# EXERCISE ANSWERS
# Session 1: Introduction to genetic variation and personalised medicine

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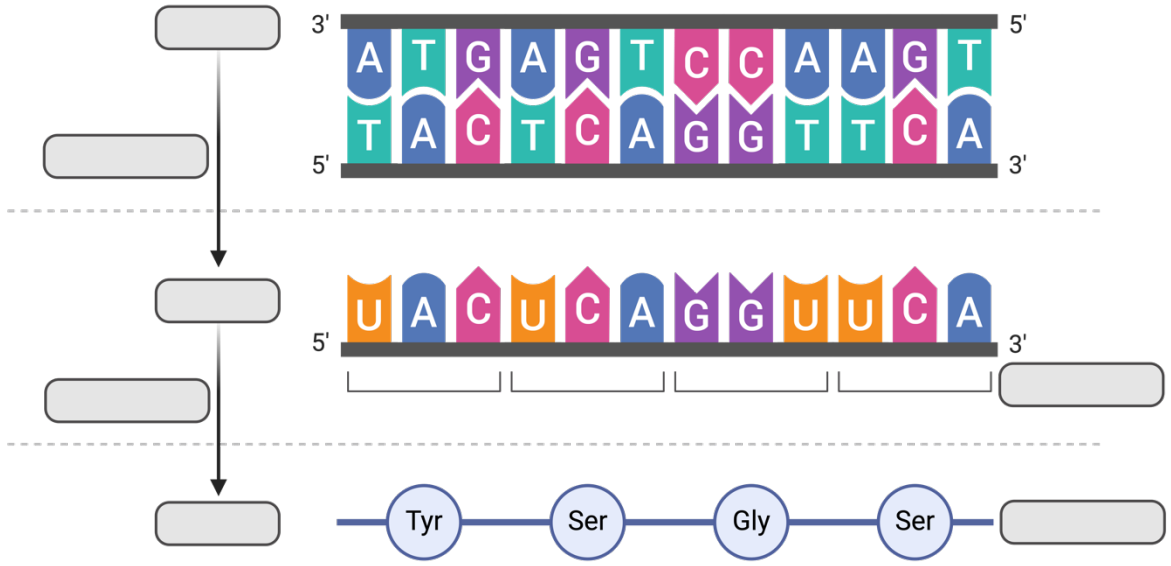
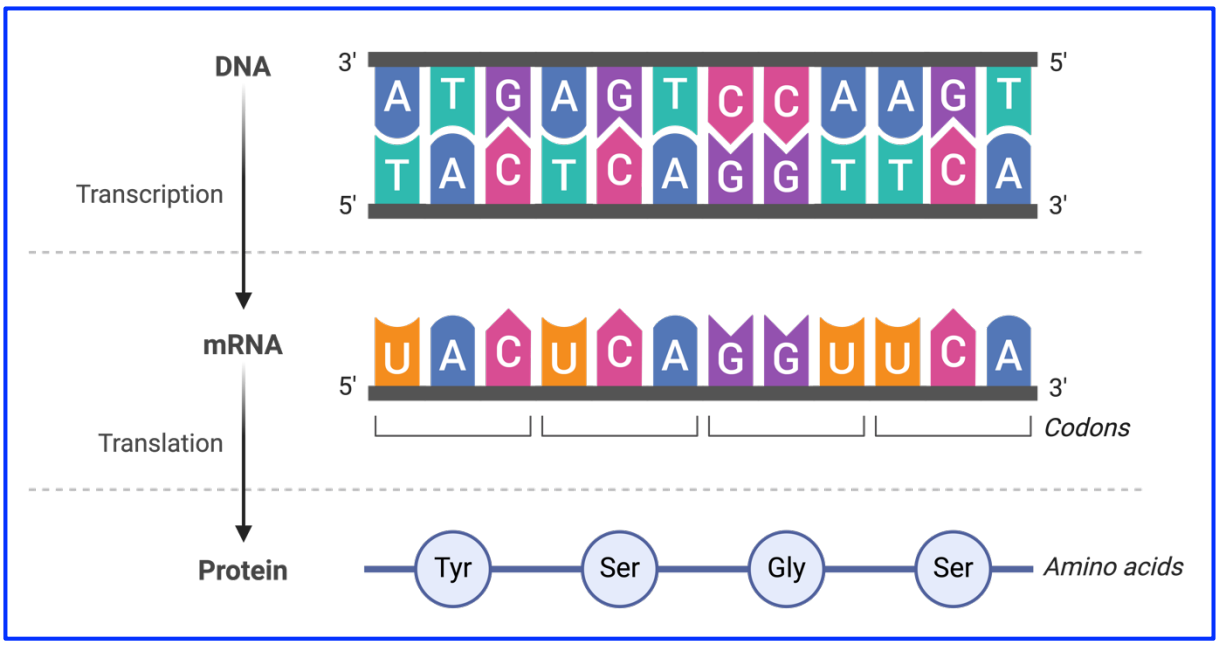
## Exercise 1 (central dogma)

