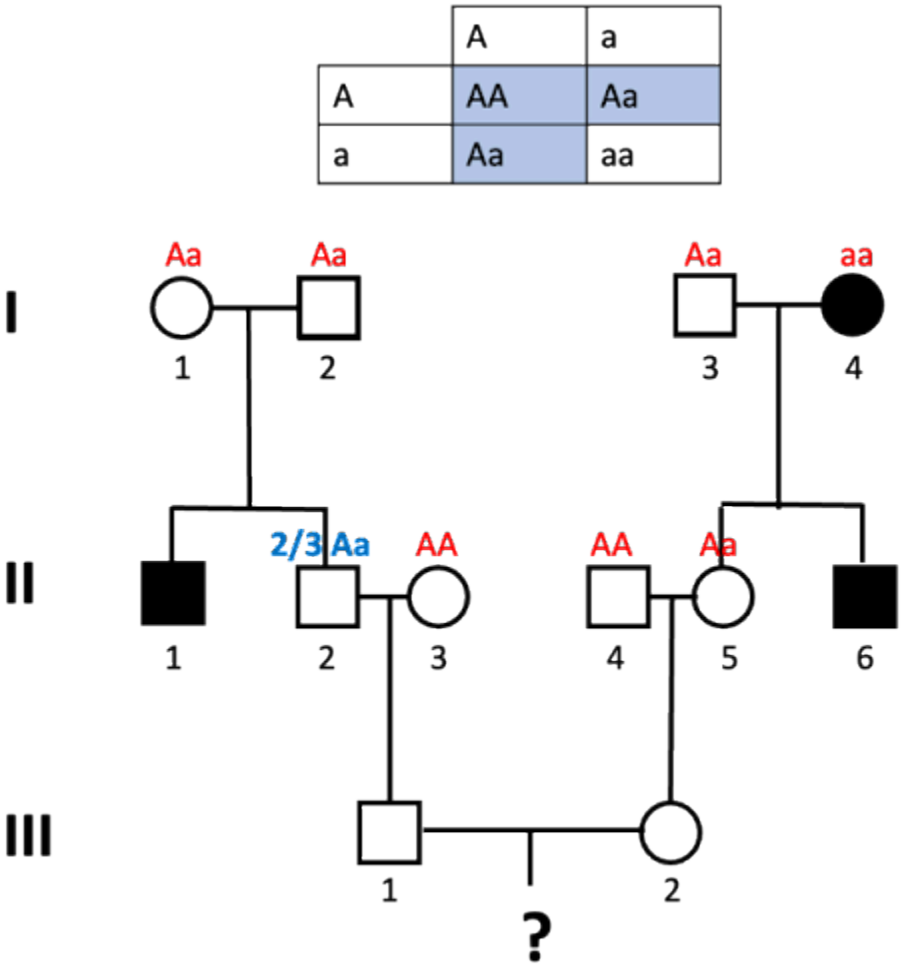


Figure 6.16 Pedigree used to calculate the probability of a child in the 4th generation having the autosomal recessive trait tracked in this family. Genotypes of all individuals in generation I are indicated as well as II-3, II-4, and II-5. Individual II-2 is labeled as having a 2/3 chance of genotype Aa. **Source:** *Chromosomes, Genes, and Traits: An Introduction to Genetics*, CC BY-SA 4.0.

5. In generation III, we likewise need to determine the probability of III-1 and III-2 carrying the allele. We do this as we did for II-2: we draw a Punnett square to illustrate the cross, and determine which fraction of offspring carry the allele. For both III-1 and III-2, there is a ½ probability that they will carry the allele (and have the Aa genotype).

