SEX-LINKED INHERITANCE

Dr Rasime Kalkan
Human Karyotype
Picture of Human Chromosomes
22 Autosomes and 2 Sex Chromosomes

[Diagram of human chromosomes with a question mark indicating male or female]
Autosomal vs. Sex-Linked

Traits can be either:

- **Autosomal**: traits (genes) are located on the non-sex chromosomes
- **Sex-Linked**: traits (genes) are located on the sex chromosomes
- **Sex chromosomes** determine gender (X & Y)
- **XX** genotype for females
- **XY** genotype for males
Sex-Linked Genes

The Y chromosome is much smaller than the X chromosome and appears to contain fewer genes.

- Duchenne muscular dystrophy
- Melanoma
- X-inactivation center
- X-linked severe combined immunodeficiency (SCID)
- Colorblindness
- Hemophilia

Y Chromosome
- Testis-determining factor
Sex-Linked Genes

- Genes unrelated to gender on the X chromosome.
- Females have two X chromosomes (so they can be heterozygous or homozygous for each of these genes).
- Males have one copy of the sex-linked genes.
- Thus, the male is referred to as hemizygous.
X - linked Recessive Inheritance

- Refers to those situations where a recessive allele on the X chromosome can lead to a trait/condition or disorder.
X-linked Recessive Inheritance

- Males are affected more often than females.
- Affected males will transmit the allele to all daughters, but not to sons.
- Homozygous recessive females can arise only from matings in which the father is affected and the mother is affected or a carrier.
Typical features of X-linked recessive inheritance

- Never passed from father to son.

- Males are much more likely to be affected because they only need one copy of the mutant allele to express the phenotype.

- Affected males get the disease from their mothers and all of their daughters are obligate carriers.

- Sons of heterozygous females have a 50% chance of receiving the mutant allele.

- These disorders are typically passed from an affected grandfather to 50% of his grandsons.
**X-linked recessive**

- Heterozygous females are usually unaffected, but some may express the condition with variable severity as determined by the pattern of \(X\) inactivation.

- The mutant allele may be transmitted through a series of carrier females; if so, the affected males in a kindred are related through females.

- A significant proportion of isolated cases are due to new mutation.

- Many X-linked recessive disorders are well-known, including color blindness, hemophilia, and Duchenne muscular dystrophy.
Manifesting Heterozygous or unbalanced (skewed) inactivation for X linked disease

• In those rare instances in which a female carrier of a recessive X linked allele has phenotypic expression of the disease, she is referred to as a Manifesting Heterozygous.
The pattern for the pedigree of X-linked recessive inheritance
X - linked Recessive Disorders

- **Hemophilia** which is the inability of the blood to clot properly.
- **Duchenne Muscular Dystrophy** which causes progressive and degenerative muscle weakness.
Hemophilia

• Disease that affects a single protein in a cascade of proteins involved in the formation of blood clots

• Form of hemophilia is caused by an X-linked recessive allele
  – Heterozygous females are asymptomatic carriers

• Allele for hemophilia was introduced into a number of different European royal families by Queen Victoria of England
The Royal Hemophilia Pedigree
Example: hemophilia A

Predict possible fetal outcomes
Example: hemophilia A
Overview of XR trait

- A number of recessive mutations are X linked.
- Their transmission is described by the following rules:
  - Females can be carriers of recessive disorders
  - Males express the respective phenotype because they are HEMIZYGOUS for X chromosome. They receive their X from the mother.
  - Sons of affected males are healthy but daughters become carriers.
X - Linked Dominant Inheritance

• Refers to situations where a single dominant allele on the X chromosome can lead to a trait/condition.
• XD can distinguished from autosomal dominant inheritance by the lack of **male to male transmission**.
**X-Linked Dominant Inheritance**

- **Affected fathers** transmit the disorder to **ALL** of their daughters **none** of their sons.
- The pattern of inheritance through females is no different from **AD** pattern.
- Each child of an affected female has a 50% chance of inheriting the trait, regardless of sex.
- Rare **X**-linked dominant phenotypes are about twice as common in females, though the expression is much milder in females who are almost always heterozygous.
X - Linked Dominant Inheritance

1. Usually half the children of an affected female will be affected, regardless of sex.
2. All the daughters of an affected male will be affected but none of the sons.
3. Affected females typically have milder expression of the phenotype.

Pedigree 5. X-linked dominant inheritance.
X-linked dominant

- Hereditary pattern in which a dominant gene on the X chromosome causes a characteristic to be manifested in the offspring.

