Genetic variation – background and basic concepts

PPU-genetic epidemiology 2022

Maiken Elvestad Gabrielsen, PhD
K.G. Jensen Center for Genetic Epidemiology
Norwegian University of Science and Technology (NTNU)

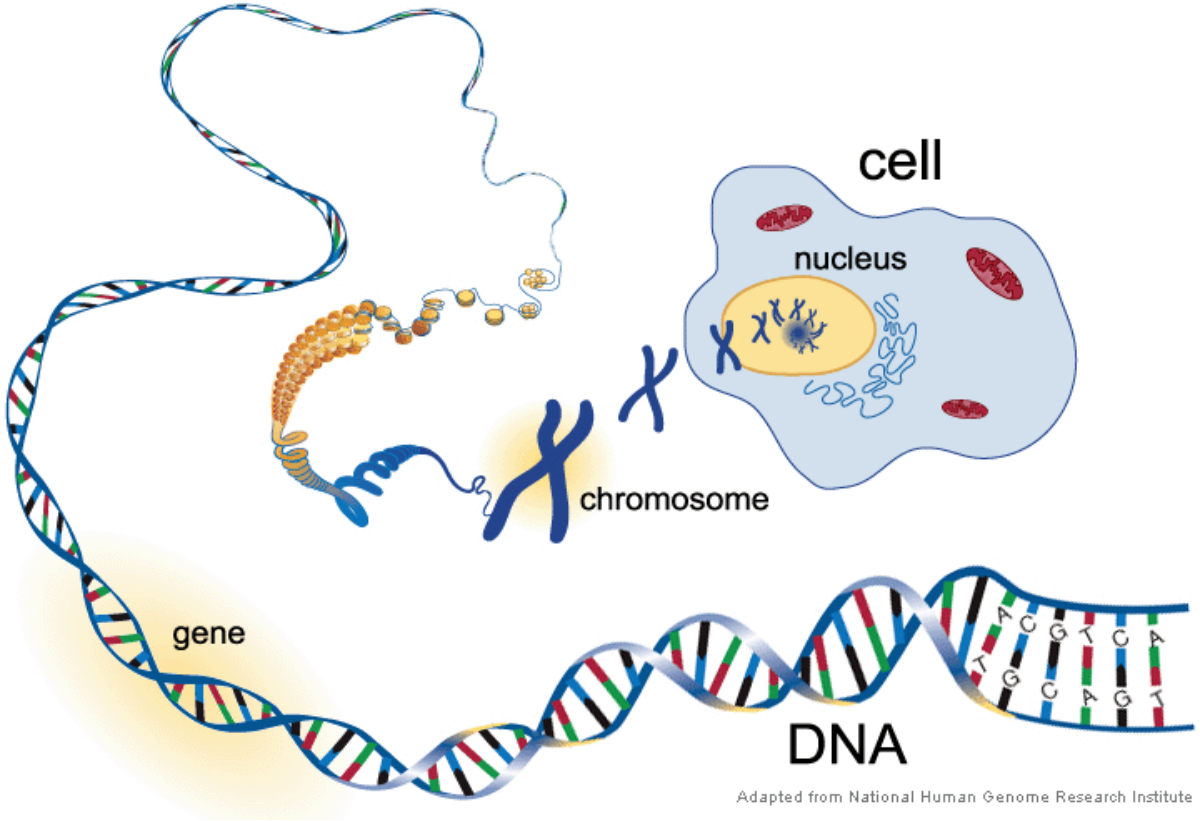
NTNU
K.G. Jebsen Center for Genetic Epidemiology