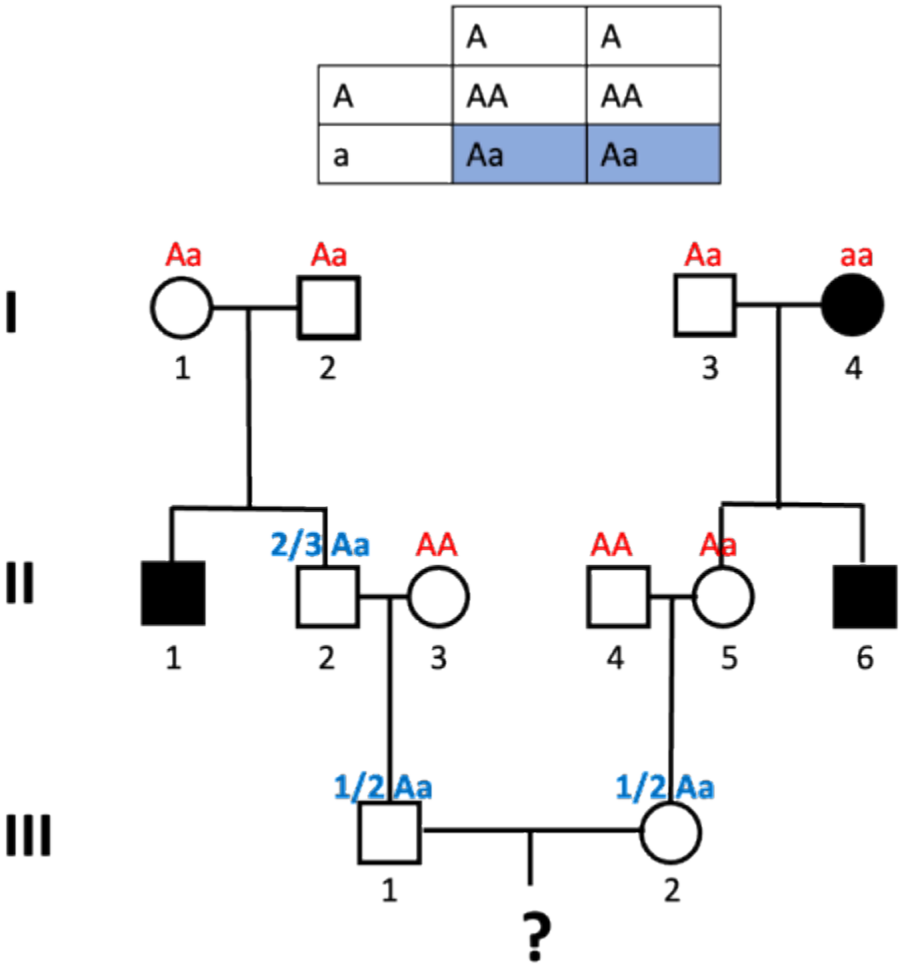


Figure 6.17 Pedigree used to calculate the probability of a child in the 4th generation having the autosomal recessive trait tracked in this family. Genotypes of all individuals in generation I are indicated as well as II-2, II-3, II-4, and II-5. Individuals III-1 and III-2 are labeled with a 1/2 probability of having genotype Aa. **Source:** *Chromosomes, Genes, and Traits: An Introduction to Genetics*, CC BY-SA 4.0.