Using the figure below, explain the central dogma of molecular biology and complete the empty boxes.

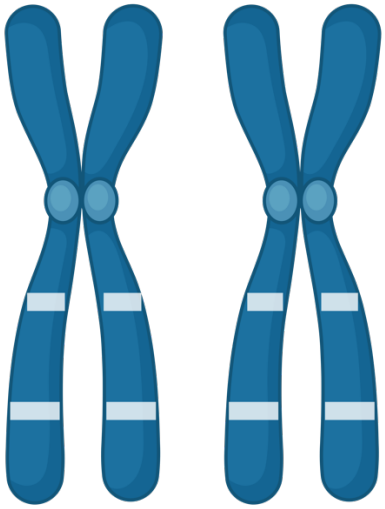



Answer



## Exercise 2 (genetic terminology)

Below you see two homologous chromosomes (in the metaphase).

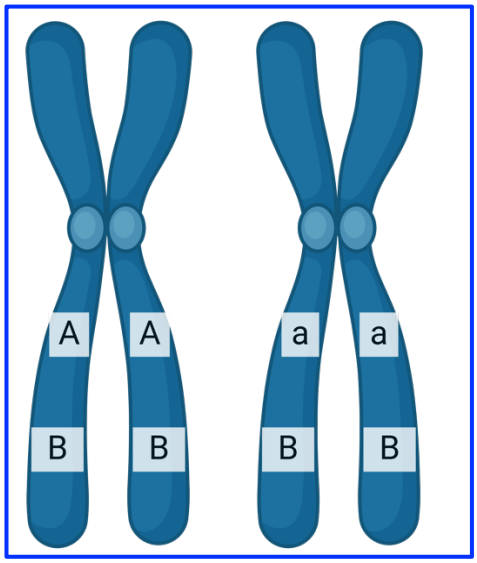


*i.* What is the definition of a locus?
The specific location of e.g. a gene on a chromosome

*ii.* How many loci are depicted in the figure?
Two

*iii.* What are the genotypes at each locus when the possible alleles in the gene pool are {A, a, B}?
A,a and B,B

*iv.* What is a haplotype, and what haplotypes can be identified from the figure?
A-B; a-B



## Exercise 3 (Mendelian genetics)

In mice, coat color is controlled by the A locus, where the dominant allele A results in a brown coat, while the recessive allele a leads to a white coat when inherited in a homozygous state (aa). Tail length is determined by the B locus, with the dominant allele B producing normal tail length, whereas individuals with the homozygous recessive genotype (bb) have short tails.

What are the expected genotype and phenotype frequencies in the offspring of a cross between two mice that are heterozygous for both traits?

| | **AB** | **Ab** | **aB** | **ab** |
|---|---|---|---|---|
| **AB** | *AABB* | *AABb* | *AaBB* | *AaBb* |
| **Ab** | *AABb* | *AAbb* | *AaBb* | *Aabb* |
| **aB** | *AaBB* | *AaBb* | *aaBB* | *aaBb* |
| **ab** | *AaBb* | *Aabb* | *aaBb* | *aabb* |

**Expected genotype frequencies:**

AABB: 1/16
AABb: 2/16
AAbb: 1/16
AaBB: 2/16
AaBb: 4/16
Aabb: 2/16
aaBB: 1/16
aaBb: 2/16
aabb: 1/16