STIFTELSEN KRISTIAN GERHARD JEBSEN

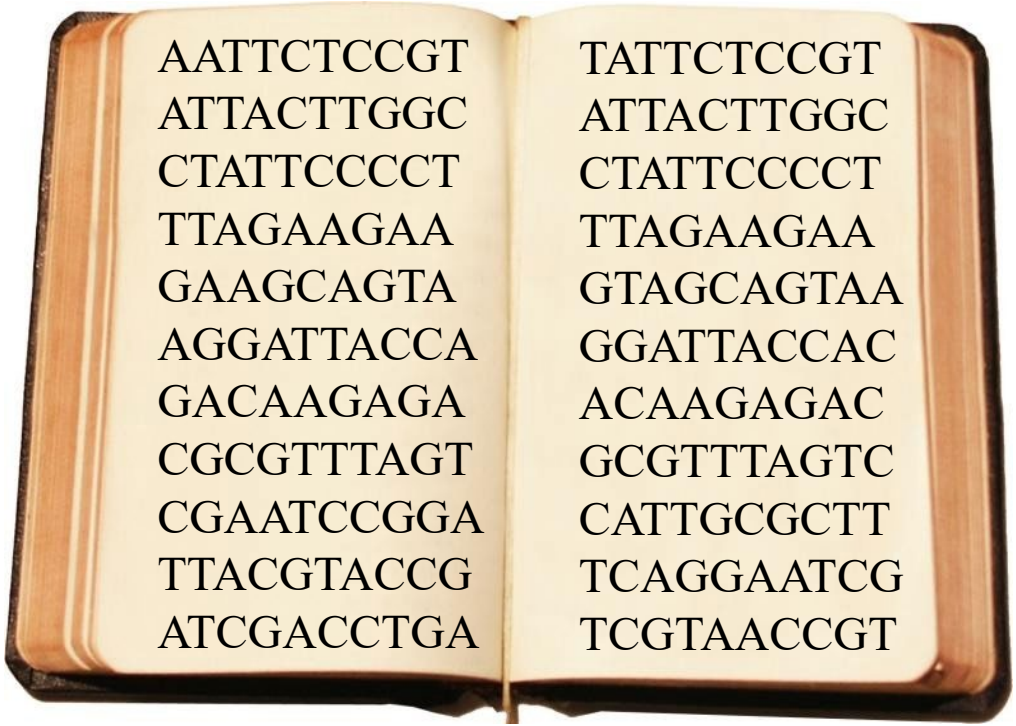
Topics to be addressed

- **Short introduction**
- Mutations and polymorphisms
  - Sources and causes of mutations
  - Different types of mutations and polymorphisms
  - Consequences of different variants

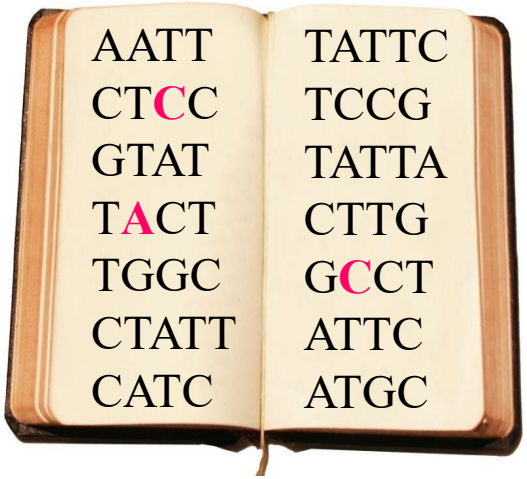
The Basic Concept

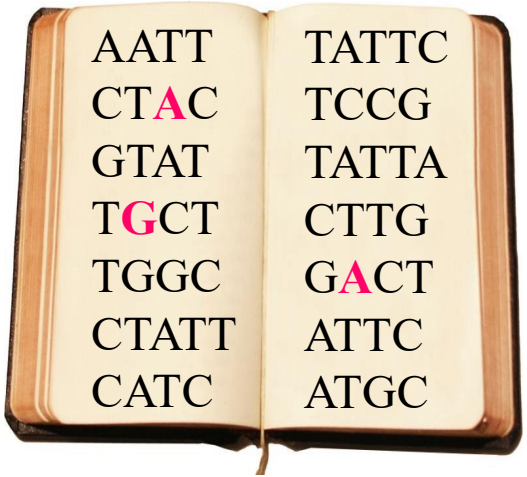


“How to create a human”



NTNU
K.G. Jebsen Center for Genetic Epidemiology
STIFTELSEN KRISTIAN GERHARD JEBSEN





GENETIC VARIATION

Genetic differences between individuals

The sequence of nuclear DNA is nearly 99.9% identical between any two humans

This small fraction of 0.1% difference is responsible for the genetically determined variability among humans

NTNU
K.G. Jebsen Center for Genetic Epidemiology

STIFTELSEN KRISTIAN GERHARD JEBSEN

Created by Cara Foster
from Noun Project

Different appearance of people

Different susceptibility to disease

Created by Adrien Coquet
from Noun Project

Different responses to drugs or other exposures

Created by Kiran Shastry
from Noun Project

Phenotype

The set of observable characteristics or traits of an organism

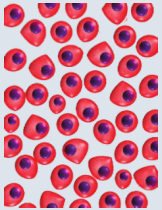
What is the difference between mutation and polymorphism?

Mutation	Polymorphism	Variant
A change in the DNA occurring in a single cell (somatic or germline)	A change in the DNA present in all cells where minor allele frequency is > 1%	All variation (including mutation and polymorphism)

Mutations in somatic cells versus germ cells

Mutation in somatic cells:

- Mutations may cause disease (e.g. cancer) in the individual carrying the mutation, but the mutation is *not* inherited by offspring.

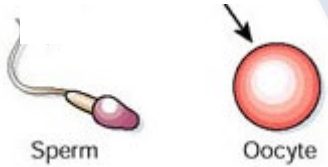


- More than 80% of cancers may be caused by somatic mutations

Mutations in germ cells (sperm cells and oocytes):

- Mutations cause nonsymptomatic genetic polymorphisms or inheritable disease of many types.