6. Lastly, we can't forget the child! A Punnett square of Aa x Aa shows that there is a ¼ chance of aa offspring.

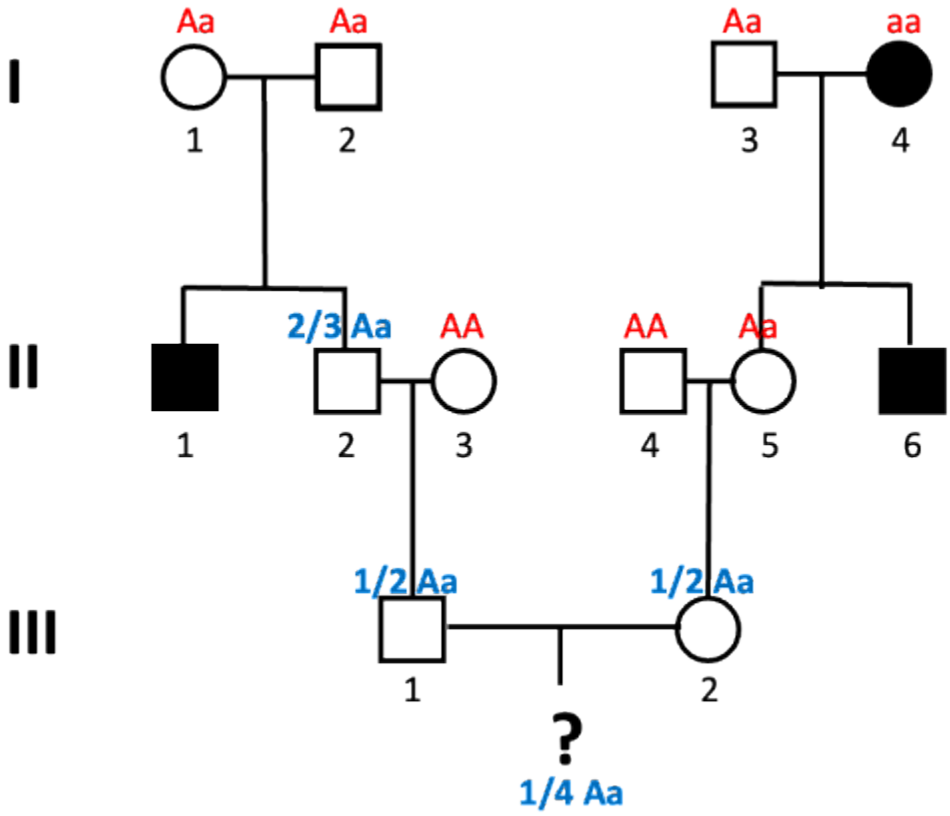


Figure 6.18 Pedigree used to calculate the probability of a child in the 4th generation having the autosomal recessive trait tracked in this family. Genotypes of all individuals in generation I, II, and III are labeled. The probability that unborn child that would inherit two "a" alleles is indicated: 1/4 aa. **Source:** *Chromosomes, Genes, and Traits: An Introduction to Genetics*, CC BY-SA 4.0.

In order for the child of III-1 and III-2 to show the trait, all these four things shown in blue in the images must be true: II-2 must be Aa, III-1 must be Aa, III-2 must be Aa, *and* the child must be aa. We use the multiplication rule to determine the overall probability:

2/3 * 1/2 *1/2 * 1/4 = 2/48

Some things to keep an eye out for, as you solve these problems: it's *very common to forget the last step: the probability of the final offspring showing the trait*! Don't forget to do this, even if there isn't a symbol representing the unborn child. And watch out for those Aa x Aa crosses, where you can rule out aa as a possible genotype. 2/3 of the possible unaffected offspring are Aa, not ½.

Practice exercises are provided in the next unit.

Attribution & References

Except where otherwise noted, this section is adapted from Pedigree Analysis In *Chromosomes, Genes, and Traits: An Introduction to Genetics*, by Amanda Simons, Framingham State University, CC BY-NC-SA 4.0

References

MagView. (2024). *Tyrer-Cuzick risk assessment calculator.* https://ibis-risk-calculator.magview.com/

National Cancer Institute (NCI). (2024). *Breast cancer risk assessment tool: Online calculator (The Gail Model).* NIH. https://bcrisktool.cancer.gov/

The University of Cambridge. (2024). *CanRisk for breast and ovarian cancer.* https://www.canrisk.org/

6.6 POLYGENIC RISK SCORES

Beyond Family History: Sporadic and Non-Heritable Diseases

Not all the characterized human traits and diseases are attributed to mutant alleles at a single gene locus. Many diseases that have a heritable component, have more complex inheritance patterns due to (1) the involvement of multiple genes, and/or (2) environmental factors. On the other hand, some non-genetic diseases may appear to be heritable because they affect multiple members of the same family, but this is due to the family members being exposed to the same toxins or other environmental factors (e.g., in their homes).

Finally, diseases with similar symptoms may have different causes, some of which may be genetic while others are not. One example of this is Amyotrophic lateral sclerosis (ALS) (https://www.mayoclinic.org/diseases-conditions/amyotrophic-lateral-sclerosis/symptoms-causes/syc-20354022); approximately 5–10% of cases are inherited in an AD pattern, while most of the remaining cases appear to be **sporadic**, in other words, not caused by a variant inherited from a parent. We now know that different genes or proteins are affected in the inherited and sporadic forms of ALS. The physicist Stephen Hawking and baseball player Lou Gehrig both suffered from sporadic ALS.

Watch the video *Neuroscience: Amyotrophic Lateral Sclerosis (ALS)*video (2 mins), by Neuroscientifically Challenged (2017) on YouTube (https://youtu.be/kOnk9Hh20eg), which describes how ALS arises in humans.

Polygenic Risk

Concept in Action

Watch this What Your Family History Can't Tell you (7 mins) on YouTube (https://youtu.be/tkJhdXt2G8k) to learn about how genes can interact to create a combined risk for developing disease.

