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CELS191 LECTURE MATERIAL

Department of Biochemistry

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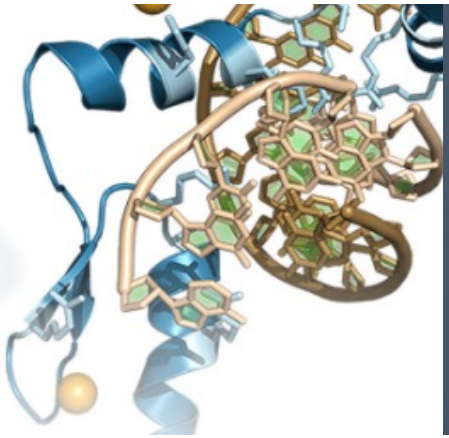

Genetics

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Evolution, Development & Genome Evolution

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CELS191 2025

Human Molecular Genetics

Lecture 24

The Human Genome & Disease

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Lecture 24 Objectives

After you have revised this lecture you should be able to:

- Apply pedigree analysis to explain different ways in which mutations can be inherited.
- Explain how disease-causing genes are found with next generation sequencing.
- Outline examples of monogenic and polygenic diseases.
- Describe determinism in genetics and gene environment interactions.

This Lecture

- What kinds of mutations cause genetic disease?
- Pedigree analysis
- Examples of monogenic diseases
  - Haemophilia
  - Huntington disease
  - Cystic fibrosis
- Finding genes linked to disease
- Polygenic or complex disorders
- Finding genes associated with polygenic disease

Mutations

- Mutations can be inherited or acquired.
- Mutations are permanent changes to the DNA sequence.

Mutations that are inherited are called germline mutations and are passed on via the gametes (eggs and sperm).

Mutations can also be acquired by somatic cells if DNA gets damaged or is copied incorrectly. Somatic mutations are not passed to the next generation.

What do mutations do?

- Genetic variations/mutations are a driving force for evolution.
- Mutations can have a beneficial effect, no effect, or a deleterious *(damaging or harmful)* effect on the organism.
- The vast majority of mutations have no effect at all.
- The outcome of a mutation can also depend on:
  - Environmental effects *(e.g. diet, exposure to toxins)*
  - Other genes *('genetic background')*

Classifying Mutations

- Mutations can be classed in lots of different ways because they are complex and biological: hence messy.
- The molecular basis of a mutation often is not consistent.
- Mutations in a single gene can have different effects. That's why we talk about alleles.
- Here we are going to concentrate on two ways of thinking about mutations:
  - Dominant vs Recessive
  - Loss of function vs Gain of function

Dominant vs Recessive Alleles

- Humans, like many eukaryotes, are diploid
- That means they have two copies of each of their genes (one maternal, one paternal)
- A mutation (allele) can thus be either:
  - heterozygous (one mutant, one wildtype allele) OR
  - homozygous (both alleles mutant)
- A dominant mutation is one that causes a phenotype when heterozygous
- A recessive mutation is one that causes a phenotype only when homozygous

Loss of function vs Gain of function

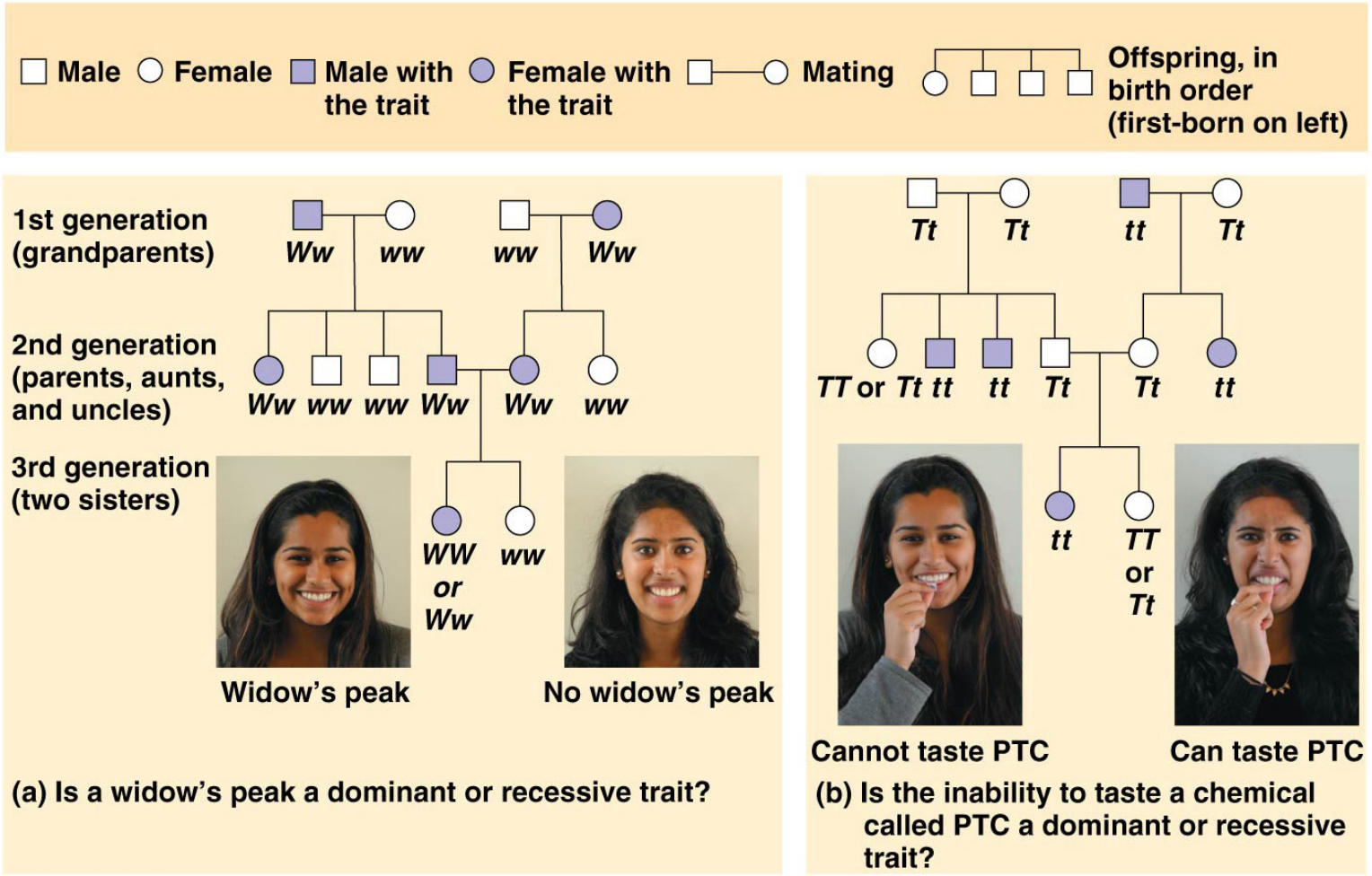
- For a mutation (allele) to have a phenotype, it must affect the function of a gene.
- A mutation might break a gene to cause it to not work as well as normal, or not work at all.
- This is called a '**Loss of function**' mutation
  - Loss of function mutations are often recessive, because a normal copy of the gene exists on the other chromosome which can replace the lost function.
- Sometimes a mutation can cause a gene to work too well, or to do something unexpected.
- This is called a '**Gain of function**' mutation
  - Gain of function mutations are often dominant, because having an allele that works too well or does something novel, will not be replaced by the normal copy of the gene.