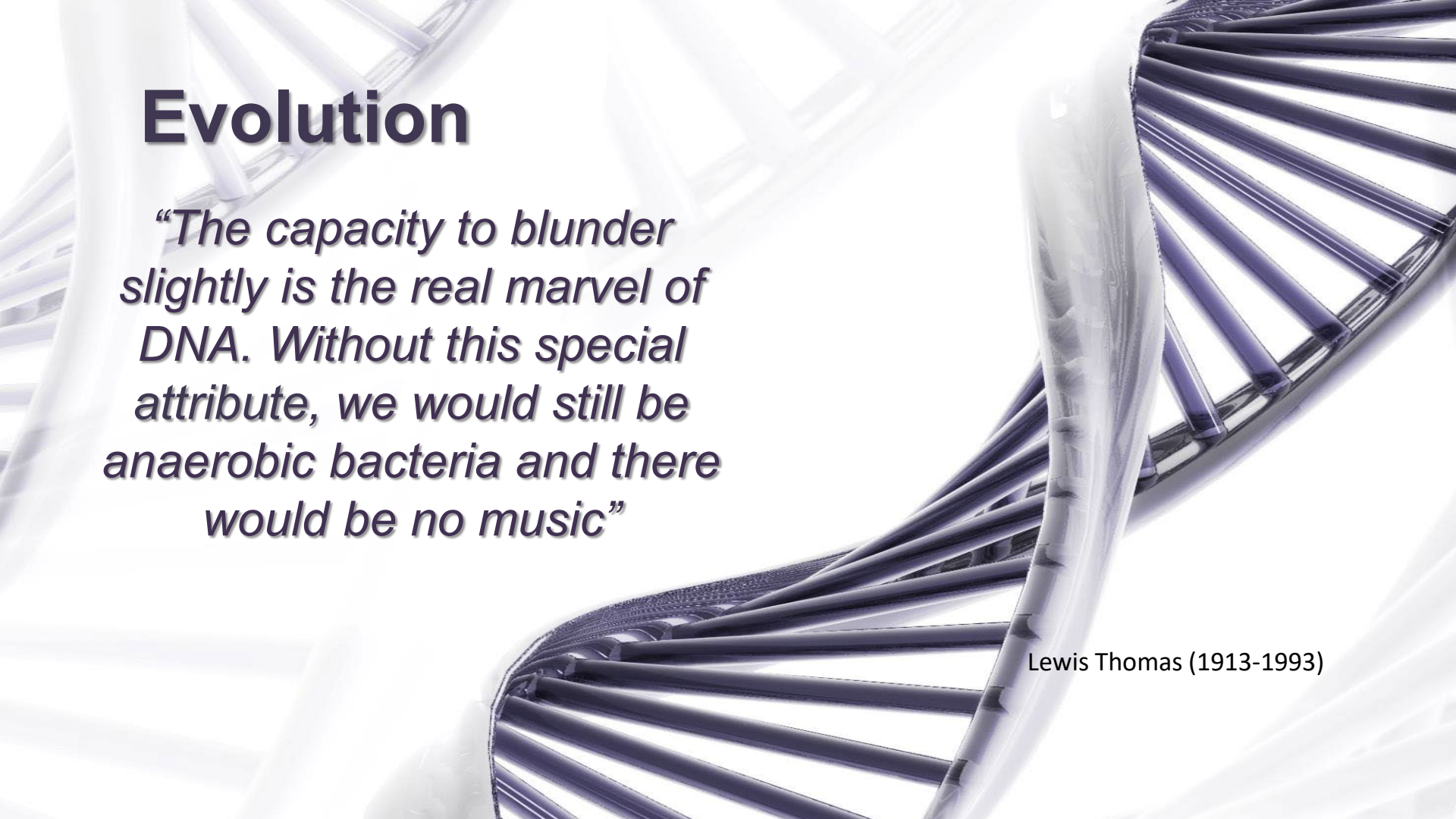
- The mutation is transmitted to offspring



Evolution

"The capacity to blunder slightly is the real marvel of DNA. Without this special attribute, we would still be anaerobic bacteria and there would be no music"

Lewis Thomas (1913-1993)



Causes of mutations

Spontaneous replication errors

- The DNA replication machinery make mistakes at a frequency of ~ 10^{-9} or less.
- Different polymerases have different fidelity.
- In some sequence contexts, e.g. dinucleotide or trinucleotide repeats the error frequency is higher due to ”slippage” in the new strand (causing ”insertions”) or template (causing ”deletions”).