Calculating polygenic risk scores

Researchers identify genomic variants associated with complex diseases by comparing the genomes of individuals with and without those diseases. The enormous amount of genomic data now available enables researchers to calculate which variants tend to be found more frequently in groups of people with a given disease. There can be hundreds or even thousands of variants per disease. Researchers put this information into a computer and use statistics to estimate how the collection of a person's variants affect their risk for a certain disease.

This yields **polygenic risk scores**. A polygenic risk score is one way by which people can learn about their risk of developing a disease, based on the total number of changes related to the disease. All of this can be done without knowing the specific genes involved in the complex disease. While we may someday know all the genes involved, researchers can estimate risk now without this link.

Interpreting polygenic risk scores

A polygenic risk score can only explain the **relative risk** for a disease. Why relative? The data used for generating a polygenic risk score comes from large scale genomic studies. These studies find genomic variants by comparing groups with a certain disease to a group without the disease.

A polygenic risk score tells you how a person's risk compares to others with a different genetic constitution. However, polygenic scores do not provide a baseline or timeframe for the progression of a disease. For example, consider two people with high polygenic risk scores for having coronary heart disease. The first person is 22 years old, while the latter is 98. Although they have the same polygenic risk score, they will have different lifetime risks of the disease. Polygenic risk scores only show correlations, not causations.

Absolute risk is different. Absolute risk shows the likelihood of a disease occurring. Women who carry a *BRCA1* variant have a 60-80% absolute risk of breast cancer. This would be true even without any comparison to any groups of people.

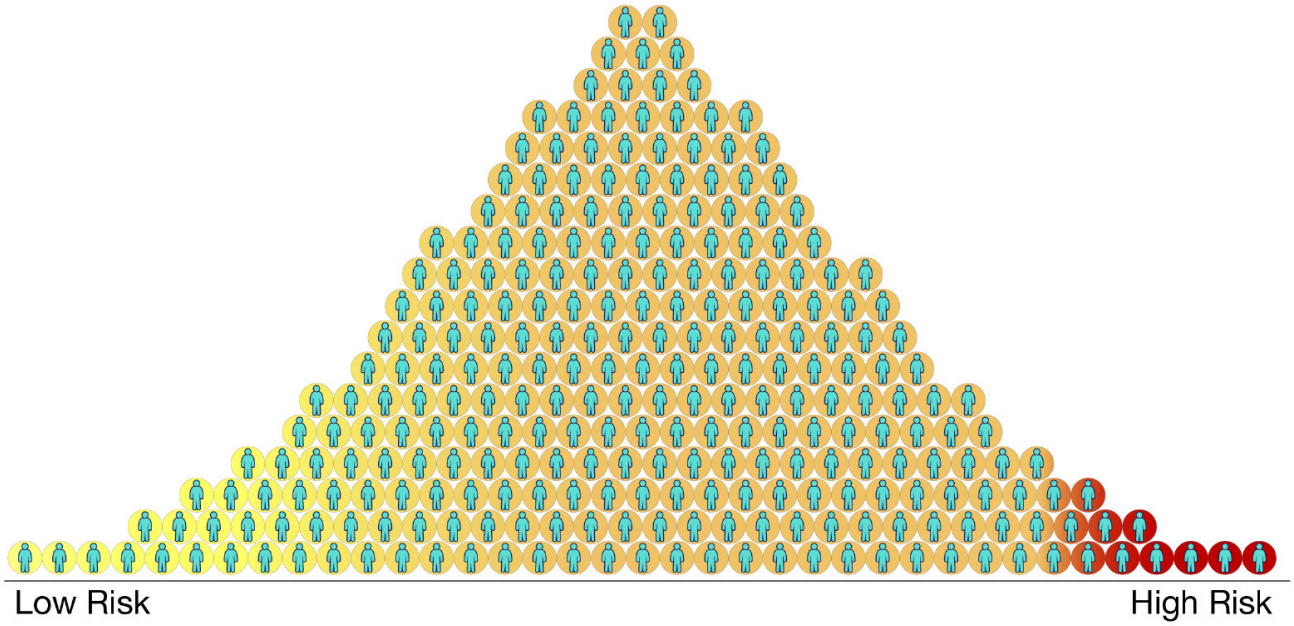


Figure 6.19 Each polygenic risk score can be put on a bell curve distribution. Most people will find their scores to be in the middle, indicating average risk for developing a disease. Others may find themselves on the tail ends, putting them at either low or high risk. People with scores on the high-risk portion of the spectrum may benefit from discussions about this risk with their physicians and genetic counselors for further health assessments. **Source:** Courtesy National Human Genome Research Institute, PDM with attribution.