Core Slide

Textbook Figure 14.15

By examining the inheritance pattern of an allele we can determine if it is dominant or recessive.

Also if it is X-linked, Y-linked or autosomal



Monogenic Diseases: Haemophilia A & B

- Haemophilias are disorders of blood clotting.
- Haemophilia A (classic haemophilia)is the most common affecting 1/5000 males worldwide. Results from impaired or absent clotting factor VIII.
- Haemophilia B clinically indistinguishable, affects factor XI.
- Untreated, high risk of death from uncontrolled bleeding.
- Pain and tissue damage from internal bleeding.
- Treated by intravenous infusion of missing protein.

Inheritance of Haemophilia

- Haemophilia A caused by mutations (most commonly an inversion) in Factor VIII gene found on the X-chromosome.
- Mutations are "loss of function".
- One intact copy protects against disease.
- Women have 2 X-chromosomes and are rarely affected.
- Both Haemophilia A and B are X-linked recessive disorders.
- Sons of women who are carriers have a 0.5 probability of inheriting the disease.
- Around 30% of cases have no family history (sporadic).

Queen Victoria carried Haemophilia *(probably B)*

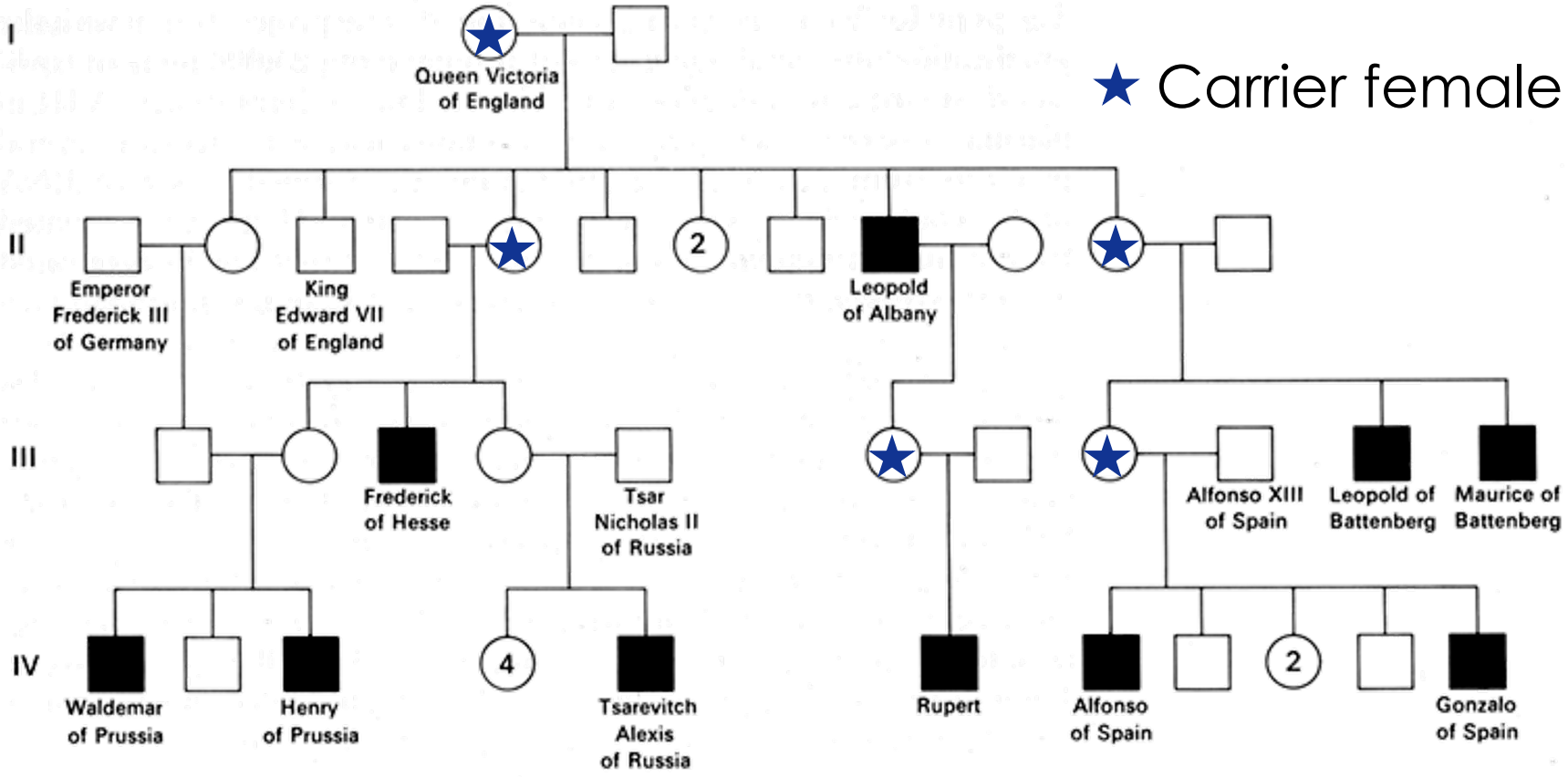
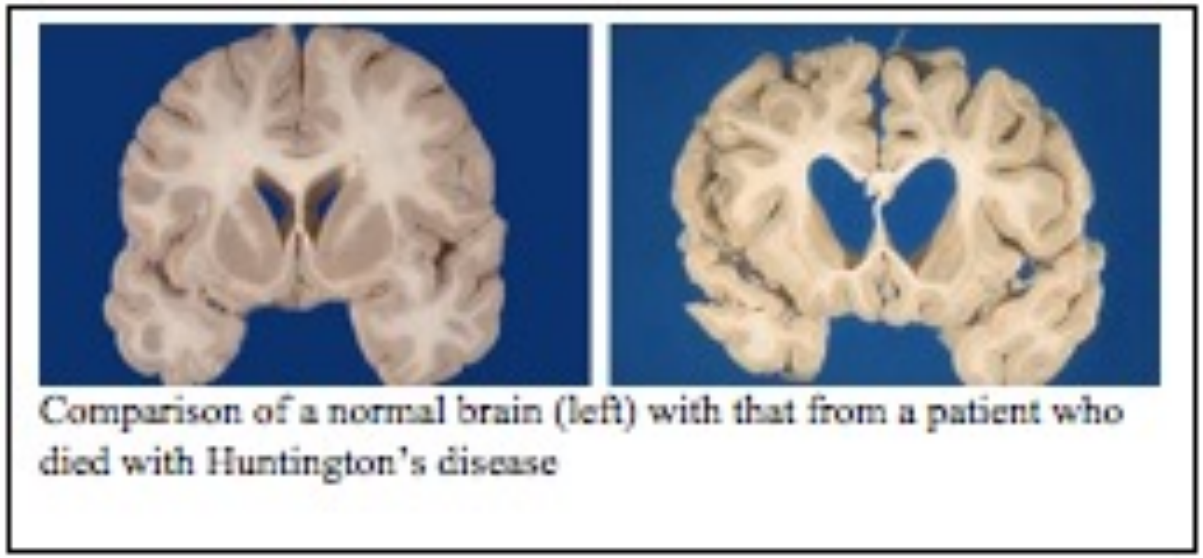


Image: http://www.brc.cam.ac.uk

Huntington Disease

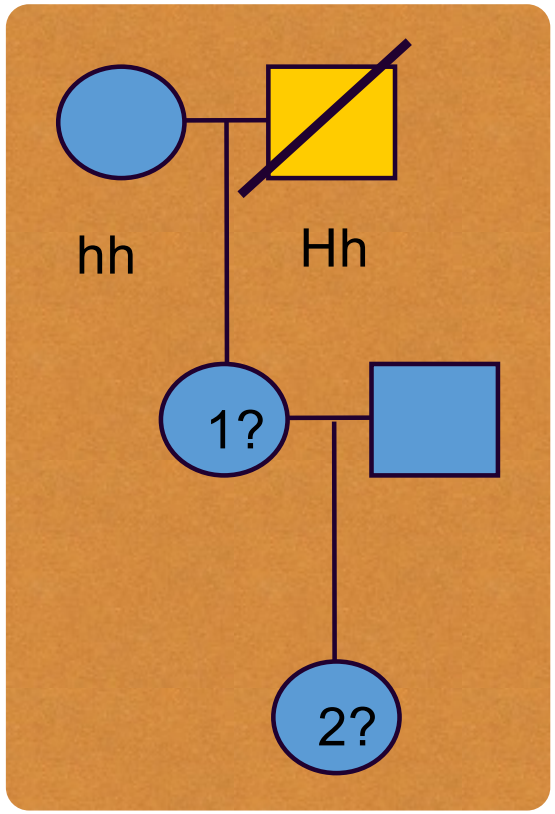
- Progressive tremor, involuntary movements, neurodegeneration
- Onset in mid-life *(usually 30-50)*
- No effective treatment