- X-linked dominant diseases are those that are expressed in females when only a single copy of the mutated gene is present.

- Very few X-linked dominant diseases have been identified (e.g. hypophosphatemic rickets, Alport syndrome, diabetes insipidus)
  - hypophosphatemic rickets or vitamin D resistant rickets >>>low serum phosphorus, skeletal abnormalities
  - Alport syndrome, which involves progressive hearing loss and progressive kidney problems.
Characteristics of X-linked dominant diseases include:

- Never passed from father to son.

- Affected males produce only affected females. An affected male only has one X chromosome to pass on to his daughters.

- Affected females produce 50% normal and 50% affected offspring. >>>> heterozygous

- Males are usually more severely affected than females. Some X-linked dominant traits may even be lethal to males.

- Females are more likely to be affected. Since females have 2 X chromosomes, they have 2 “chances” to inherit the mutated allele.
Characteristics of X-Linked Dominant Inheritance

- **Affected fathers** with normal mates have **no affected sons** and **no normal daughters**

- For rare phenotypes, affected females are about **twice as common as affected males** (unless disease is lethal in males), but affected females typically have milder (though variable) expression.

- Both male and female offspring of a heterozygous female have a **50% risk of inheriting the phenotype**. The pedigree pattern is similar to AD inheritance.
X-Linked Dominant Example

- **Vitamin D resistant rickets** which can lead to bone deformities, particularly in the lower limbs (bowed legs).

Pedigree 5. X-linked dominant inheritance.
The pattern for the pedigree of X-linked dominant inheritance
X-linked Dominant Disorders with Male Lethality

- Some rare genetic defects expressed exclusively or almost exclusively in females appear to be XD lethal in males before birth or early infancy.
- Typical pedigrees: transmission by affected female → affected daughters, normal daughters, normal sons in equal proportions.
- Rett syndrome meets criteria for an XD that is usually lethal in hemizygous males.
- The syndrome is characterized by normal prenatal and neonatal growth and development, followed by rapid onset of neurological symptoms and loss of milestones between 6 and 18 months of age.
Rett syndrome cont.

- Children become spastic and ataxic, develop autistic features and irritable behavior with outbursts of crying, and demonstrate characteristic purposeless wringing or flapping movements of hands and arms.
- Head growth slows and microcephaly develops. Seizures are common (~50%).
- Mental deterioration stops after a few years and the patients can then survive for many decades with a stable but severe neurological disability.

Typical appearance and hand posture of girls with Rett syndrome.
Rett syndrome cont.

- Males who survive with the syndrome usually have two X chromosomes (as in 47,XXY or in a 46,X,der(X) male with the male determining SRY gene translocated to an X) or are mosaic for a mutation that is absent in most of their cells.

- There are a few apparently unaffected women who have given birth to more than one child with Rett syndrome. An X-inactivation pattern in a heterozygous female. Germline mosaic
Pedigree pattern demonstrating an X-linked dominant disorder, lethal in males during the prenatal period.
New Mutation in X-linked Disorders

- For a sex-linked recessive disorder with zero fitness, such as Duchenne muscular dystrophy, 1/3 of disease alleles are in males and are lost with each generation. Thus, 1/3 of disease alleles must be replaced with a new mutation in each generation.
- DMD is said to be genetic lethal because affected males usually fail to reproduce.
- For hemophilia, in which reproduction is reduced but not eliminated, a proportionately smaller fraction of cases will be due to new mutation.

- New mutation constitute a significant fraction of isolated cases of many X linked diseases.
Y-Linked Traits

• Only males have Y chromosomes
• Passed from father to sons
• All Y-linked traits are expressed
• Approximately three dozen Y-linked traits have been discovered
Pedigree for Y-Linked Trait
Y-Linked Traits

- No affected **females**
- **ALL sons** of affected males are also affected
Y-linked Inheritance

- **Y-linked (holandric) genes:** < than 50 and NOT essential. They are transmitted from father to son and appear only in males.

- **ZFY:** The terminal portion of the short arm of the human Y (Yp) chromosome encodes a zinc-finger DNA binding protein (ZFy) with the potential for regulating the expression of other genes. A highly homologous gene, ZFX, is encoded on Xp.

- **H-YA:** Male specific Histocompatibility Antigen

- **AZF2:** Azoospermia factor

- **TSPY:** Testis-specific protein

- **SRY:** Sex-determining Region Y gene. Testis determining factor

- **X-linked several genes:** many, not involved in sex determination