

Pedigree analysis reveals Mendelian patterns in human inheritance

- Rather than manipulate mating patterns of people, geneticists analyze the results of matings that have already occurred.
- In a **pedigree analysis**, information about the presence/absence of a particular phenotypic trait is collected from as many individuals in a family as possible and across generations.
- The distribution of these characters is then mapped on the family tree.
 - For example, the occurrence of widows peak (W) is dominant to a straight hairline (w).
 - The relationship among alleles can be integrated with the phenotypic appearance of these traits to predict the genotypes of members of this family.
 - If an individual in the third generation lacks a widow's peak, but both her parents have widow's peaks, then her parents must be heterozygous for that gene
 - If some siblings in the second generation lack a widow' peak and one of the grandparents (first generation) also lacks one, then we know the other grandparent must be heterozygous and we can determine the genotype of almost all other individuals.
- We can use the same family tree to trace the distribution of attached earlobes (f), a recessive characteristic.
 - Individuals with a dominant allele (F) have free earlobes.
 - Some individuals may be ambiguous, especially if they have the dominant phenotype and could be heterozygous or homozygous dominant.
- A pedigree can help us understand the past and to predict the future.
- We can use the normal Mendelian rules, including multiplication and addition (pgs. 254-255), to predict the probability of specific phenotypes.
 - For example, these rules could be used to predict the probability that a child with WwFf parents will have a widow's peak and attached earlobes.
 - The chance of having a widow's peak is $\frac{3}{4}$ ($\frac{1}{2}$ [WW] + $\frac{1}{4}$ [Ww]).
 - The chance of having attached earlobes is $\frac{1}{4}$ [ff].
 - This combination has a probability of $\frac{3}{4} + \frac{1}{4} = \frac{3}{16}$.

Many human disorders follow Mendelian patterns of inheritance

- Thousands of genetic disorders, including disabling or deadly hereditary diseases, are inherited as simple recessive traits.
 - These range from the relatively mild (albinism) to life-threatening (cystic fibrosis).
- The recessive behavior of the alleles occurs because the allele codes for either a malfunctioning protein or no protein at all.
 - Heterozygotes have a normal phenotype because one “normal” allele produces enough of the required protein.
- A recessively inherited disorder shows up only in homozygous individuals who inherit one recessive allele from each parent.
- Individuals who lack the disorder are either homozygous dominant or heterozygotes.
- While heterozygotes may have no clear phenotypic effects, they are **carriers** who may transmit a recessive allele to their offspring.
- Most people with recessive disorders are born to carriers with normal phenotypes.
 - Two carriers have a 1/4 chance of having a child with the disorder, 1/2 chance of a carrier, and 1/4 free.
- Genetic disorders are not evenly distributed among all groups of humans.
- This results from the different genetic histories of the world’s people during times when populations were more geographically (and genetically) isolated.
- One such disease is **cystic fibrosis** which strikes one of every 2,500 whites of European descent.
 - One in 25 whites is a carrier.
 - The normal allele codes for a membrane protein that transports Cl⁻ between cells and the environment.
 - If these channels are defective or absent, there are abnormally high extracellular levels of chloride that causes the mucus coats of certain cells to become thicker and stickier than normal.
 - This mucus build-up in the pancreas, lungs, digestive tract, and elsewhere favors bacterial infections.
 - Without treatment, affected children die before five, but with treatment can live past their late 20’s.
- Tay-Sachs disease is another lethal recessive disorder.
 - It is caused by a dysfunctional enzyme that fails to break down specific brain lipids.
 - The symptoms begin with seizures, blindness, and degeneration of motor and mental performance a few months after birth.
 - Inevitably, the child dies after a few years.
 - Among Ashkenazic Jews (those from central Europe) this disease occurs in one of 3,600 births, about 100 times greater than the incidence among non-Jews or Mediterranean (Sephardic) Jews.

- Although most harmful alleles are recessive, many human disorders are due to dominant alleles.
- For example, *achondroplasia*, a form of dwarfism, has an incidence of 1 case in 10,000 people.
 - Heterozygous individuals have the dwarf phenotype.
 - Those who are not achondroplastic dwarfs, 99.99% of the population, are homozygous recessive for this trait.
- Lethal dominant alleles are much less common than lethal recessives because if a lethal dominant kills an offspring before it can mature and reproduce, the allele will not be passed on to future generations.
- A lethal dominant allele can escape elimination if it causes death at a relatively advanced age, after the individual has already passed on the lethal allele to his or her children.
- One example is **Huntington's disease**, a degenerative disease of the nervous system.
 - The dominant lethal allele has no obvious phenotypic effect until an individual is about 35 to 45 years old.
 - The deterioration of the nervous system is irreversible and inevitably fatal.
- Any child born to a parent who has the allele for Huntington's disease has a 50% chance of inheriting the disease and the disorder.
- Recently, molecular geneticists have used pedigree analysis of affected families to track down the Huntington's allele to a locus near the tip of chromosome 4.
- While some diseases are inherited in a simple Mendelian fashion due to alleles at a single locus, many other disorders have a multifactorial basis.
 - These have a genetic component plus a significant environmental influence.
 - Multifactorial disorders include heart disease, diabetes, cancer, alcoholism, and certain mental illnesses, such as schizophrenia and manic-depressive disorder.
 - The genetic component is typically polygenic.
- At present, little is understood about the genetic contribution to most multifactorial diseases
 - The best public health strategy is education about the environmental factors and healthy behavior.

Technology is providing new tools for genetic testing and counseling

- Mendel's laws are simply the rules of probability applied to heredity.
- A preventative approach to simple Mendelian disorders is sometimes possible.
- The risk that a particular genetic disorder will occur can sometimes be assessed before a child is conceived or early in pregnancy.
- Many hospitals have genetic counselors to provide information to prospective parents who are concerned about a family history of a specific disease.
- Most children with recessive disorders are born to parents with a normal phenotype.
- A key to assessing risk is identifying if prospective parents are carriers of the recessive trait.
- Recently developed tests for several disorders can distinguish between normal phenotypes in heterozygotes from homozygous dominants.
- The results allow individuals with a family history of a genetic disorder to make informed decisions about having children.
- However, issues of confidentiality, discrimination, and adequate information and counseling arise.
- Tests are also available to determine in utero if a child has a particular disorder.
- One technique, **amniocentesis**, can be used beginning at the 14th to 16th week of pregnancy to assess the presence of a specific disease.
 - Fetal cells extracted from amniotic fluid are cultured and karyotyped to identify some disorders.
 - Other disorders can be identified from chemicals in the amniotic fluids.
- Other techniques, *ultrasound* and *fetoscopy*, allow fetal health to be assessed visually in utero.
- Both fetoscopy and amniocentesis cause complications in about 1% of cases.
 - These include maternal bleeding or fetal death.
 - Therefore, these techniques are usually reserved for cases in which the risk of a genetic disorder or other type of birth defect is relatively great.
- If fetal tests reveal a serious disorder, the parents face the difficult choice of terminating the pregnancy or preparing to care for a child with a genetic disorder.
- Some genetic tests can be detected at birth by simple tests that are now routinely performed in hospitals.
- One test can detect the presence of a recessively inherited disorder, phenylketonuria (PKU).
 - This disorder occurs in one in 10,000 to 15,000 births.
 - Individuals with this disorder accumulate the amino acid phenylalanine and its derivative phenylpyruvate in the blood to toxic levels.
 - This leads to mental retardation.
 - If the disorder is detected, a special diet low in phenylalanine usually promotes normal development.