Comparison of a normal brain (left) with that from a patient who died with Huntington's disease

Inheritance of Huntington Disease

- Autosomal dominant inheritance
- Probability that individual 1 will contract HD is **0.5**
- Probability that 2 will contract HD is **0.5 x 0.5 = 0.25**



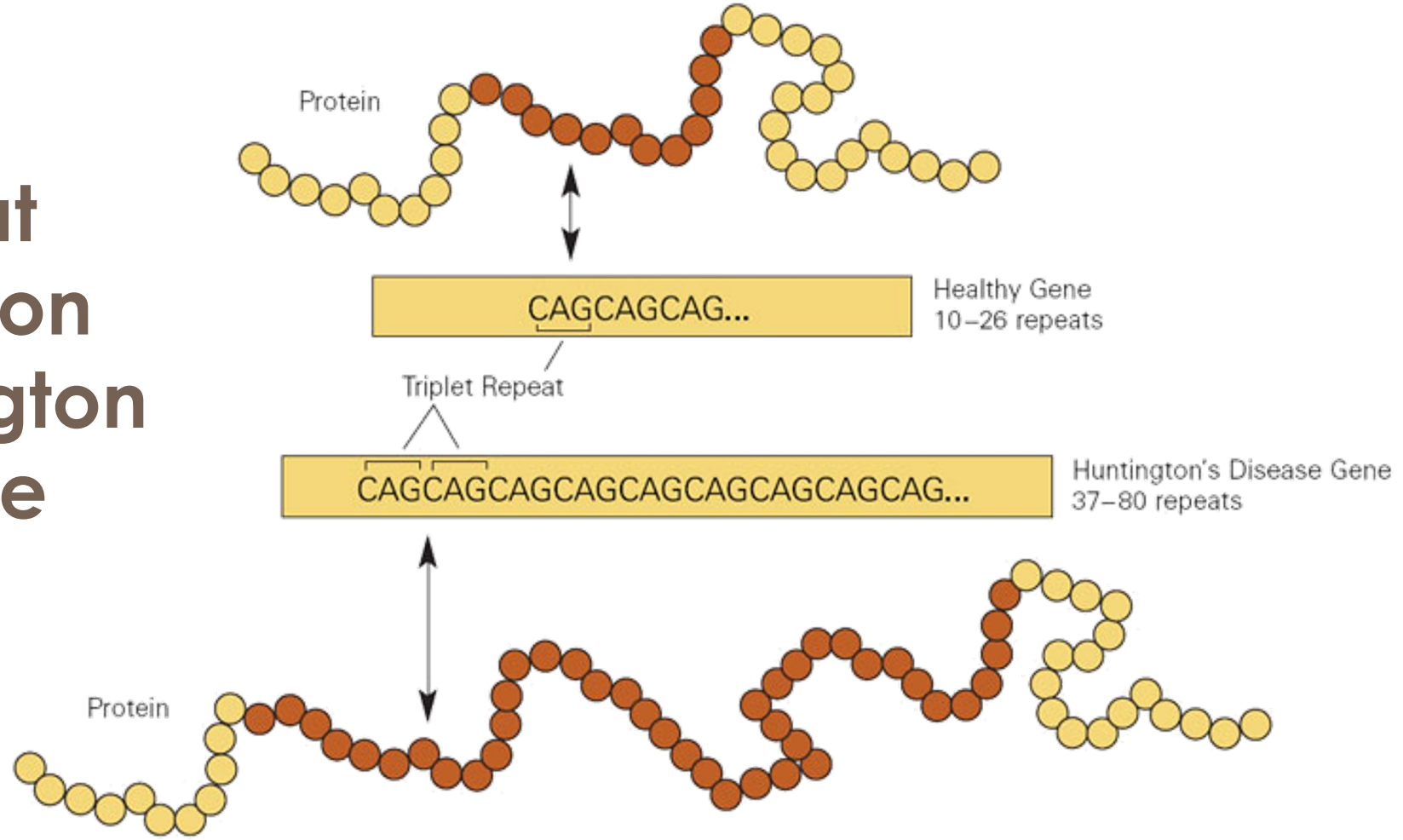
The Genetic Cause of Huntington Disease

- Mapped to chromosome 4 (autosomal).
- Gene codes for a previously unknown protein called huntingtin (HTT gene).
- HD is caused by expansion of a CAG triplet repeat in the HTT gene.
- CAG codes for glutamine; protein has long polyglutamine tract.
- The protein becomes unstable and fragments, clumping together in nerve cells and damaging them.