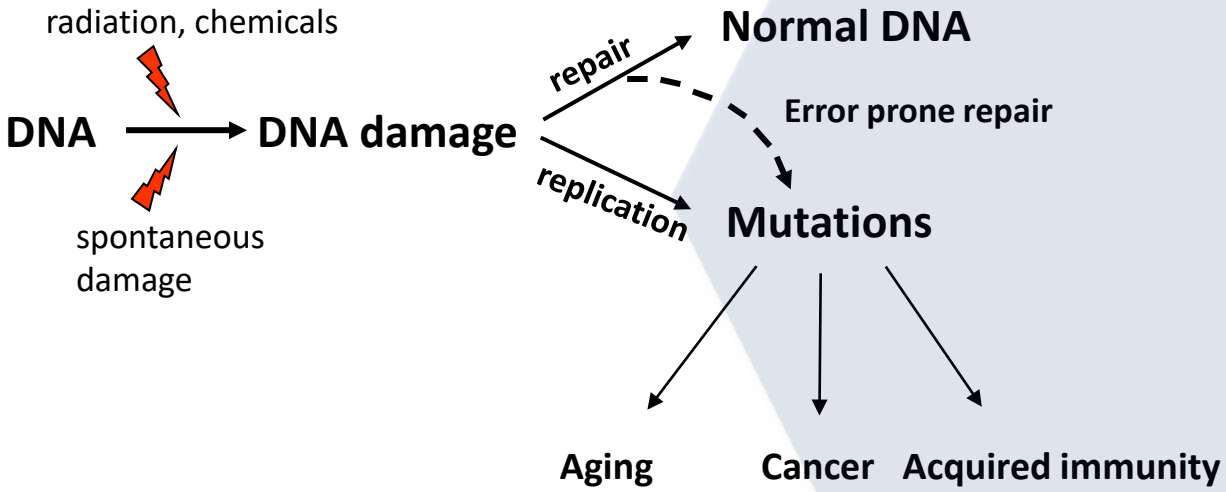
Replication over damaged bases or abasic sites in DNA

- DNA is subject to spontaneous or induced damage, e.g. from radiation, chemicals or spontaneous base lesions. This may alter base pairing properties.

If the damage is not repaired prior to replication it may cause mis-insertion of nucleotides.

- In principle all genetic diseases are caused by replication errors or damage that are not repaired.

Repair of damaged DNA before replication restores normal DNA



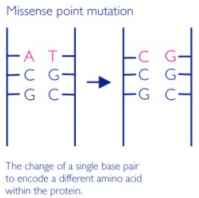
NTNU
K.G. Jebsen Center for Genetic Epidemiology

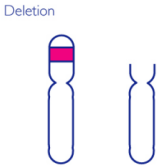
STIFTELSEN KRISTIAN GERHARD JEBSEN

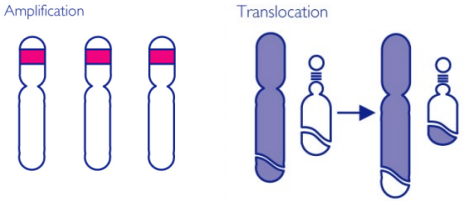
Replication of damaged DNA before repair causes mutation and cancer, but is required for evolution and for generation of specific antibodies

Types of Mutations

Point Mutation	Small deletions or insertions	Chromosomal aberrations
Only affecting one nucleotide	These are detected by DNA sequencing and are *not* visible by microscopy (e.g. 2-100 nucleotides)	-large – can be diagnosed via microscopy -change in chromosome number (aneuploid cancer cells) -change in the gross structure of a chromosome (translocations)