**Expected phenotype frequencies:**

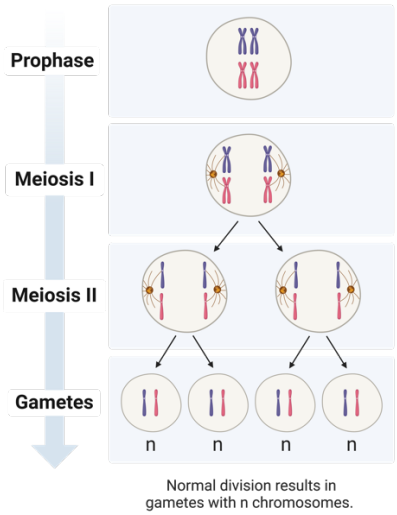
Brown, Long tails (A-B-): 9/16
Brown, short tails (A-bb): 3/16
White, long tails (aaB-): 3/16
White, short tails (aabb): 1/16

## Exercise 4 (non-disjunction during meiosis)

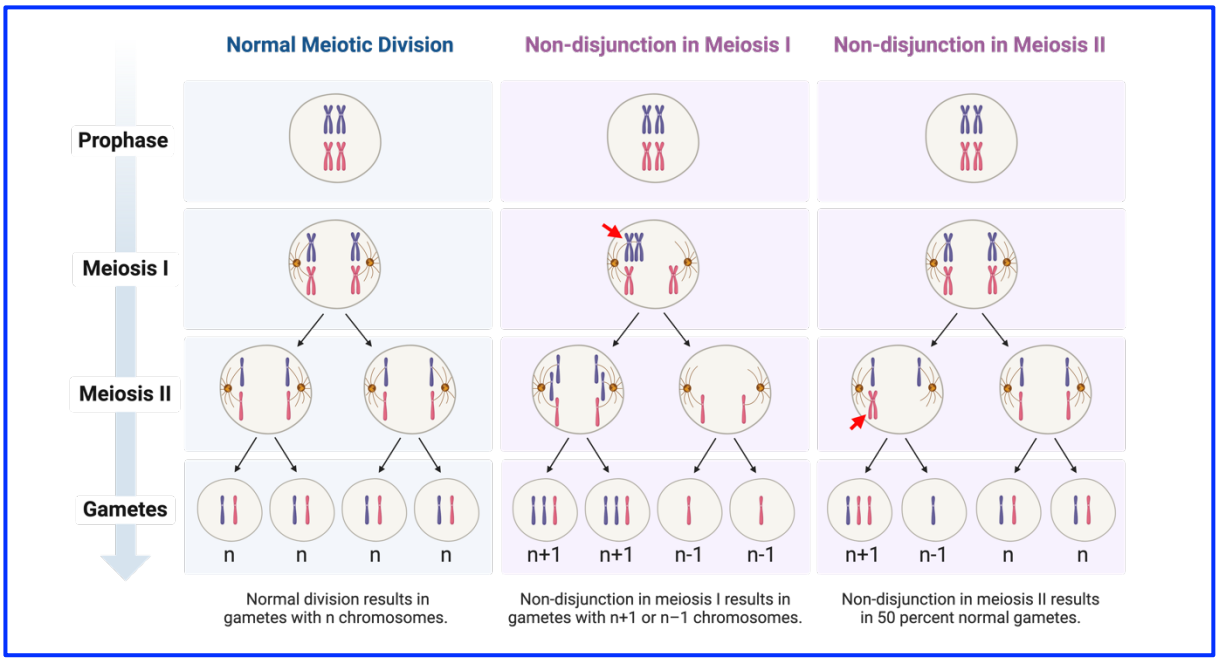
The diagram below illustrates the normal segregation of chromosomes during meiosis.