Context Slide

Image: Gene from Huntington's disease patient.
https://www.nist.gov/image-17588

Repeat Expansion in Huntington Disease



See Lab 4

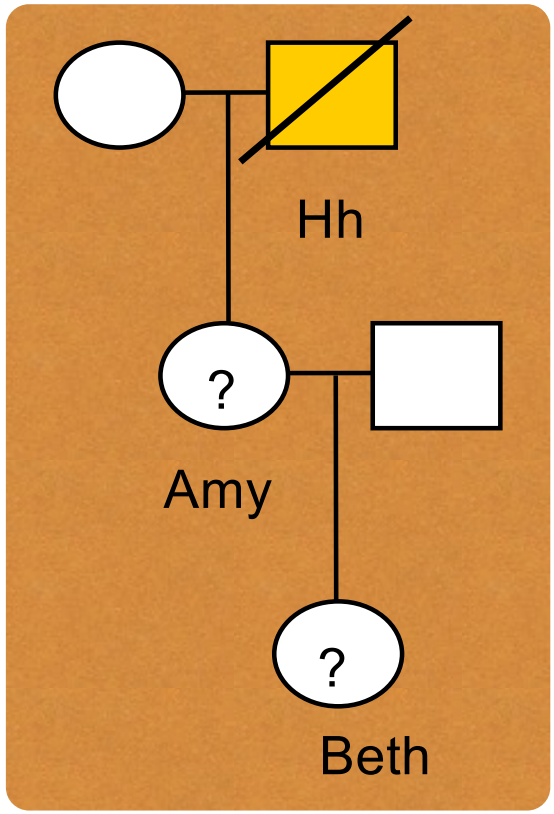
Genetic Testing for Huntington Disease

- Use PCR to determine length of CAG repeat

- Can determine who will develop the disease before the age at which symptoms develop
- 10-26 copies – normal
- 27-35 copies – risk of descendants developing HD
- 36-40 copies – risk of developing disease
- 40+ copies – disease develops

Genetic Testing for Huntington Disease

- NOT EVERYONE WANTS TO KNOW
- Autosomal dominant inheritance
- Only affected people can pass on the allele
- Beth's test result will tell Amy whether she carries the allele



Cystic Fibrosis

"Woe to that child which when kissed on the forehead tastes salty. He is bewitched and soon must die". *[German Folklore]*

- 1606, Alonso y de los Ruyzes de Fonteca, Professor of medicine in Spain, **"fingers taste salty after rubbing the forehead of the bewitched child."**

- Refers to the observation that the Cystic Fibrosis mutation increases the saltiness of sweat - a method still used to screen for the disease.

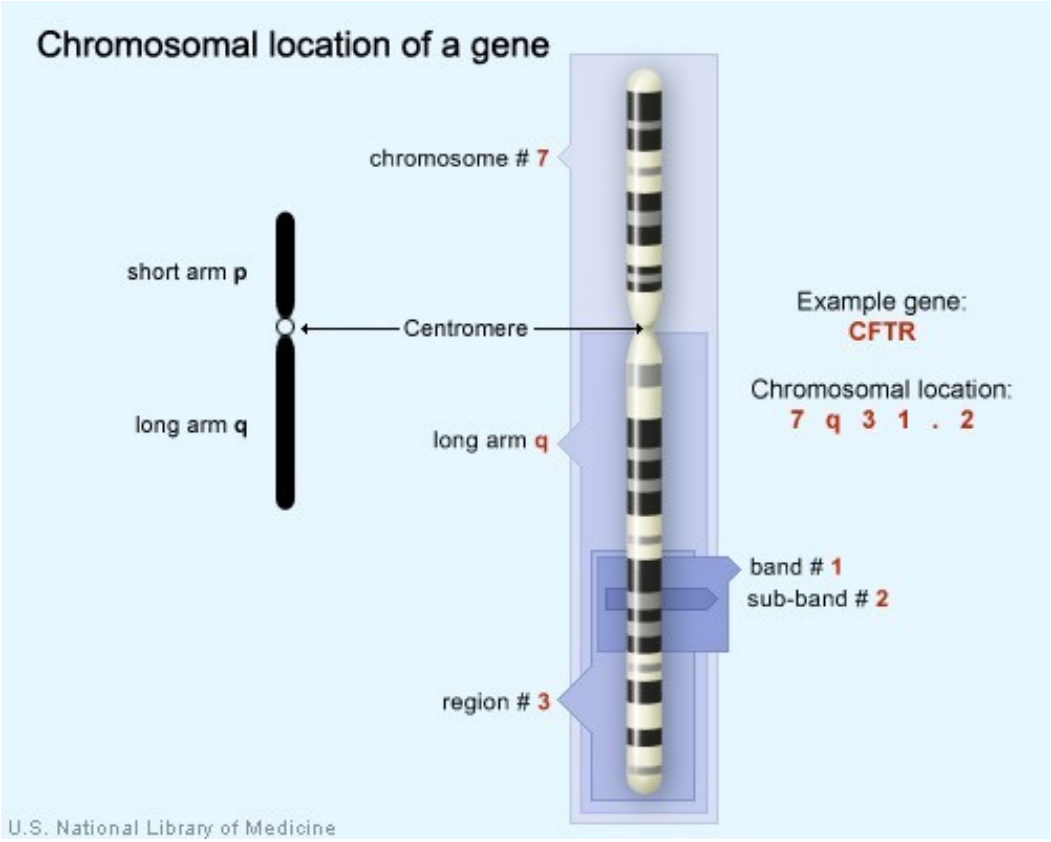
Cystic Fibrosis: Symptoms

- Strange combination of symptoms including;
  - Lung infections, pancreatic insufficiency, congenital absence of vas deferens in males, salty tasting skin
- Range from mild to severe
- Severe form
  - Frequent infections and hospitalisation
  - Reduced life expectancy
- Inheritance is autosomal recessive