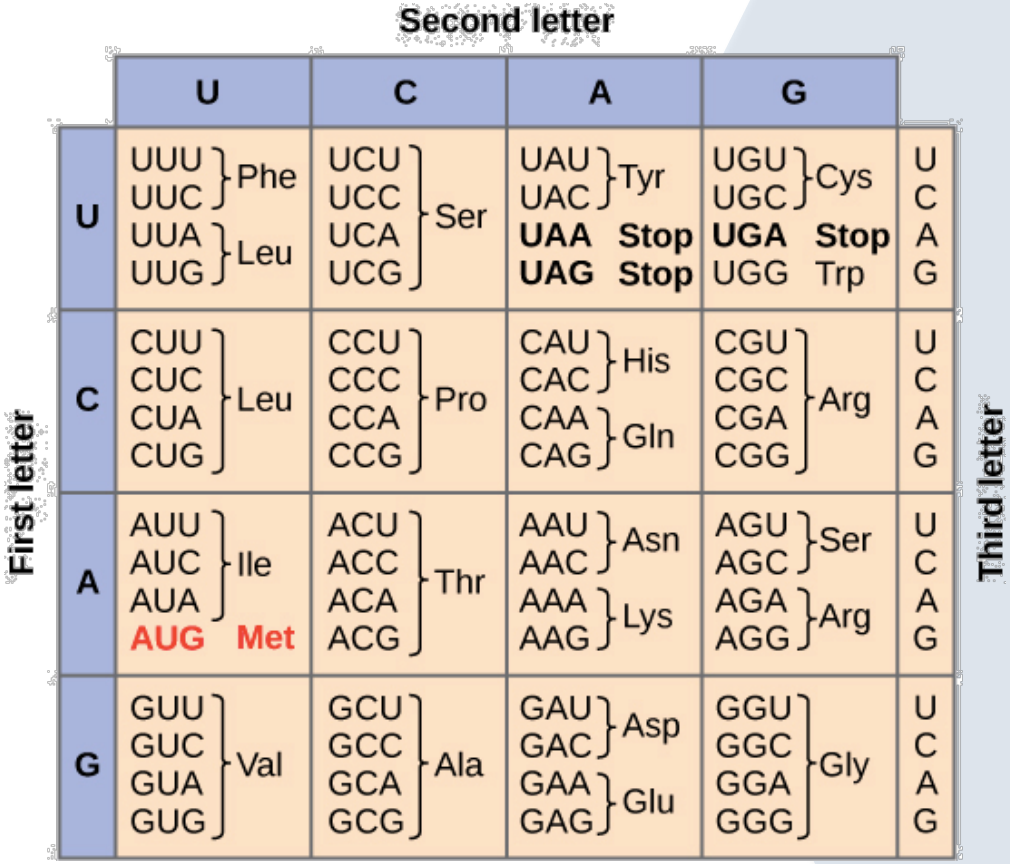




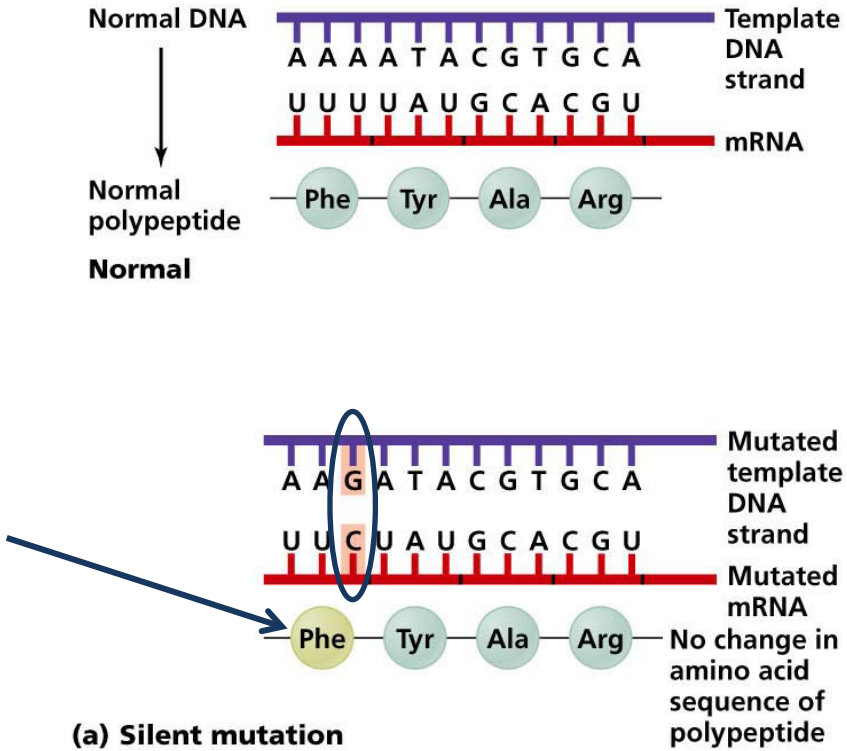


Effect of a mutation on phenotype ranges from none to lethal; depending on type of mutation, and where in the genome

