Single Gene (Monogenic) Disorders

Mendelian Inheritance: Definitions

- A genetic **locus** is a specific position or location on a chromosome. Frequently, locus is used to refer to a specific gene.
- **Alleles** are alternative forms of a gene, or of a DNA sequence, at a given locus.
- **Polymorphism** means the existence of multiple allelic forms at a specific locus.
- Not all loci are polymorphic. In fact, 99% of all of our genetic code is identical.

Mendelian Inheritance: Definitions

- If both alleles at a locus are identical, the individual is **homozygous** at that locus (a **homozygote** for that condition).
- If the alleles at a locus are different, he or she is **heterozygous** (a **heterozygote**).
- The **genotype** is the genetic constitution or composition of an individual, often referring to the alleles at a specific genetic locus.
- The **phenotype** is the observable expression of the particular gene or genes; phenotype is influenced by environmental factors and interactions with other genes.
Mendelian Inheritance: Definitions

- Mendelian disorders are defined as those diseases that are the result of a single mutant gene that has a large effect on phenotype, and that are inherited in simple patterns resembling those described by Mendel for garden peas.
- Mendelian disorders/traits are autosomal if they are encoded by genes on one of the 22 pairs of autosomes (non-sex chromosomes).
- Mendelian disorders/traits are X-linked if encoded by a gene on the X chromosome.

Mendelian Inheritance: Definitions

- Dominant conditions are those expressed in heterozygotes, i.e., individuals with one copy of a mutant allele and one copy of a normal (wild-type) allele.
- Recessive conditions are clinically manifest only in individuals homozygous for the mutant allele (or compound heterozygotes for two different mutant alleles), i.e., carrying a “double dose” of an abnormal gene.

Mendelian Inheritance: Definitions

- Variable expression: Different degrees of clinical expression given the same genotype
- Pleiotropism: Multiple clinical effects of a single gene
Relatives may be:

- **First Degree**: Parents, siblings, offspring of the proband
- **Second Degree**: Grandparents, grandchildren, uncles, aunts, nieces, nephews.
- **Third Degree**: Cousins, etc.

**Proband** = First person brought to medical attention

---

**Sex-limited Phenotype**

- The expression of a trait in only one of the sexes, due, for instance, to anatomical differences.
  - Example: Uterine or testicular defects.

---

**Sex-influenced Phenotype**

- A phenotype which occurs in both males and females, but with different frequencies.
  - Example: Male pattern baldness.
Sex-linked Inheritance

Sex-linked genes are those located on either the X or the Y chromosome. Because few genes are known to be located on the human Y chromosome, we will focus on X-linked disorders.

Autosomal Dominant Inheritance: Classic Characteristics

- Only one copy of the abnormal gene is required for the individual to be affected.
- Every affected person has an affected parent.
- The disorder is passed from one generation to the next (vertical transmission).
- Both males and females are affected and may transmit the gene to offspring of either sex.

Autosomal Dominant Inheritance: Recurrence Risks

- For matings of an affected heterozygote with a normal homozygote, there is a 50% chance that each offspring will be affected and a 50% chance that each offspring will be unaffected.
- For the rare matings of two affected heterozygotes, the recurrence risks for each offspring are as follows:
  - 25% chance affected homozygote
  - 50% chance affected heterozygote
  - 25% chance normal homozygote
- Total recurrence risk for an affected child: 75%.
Autosomal Dominant Inheritance: Considerations

- In general, affected individuals are heterozygotes.
- Because homozygous affected individuals are very rare, the usual mating in dominantly inherited diseases is between a homozygous normal and a heterozygous affected individual.
- However, if the gene is sufficiently common, matings between heterozygous affected parents resulting in homozygous affected offspring are seen. Usually affected homozygotes have a more abnormal phenotype than heterozygotes (e.g., homozygous achondroplasia and Marfan syndrome are lethal in infancy), although in some conditions the phenotypes are indistinguishable.

Variable Expression

- Even when penetrance of a condition is complete, the severity of the disease may vary greatly.
- Possible causes: Environmental factors, modifier genes.

Variable Expression

- Variability is disease specific:
  - Little / none
  - Little intra-familial variability (Marfan syndrome)
  - Intra- and inter-familial variability (Neurofibromatosis)
  - Incomplete penetrance as extreme expression of variable expression (Holt - Oram)
**Incomplete Penetrance**

- An individual who has the genotype for a disease may not exhibit the disease phenotype at all, even though he or she can transmit the disease gene to the next generation. Penetrance rates are estimated by examining a large number of families to determine what proportion of obligate carriers (AD) or homozygotes (AR) develop the disease phenotype.

---

**Parental Age Effect**

- Well known association with advanced maternal age and chromosome aneuploidy
- Increased incidence of single gene mutations with advanced paternal age
- Difference is due to different ontogeny of the germ cells (oocytes versus sperm)

---

**Some Dominant Conditions with Documented Paternal Age Effect**

- Achondroplasia
- Marfan syndrome
- Neurofibromatosis
- Treacher - Collins syndrome
- Crouzon syndrome
- Progeria
- (?) all single gene loci
Autosomal Dominant Inheritance: Exceptions to Classic Rules

There may be no affected parent if:
- The condition is caused by a new mutation.
- There is reduced penetrance.
- A parent has gonadal (germline) mosaicism for a dominant mutation; this may cause multiple affected siblings (resembles AR inheritance pattern).