Who benefits from a polygenic risk score?

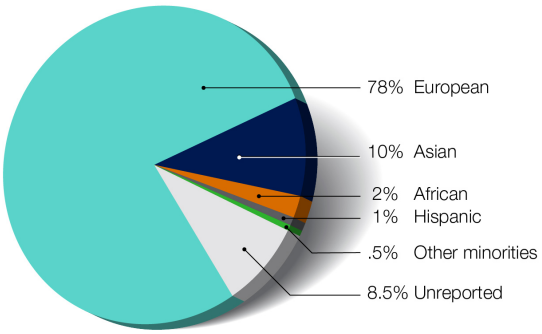


Figure 6.20 The percentage of ancestry populations included in large-scale genomic studies is overwhelmingly European. **Source:** Courtesy National Human Genome Research Institute, PDM with attribution.

Because the majority of genomic studies to date have examined individuals of European ancestry, there may not be adequate data about genomic variants from other populations for calculating a polygenic risk score in those populations. This historic lack of diversity in genomic studies is also a concern for other genomics-related research areas and contributes to a widespread concern about increasing health disparities beyond polygenic risk scores. At this point in time, the accuracy of polygenic risk scores may only be valid and useful for European ancestry populations. More research is needed to derive the data for making polygenic risk scores useful for other populations.

Looking into the future

Polygenic risk scores are not yet routinely used by health professionals because there are no guidelines for practice and researchers are still improving how these scores are generated. However, private healthcare and direct-to-consumer companies (private commercial companies that individuals can pay for out-of-pocket) have already begun generating polygenic risk scores for their consumers and they may someday serve as an important new tool to guide healthcare decisions.

Polygenic risk scores will always be probabilities, not certainties. Understanding how polygenic risk scores can impact peoples' lives and health is an active area of research being supported by the National Human Genome Research Institute.

Attribution & References

Except where otherwise noted, this section is adapted from

- 4.4 Sporadic and Non-Heritable Diseases In *Introduction to Genetics* by Natasha Ramroop Singh, Thompson Rivers University, CC BY-NC-SA 4.0
- Polygenic risk scores courtesy: National Human Genome Research Institute (NHGRI), Public Domain with attribution

References

Mayo Clinic Staff (n.d.). Amyotrophic lateral sclerosis (ALS). MayoClinic.org. https://www.mayoclinic.org/diseases-conditions/amyotrophic-lateral-sclerosis/symptoms-causes/syc-20354022

6.7 UNIT SUMMARY AND REVIEW

Key Takeaways

Taking a family health history is crucial for assessing genetic risks and identifying heritable conditions. It remains the gold standard for initial risk assessment, helping to reveal genetic components, inheritance patterns, and inform testing and treatment decisions.

Constructing a genetic pedigree involves creating a visual representation of a patient's family health history across multiple generations, which helps in diagnosing inherited conditions, understanding inheritance patterns, and informing clinical decisions. Standardized symbols and lines are used to depict family relationships and medical conditions, making the pedigree easy to read and update for healthcare professionals.

When analyzing pedigree charts to determine genotype, the goal is to identify the most likely mode of inheritance for a trait, which helps in predicting its inheritance in future offspring. This involves considering five major types of inheritance (autosomal dominant, autosomal recessive, X-linked dominant, X-linked recessive, and Y-linked) and making assumptions about complete penetrance and the rarity of the trait in the population. Different modes of inheritance can be identified through characteristic patterns in pedigree charts. These charts help determine how a disease or trait is passed down through generations, aiding in predicting the likelihood of inheritance in future offspring.

Not all diseases are caused by single gene mutations; many have complex inheritance patterns involving multiple genes and environmental factors. Some non-genetic diseases may appear heritable due to shared environmental exposures. Polygenic risk scores, which estimate disease risk based on multiple genetic variants, are emerging tools but currently have limitations, including a lack of diversity in genomic studies. These scores provide relative risk but not absolute certainty, and their use in healthcare is still evolving.