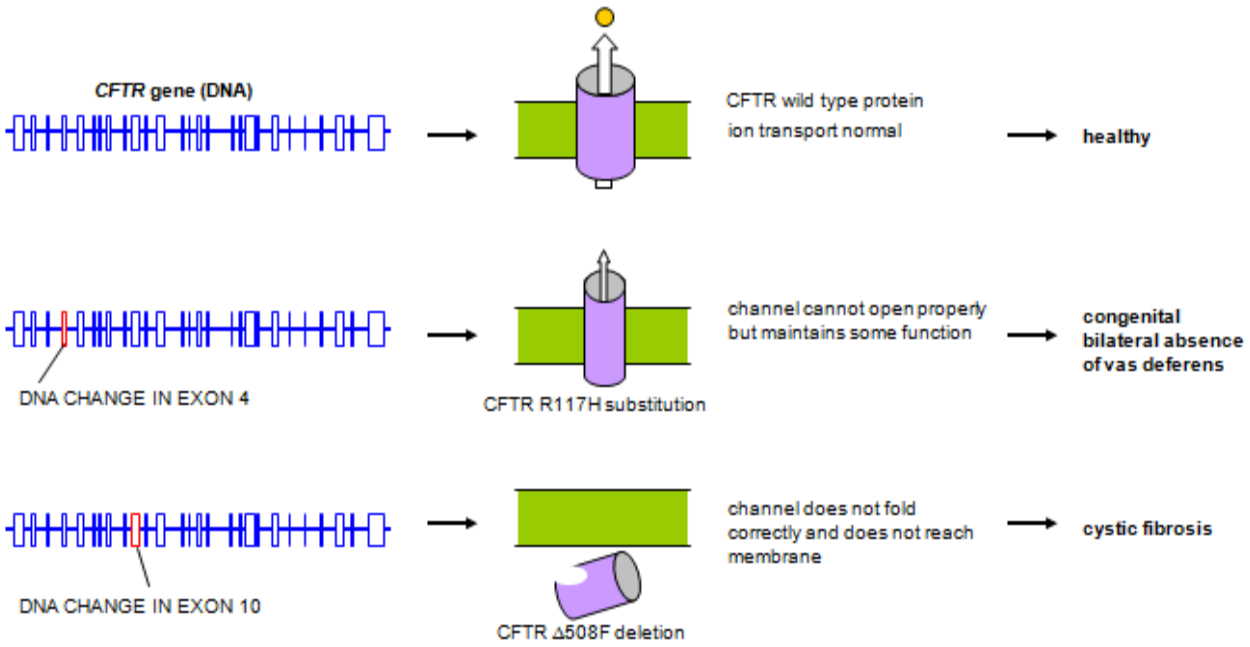
Image: U.S National Library of Medicine

The Cystic Fibrosis Gene

- Gene disrupted in CF was identified in 1979
- Predicted protein was new, function unknown
- Later proved to be chloride ion transporter (CFTR = cystic fibrosis transmembrane regulator)
- Reduced function of CFTR protein causes thickening of cell secretions