Autosomal Dominant Inheritance: Exceptions to Classic Rules

There may not appear to be an affected parent if:
- The parental phenotypic features are very mild due to variable expression.
- There is delayed onset of the condition, with manifestations occurring later in life.
- There is non-paternity (10%).

“True” Dominance

- True (complete) dominance implies identical phenotype in those heterozygous or homozygous for the mutation (e.g., Huntington Disease).
- Most ‘dominant’ conditions in humans are actually semi-dominant (e.g., achondroplasia).
**Co-Dominant**

- Co-dominance refers to the simultaneous expression of both alleles in a heterozygote (e.g. ABO blood type)

---

**Autosomal Recessive Inheritance: Classic Characteristics**

- The parents of an affected individual are both unaffected.
- Both parents are heterozygotes, or carriers.
- The family history is negative except for 1) the possibility of affected siblings, or 2) the possibility of affected relatives due to consanguinity in their parents.

---

**Autosomal Recessive Inheritance: Recurrence Risks**

- For two heterozygotes the recurrence risk to have an affected child is 25%.
- The phenotypically normal siblings of an affected child have a 2/3 chance of carrying the recessive allele.
**Autosomal Recessive Inheritance: Recurrence Risks**

- Occasionally a heterozygote (carrier) mates with an affected homozygote. In this case each offspring has a 50% risk to be affected and a 50% risk to be a carrier. This results in a pattern of inheritance resembling AD, called quasi-dominance, and is more likely to occur with common AR genes or parental consanguinity.
- The mating of two affected homozygotes results in 100% of the offspring being homozygous affected. Example: AR congenital deafness.

**Autosomal Recessive Inheritance: Considerations**

- Because the risk is only 1 in 4 that a child will be born to two carrier parents, and because most American families are small (2-3 children), most affected individuals with AR disorders will appear to be sporadic cases (only 1 case in a kindred). A genetic etiology should not be overlooked because of lack of family history.
- AR traits may be recognized by the occurrence in affected sibs, parental consanguinity, or by the demonstration of a partial defect in heterozygotes (e.g. enzyme levels).

**Consanguinity**

- Relationship by descent from a common ancestor.
**X-linked Inheritance: General Characteristics**

- X-linked mutant genes are fully expressed in males, who have only a single X chromosome, i.e., are hemizygous for X-linked genes.
- Fathers must transmit their Y chromosome to their sons, thus there is no male-to-male transmission of X-linked genes.

**X-Linked Inheritance: General Characteristics**

- Only one of the two X-chromosomes in human female somatic cells is genetically active. One of the two X chromosomes is randomly and permanently inactivated early in embryogenesis by a process called lyonization. Because of this random X-inactivation, X-linked traits are variably expressed in females heterozygotes.

**X-linked Recessive Inheritance: Characteristics**

- X-linked diseases rarely expressed clinically in heterozygous females are called X-linked recessive.
- Only males are affected.
- The disorder is transmitted by healthy heterozygous female carriers.
- Examples: Duchenne muscular dystrophy, hemophilia.
**X-linked Recessive Inheritance: Recurrence Risks**

In the usual mating between a heterozygous affected female and a normal male, the risks for offspring are as follows:
- 25% chance affected male
- 25% chance normal male
- 25% chance carrier female (normal)
- 25% chance non-carrier female (normal)

Total risk for an affected child: 25%

**X-linked Recessive Inheritance: Recurrence Risks**

Another typical mating is an affected male with homozygous normal female. Offspring:
- All males normal
- All females obligate carriers

Total: 50% chance normal male
- 50% chance carrier female

**Possible reasons for the rare expression of X-linked recessive traits in females:**
- The abnormal allele may be common enough that female homozygotes are seen.
- Female hemizygosity caused by 45,X Turner syndrome.
- X-chromosome/autosome translocations with resulting X-chromosome material deleted and preferential inactivation of the normal X.
- Random lyonization of the X bearing the normal allele.
- A female may appear to be affected due to an autosomal phenocopy of the X-linked disorder (locus heterogeneity).
X-linked Dominant Inheritance: Characteristics

- Males or females may be affected.
- The expression in heterozygous females may be variable.
- Often the clinical expression is more consistent and severe in hemizygous males than in heterozygous females, with some conditions causing lethality in males.
  Example: Aicardi syndrome

X-linked Dominant Inheritance: Recurrence Risks

- In the mating of an affected male with a normal female:
  All daughters will be affected
  All sons will be normal
- In the mating of an affected female with a normal male:
  Each daughter and each son has a 50% chance of being affected.

X-linked Semi-Dominant Inheritance: Characteristics

- In some XL conditions, mild expression in carrier females is common, and is sometimes referred to as “semi-dominance”.
  Example: hypohidrotic ectodermal dysplasia