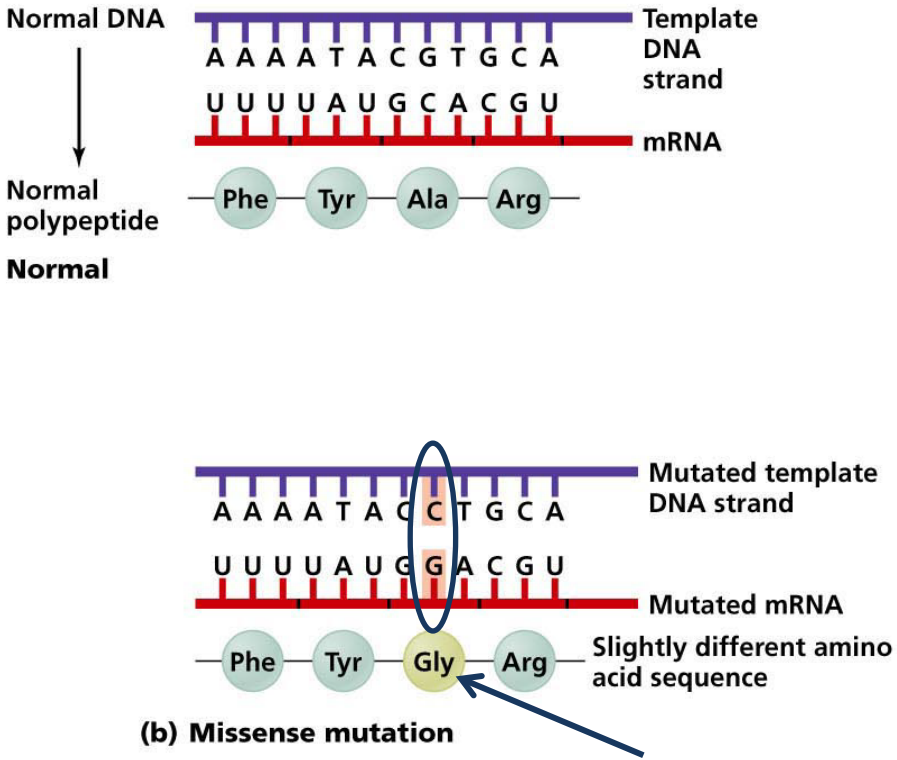
The genetic code - codons



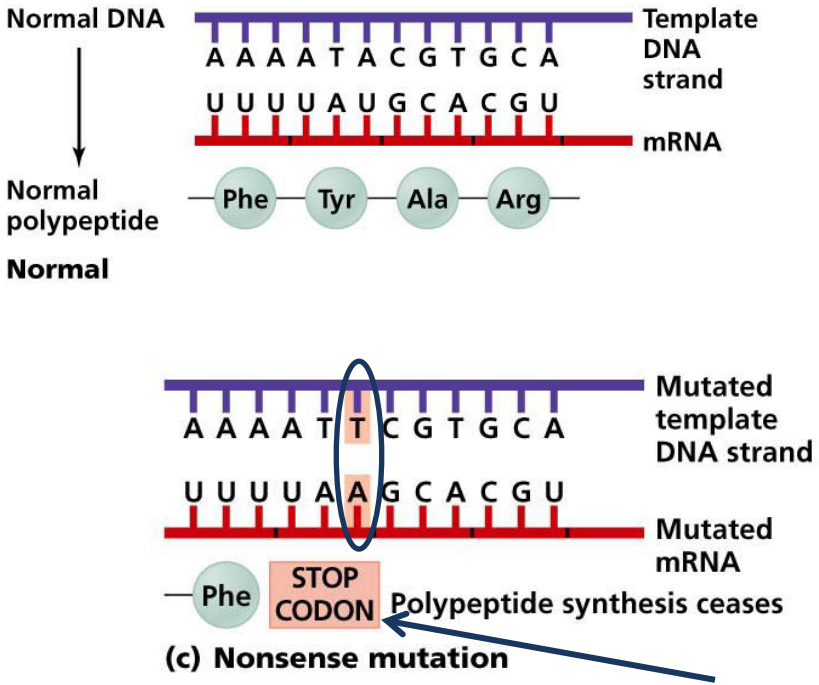
Point mutations



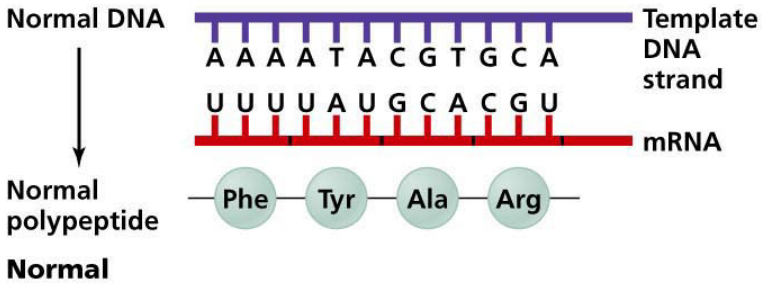
Point mutations

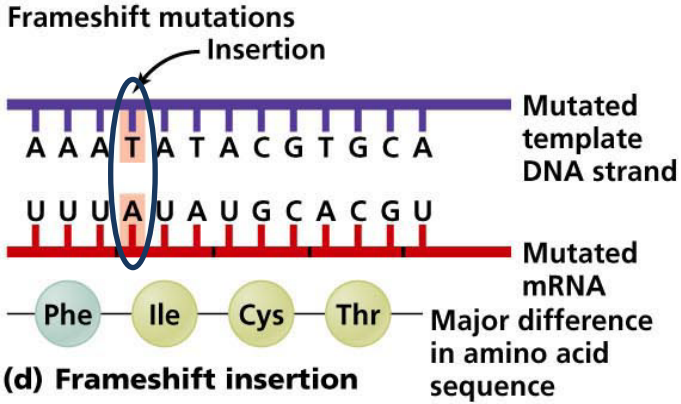


Point mutations

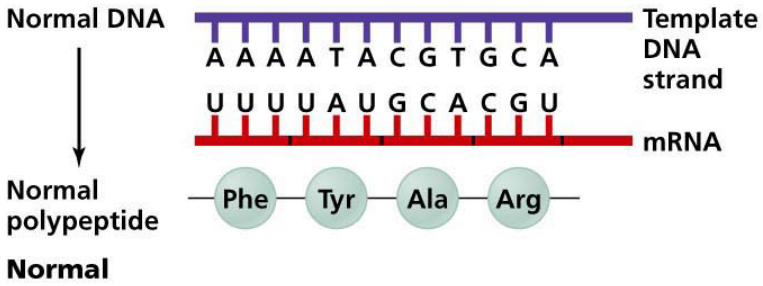


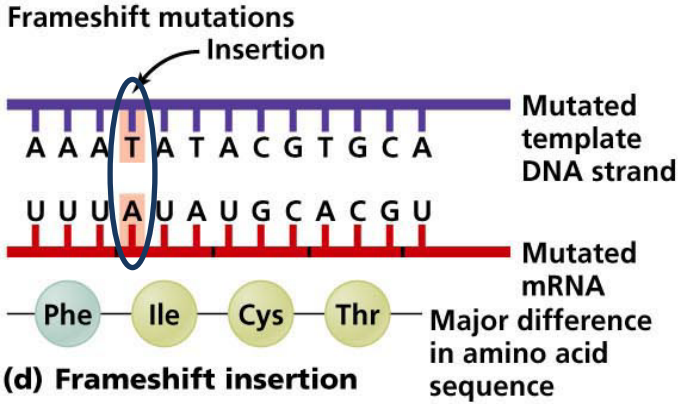
Point mutations

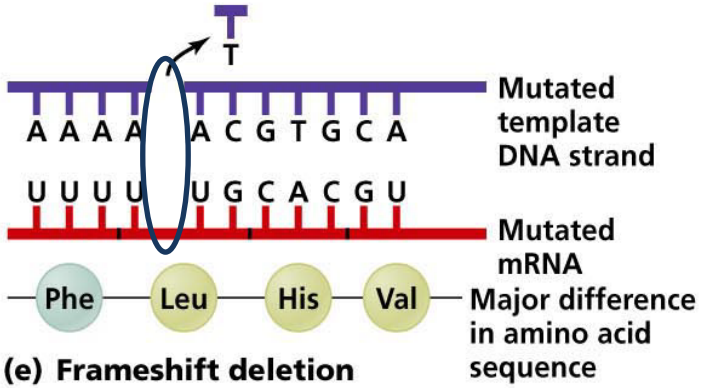