Using a similar approach, draw representations of:

1. Nondisjunction occurring in Meiosis I.
2. Nondisjunction occurring in Meiosis II




Answer:



## Exercise 5 (non-disjunction)

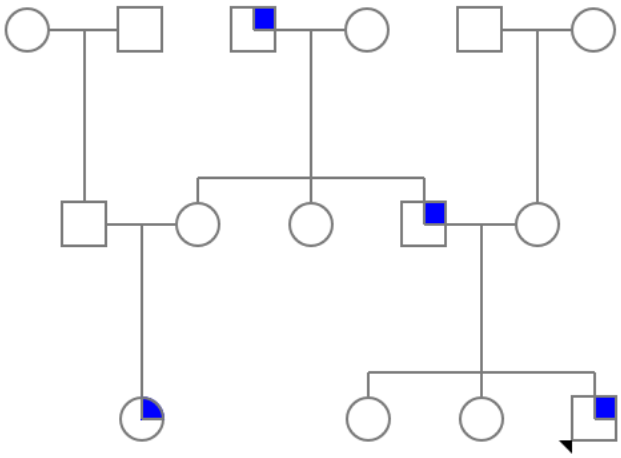
Which of the following scenarios could lead to the formation of a zygote with the karyotype 47, XYY? Support your answer with an appropriate sketch.

A. Nondisjunction in paternal meiosis I
B. Nondisjunction in paternal meiosis II
C. Nondisjunction in maternal meiosis I
D. Nondisjunction in maternal meiosis II
E. Nondisjunction in *both* paternal meiosis I *and* maternal meiosis I
F. Nondisjunction in *either* paternal meiosis II *or* maternal meiosis II
G. Error in the first cell divisions after the formation of the zygote

**B** - Nondisjunction in paternal meiosis II

## Exercise 6 (monogenic inheritance pattern)

The pedigree below illustrates a family affected by acute intermittent porphyria (AIP), a rare metabolic disorder that is characterized by deficiency of the enzyme hydroxymethylbilane synthase (HMBS), also known as porphobilinogen deaminase (PBGD), that results in the accumulation of porphyrins in the body. This buildup occurs due to a deficiency in enzymes involved in the production of heme, the oxygen-carrying molecule in red blood cells. AIP is characterized by episodes of severe abdominal pain, neurological symptoms, and other complications, which can be triggered by factors such as certain medications, stress, or fasting



*i.* Add remaining (correct) nomenclature to the pedigree.
*ii.* What mode of inheritance best fits the disease pattern seen in this family? Justify your answer.

A. Autosomal dominant with full penetrance.
B. Autosomal dominant with incomplete penetrance.
C. Autosomal recessive with full penetrance.
D. Autosomal recessive with incomplete penetrance.
E. X-linked dominant.
F. X-linked recessive.

*i.* Use Roman numerals for generations and normal numbers for individual-ID
*ii.* **B** - Autosomal dominant with incomplete penetrance

## Exercise 7 (pedigree)

A 25-year-old healthy woman seeks genetic counseling regarding a hereditary skin condition, ichthyosis, which causes dry, thickened fish-scale skin. She provides the following family history:

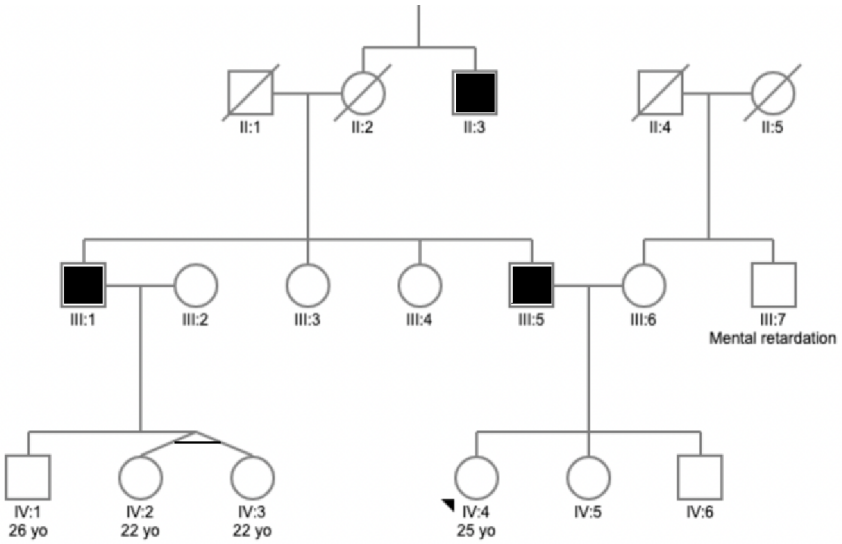
- She has a healthy younger brother and sister.
- Her father has the condition.
- Her father has an older brother who also has the disease, along with two healthy older sisters.
- Her father's brother has three healthy children: a 26-year-old son and two monozygotic 22-year-old daughters.
- Her mother has a younger brother who has mental retardation but does not have the skin condition.
- Both of her parents' families are deceased and were not affected by the disease.
- Her paternal grandmother has a brother who also has the disease.