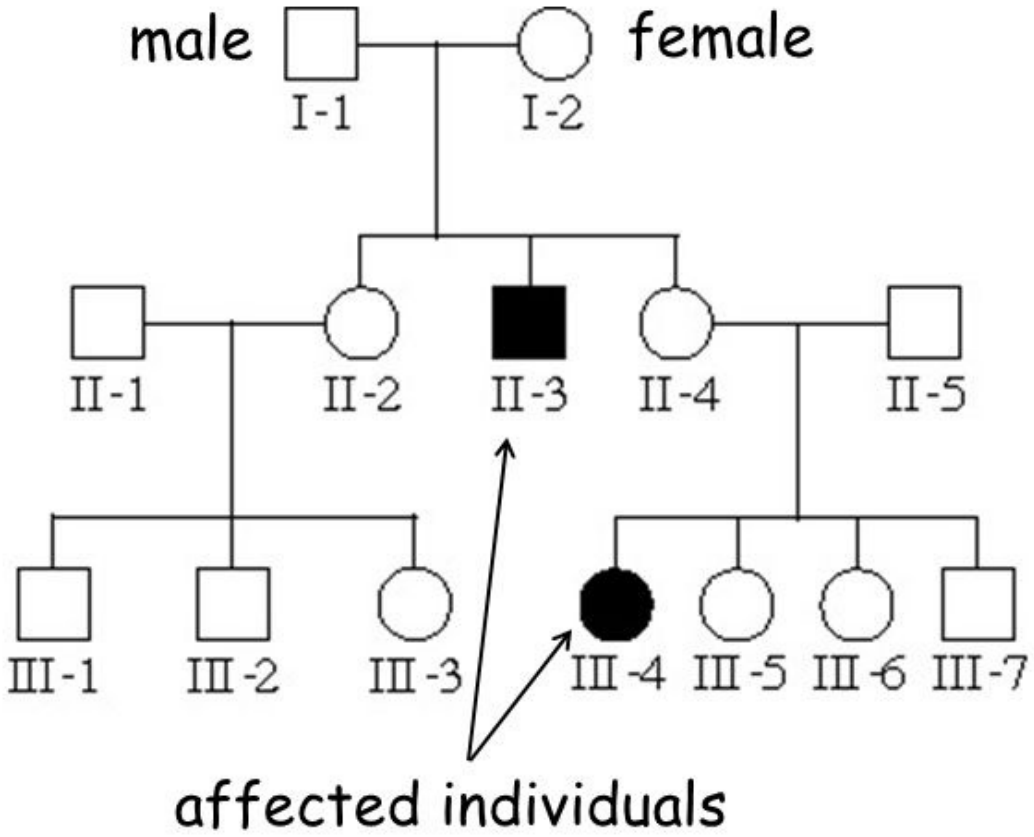


Cystic Fibrosis: Mutations



- Many different mutations in CFTR gene can cause CF
- Most common is a 3bp deletion, deltaF508
  - Protein is abnormally processed and degraded
  - 1 in 25 northern Europeans carry this mutation
  - Why is it so common?
- Speculation - may confer some benefit to heterozygotes
- New treatments available try to rescue the miss-addressed proteins (and work)

Cystic Fibrosis: Sample Pedigree



Core Slide

Image: CELS191 Supplied – P.Dearden 2020

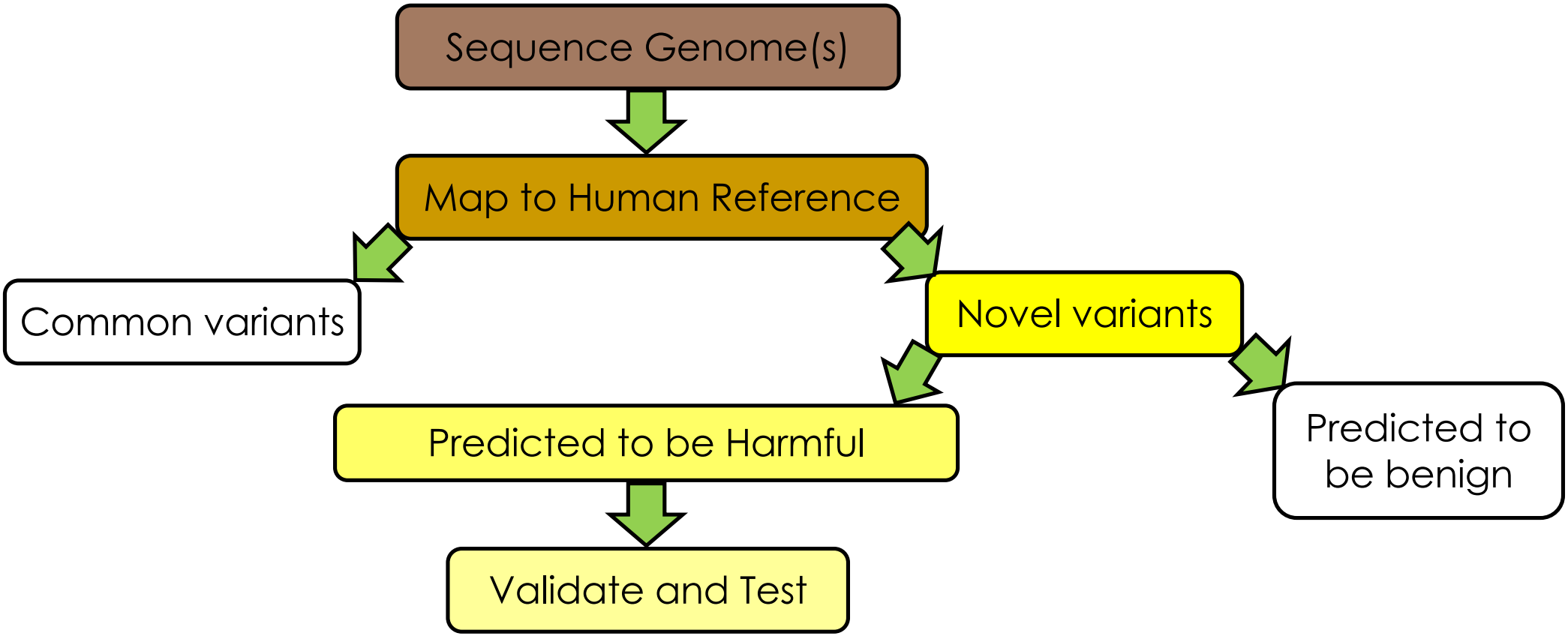
	Autosomal Recessive	Autosomal Dominant	X-linked recessive
Examples	Inability to taste PTC Cystic fibrosis	Widow's peak Huntington's disease	Haemophilia A Haemophilia B
Characteristics	Typically not seen in every generation of an affected family. Passed on by two asymptomatic carriers. Males and females equally likely to inherit	Occurs commonly in a pedigree. Affected individuals have an affected parent. Males and females equally likely to inherit	Fathers cannot pass X-linked traits to their sons. No male-to-male transmission. Most often affects males

How to determine inheritance pattern?