Point mutations







More on consequences of point mutations

Very much dependent on where in the triplet it occurs:

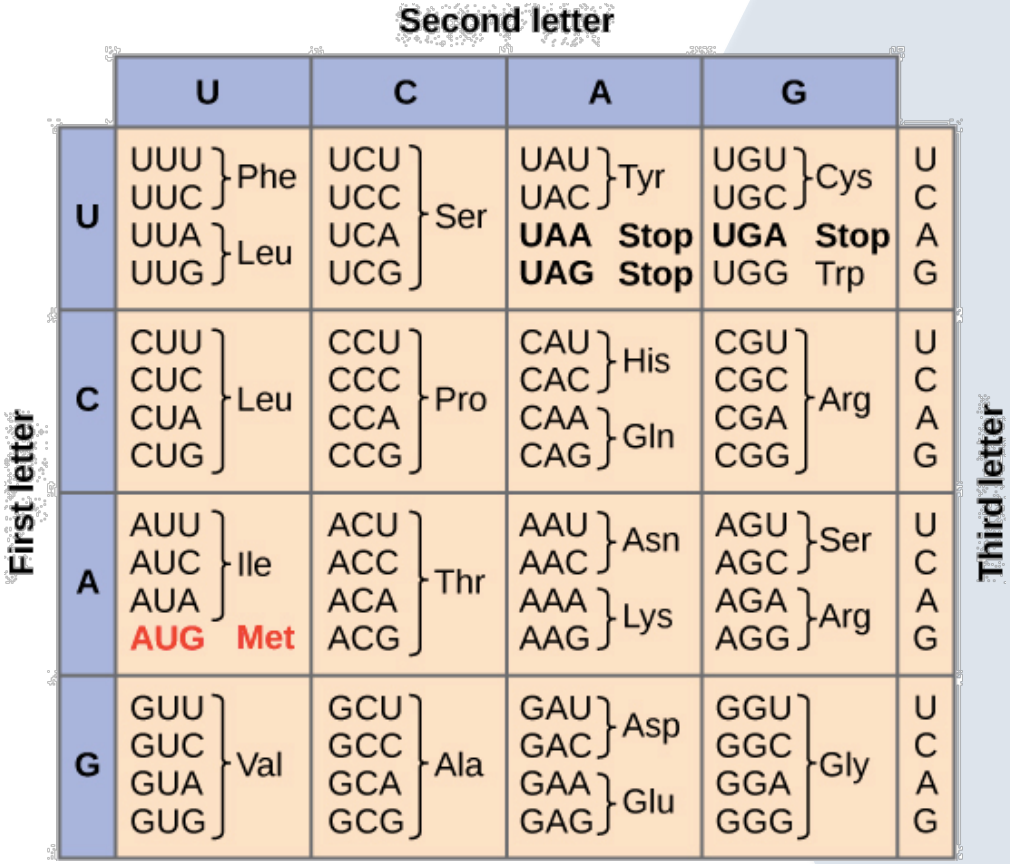
First position: 4 of 64 of bp changes are silent:
Examples: AGA→CGA (both Arg); CUA→UUA (both Leu)

Second position: only one silent mutation in stop codons:
UAA→UGA or UGA→UAA (all stop)