Based on the family history:

- Draw the pedigree for the family.
- What mode of inheritance does this disease have, and why?
- The woman stars a relationship with her father's brother's son. If they decide to have a child, what is the risk that their child would inherit ichthyosis?

Answers:

*i.* Pedigree:




*ii.* X-linked recessive (most likely – could also be X-linked dominant with incomplete penetrance). Only boys have the disease, and it is passed on by healthy female carriers.

*iii.* 25% because the woman is an obligate carrier. 50% risk of disease if the child is a boy, and 50% risk of being a carrier if the child is a girl.

| | **X** | **Y** |
|---|---|---|
| **X** | XX<br>(Healthy girl) | XY<br>(Healthy boy) |
| **X** | XX<br>(Healthy carrier girl) | XY<br>(Boy with disease) |

## Exercise 8 (advanced genetic terminology)

Below is a list of genetic terms.

A. Allele heterogeneity - different mutations at the same locus led to the same phenotypes.
B. Locus heterogeneity - mutations at multiple genomic loci can produce the same phenotype
C. Incomplete penetrance - penetrance refers to the likelihood that a clinical condition will occur when a particular genotype is present. A condition is said to show incomplete penetrance when some individuals who carry the pathogenic variant express the associated trait while others do not. Also called reduced penetrance.
D. Variable expressivity - variation in the way a trait is manifested. When there is variable expressivity, the trait may vary in clinical expression from mild to severe. For example, the condition neurofibromatosis type 1 may be mild, presenting with café-au-lait spots only, or may be severe, presenting with neurofibromas and brain tumors.
E. Co-dominance - both alleles are simultaneously expressed in the heterozygote, thus, the heterozygote can be distinguished from both homozygotes. For example, a person's MN blood type is determined by the alleles of a certain gene. An $L^M$ allele specifies production of an M marker displayed on the surface of the red blood cell, while a $L^N$ allele specifies the production of a slightly different N marker. Homozygotes ($L^M$ $L^M$ *or* $L^N$ $L^N$) have only M or an N markers, respectively, on the surface of their red blood cells. However, heterozygotes ($L^M$ $L^N$) have both types of markers in equal numbers on the cell surface.
F. Compound heterozygote - an individual who carries two different pathogenic variants in the same gene, one on each allele. Together, these variants can cause a recessive genetic disorder, even though the mutations are not identical
G. Balanced translocation - a chromosomal rearrangement in which segments from two different chromosomes are exchanged without any net gain or loss of genetic material. Individuals are usually phenotypically normal but may have an increased risk of infertility or affected offspring.

## Exercise 9 (effect of variants)

Discuss for each of the mutations in the left column of the table their effect on mRNA and protein level and fill out the table (yes/no/probably/probably not).

| | Effect on mRNA | | | Effect on protein | | |
|---|---|---|---|---|---|---|
| | Sequence | Length | Amount | Sequence | Length | Amount |
| Missense mutation | Yes | No | No | Yes | No | Probably not |
| Nonsense mutation | Yes | No | Probably (NMD) | Yes | Yes | Probably |
| 3bp deletion in exon | Yes | Yes | No | Yes | Yes | Probably not |
| 2bp deletion in exon | Yes | Yes | Probably (NMD) | Yes | Yes | Probably |
| Splice-site mutation | Yes | Yes | Probably (NMD) | Yes | Yes | Probably |
| Silent mutation | Yes | No | No | No | No | No |
| Intronic mutation | No | No | Probably not | No | No | Probably not |

**NMD** (Nonsense-mediated mRNA decay): Its main function is to reduce errors in gene expression by eliminating mRNA transcripts that contain premature stop codons.