Examine the pedigree and look for individuals that break the above rules
(ie. male to male transmission rules out X- linked.)
Identify carriers who do not have the condition, if there are none, this might mean the condition is dominant
Find the inheritance pattern that explains all the disease occurance in a pedigree.
Think!

Image: CELS191 Supplied

Finding Potential Disease Genes

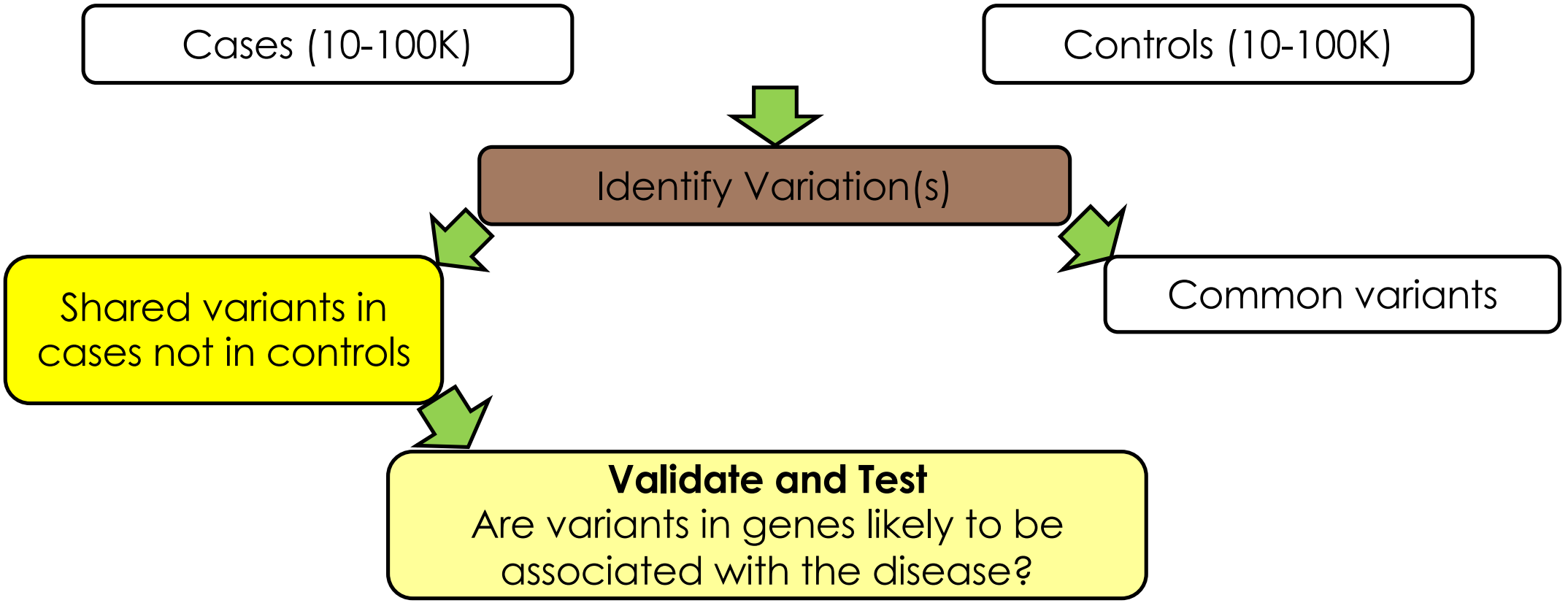


Polygenic Disorders

- Most disorders appear to have a genetic basis but do not follow straightforward inheritance patterns.
- Polygenic disorders involve several genes acting together or environmental factors interacting with genes.
- Examples include:
  - Obesity,
  - Diabetes,
  - Rheumatoid arthritis,
  - Gout,
  - Bipolar disorder.
- Identifying genes associated with polygenic disorders is very hard.

Image: CELS191 Supplied

Finding Polygenic Disease Genes



Genetic Determinism

- For most diseases, having a disease-related variation does not mean you will get the disease.
- Such diseases come about through a combination of variants and the environment.
- Different sufferers may have different disease mechanisms.
- Most genetic disorders are **probabilistic**, not deterministic.
- This is also true of most traits with a genetic component, your genes do not direct your destiny.

Lecture 24 Summary

- Mutations can be classified in many ways, we have presented dominant vs recessive and loss vs gain of function.
- The inheritance of a trait in a pedigree can tell us a lot about the location and sort of mutation.
- Simple diseases are ultimately caused by loss or alteration of the structure of the protein that is coded for by the gene.
- Examples of single gene disorders are:
  - Haemophilia A/B - X-linked recessive
  - Huntington disease - autosomal dominant
  - Cystic fibrosis - autosomal recessive
- Most disorders are influenced by multiple genes and the environment.
- Genetics is probabilistic, not deterministic.

Objective-Based Questions

- How can pedigree analysis be used to differentiate between dominant and recessive traits, as well as determine whether a trait is autosomal or sex-linked?
- What is the difference between loss-of-function and gain-of-function mutations?
- Create a flowchart to explain the process of identifying potential disease genes responsible for monogenic diseases.
- Explain how multiple genes contribute to disease risk in a probabilistic manner rather than guaranteeing disease development (deterministic) and discuss how environmental factors influence disease outcomes.
- Create a flowchart outlining the process of identifying potential disease genes for polygenic diseases, and explain why discovering genes for polygenic traits is more challenging than for monogenic traits.

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