Once the mode of inheritance for a disease is identified, we can infer the genotypes of individuals in a pedigree based on their phenotypes and positions in the family tree. Using Mendelian inheritance

rules and probability calculations, we can determine the likelihood of specific genotypes being passed to future generations, which is valuable for genetic counseling and assessing the risk of offspring inheriting certain diseases.

Additional Optional Readings

1. Andrusko, D. & Paradiso, C. (2022). Establishing a process to improve the collection of family health history. *The Nurse Practitioner, 47* (4), 32-40. https://doi.org/10.1097/01.NPR.0000822532.65525.5a.
2. Hays, L. (2023). The three-generation pedigree. Advances in Family Practice Nursing, 5(1), 77–91. https://doi.org/10.1016/j.yfpn.2022.11.006
3. Mahon, S.M. (2016). The three-generation pedigree: A critical tool in cancer genetics care. Genetics, Patient Education, Risk Assessment, 43(5), 655-660. https://doi.org/10.1188/16.ONF.655-660
4. Stanfill, A. G., & Starlard-Davenport, A. (2018). Primer in genetics and genomics, Article 7—Multifactorial concepts: Gene–gene interactions. *Biological Research For Nursing*, *20*(3), 359-364. https://doi.org/10.1177/1099800418761098
5. Wildin, R. S., Messersmith, D. J., & Houwink, E. J. F. (2021). Modernizing family health history: achievable strategies to reduce implementation gaps. *Journal of community genetics*, *12*(3), 493–496. https://doi.org/10.1007/s12687-021-00531-6
6. Xiang, R., Kelemen, M., Xu, Y., Harris, L. W., Parkinson, H., Inouye, M., & Lambert, S. A. (2024). Recent advances in polygenic scores: translation, equitability, methods and FAIR tools. *Genome Medicine, 16*, 33. https://doi.org/10.1186/s13073-024-01304-9

Tools and Resources

Pedigree Analysis

- For a visual walk-through of a pedigree analysis work through this short Khan Academy module on pedigrees (https://www.khanacademy.org/science/high-school-biology/hs-classical-genetics/hs-pedigrees/v/pedigrees) which includes practice exercises.

Family History and Pedigree Chart Tools

- Students will use My Family Health Portrait (https://cbiit.github.io/FHH/html/index.html) to create a pedigree chart for their chosen case study.

- Another good clinical resource for creating an electronic pedigree is from Progeny Genetics (https://pedigree.progenygenetics.com/)
- For those who prefer a paper template, the Jackson Laboratory provides a template and printable symbol sheet (https://www.jax.org/education-and-learning/clinical-and-continuing-education/clinical-topics/cancer-resources/pedigree-tool).
- GECKO has also created this family history tool [PDF] (https://www.geneticseducation.ca/wp-content/uploads/2013/03/Family-history-tool-GECKO-April-20141.pdf).
- The NHS Genomics Education Programme has a family history worksheet [PDF] (https://www.genomicseducation.hee.nhs.uk/wp-content/uploads/2019/05/Family-history-worksheet-blank.pdf)
- Families Sharing Health Assessment and Risk Evaluation (SHARE) (https://www.genome.gov/research-at-nhgri/Projects/Families-SHARE) helps you and your family learn how your family health history affects your risk for diseases. Includes disease risk worksheets and workbooks in multiple languages.

Variant Classification

- ClinVar (http://www.ncbi.nlm.nih.gov/clinvar/)

Landrum, M. J., Chitipiralla, S., Kaur, K., Brown, G., Chen, C., Hart, J., Hoffman, D., Jang, W., Liu, C., Maddipatla, Z., Maiti, R., Mitchell, J., Rezaie, T., Riley, G., Song, G., Yang, J., Ziyabari, L., Russette, A., & Kattman, B. L. (2024). ClinVar: updates to support classifications of both germline and somatic variants, *Nucleic Acids Research*, gkae1090, https://doi.org/10.1093/nar/gkae1090

Attribution and References

Key takeaways generated using ChatGPT. Prompt: "summarize this text in a few sentences, ignoring images, captions, citations and web references." The output was then edited by Andrea Gretchev.

References

ChatGPT: OpenAI. (2024). *ChatGPT (Version 4.0)* [Large language model]. https://openai.com