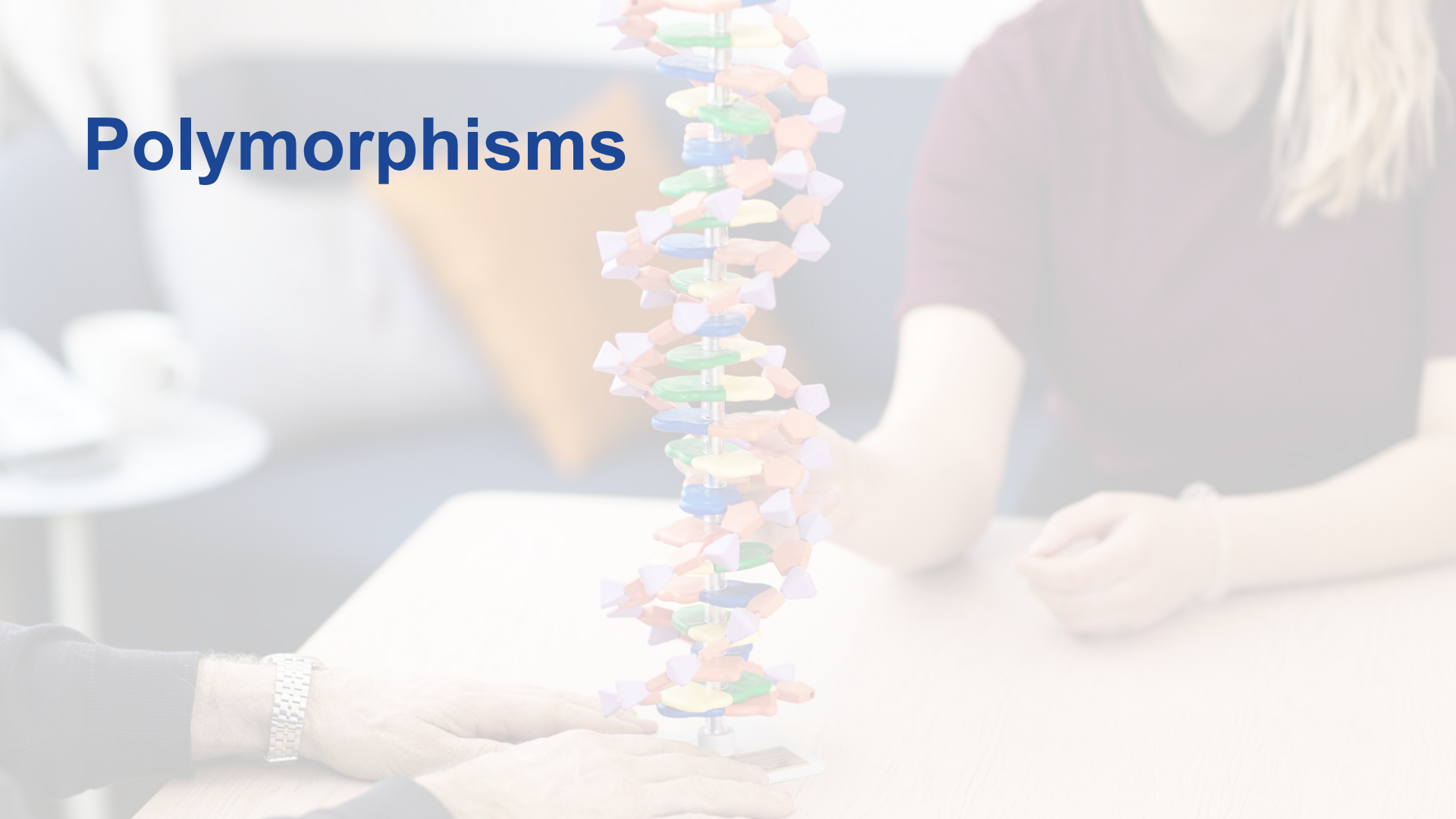
Third position in triplet: 70% of bp changes are silent

Mutations in non-translated DNA (introns or non-coding regions). Could affect splicing, snRNAs, regulation etc

The genetic code - codons

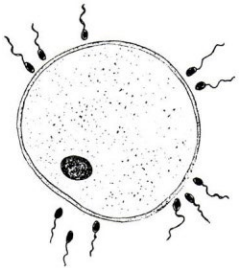


Polymorphisms



Polymorphisms

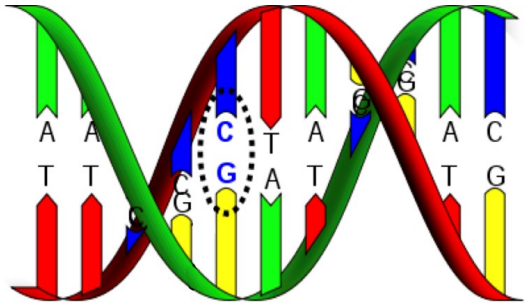
- A polymorphism has resulted from a mutation in a germ cell, and has been passed on to future generations
- A polymorphism gives rise to different versions, **alleles**, of a particular DNA segment



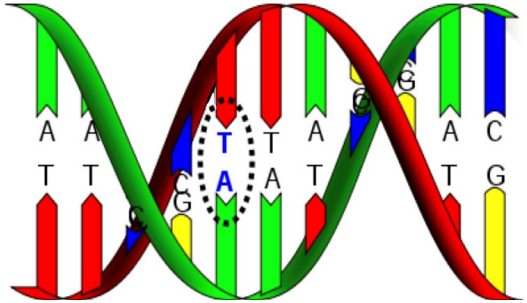
Types of Genetic Variation

Single Nucleotide Polymorphism

Single Nucleotide Polymorphism

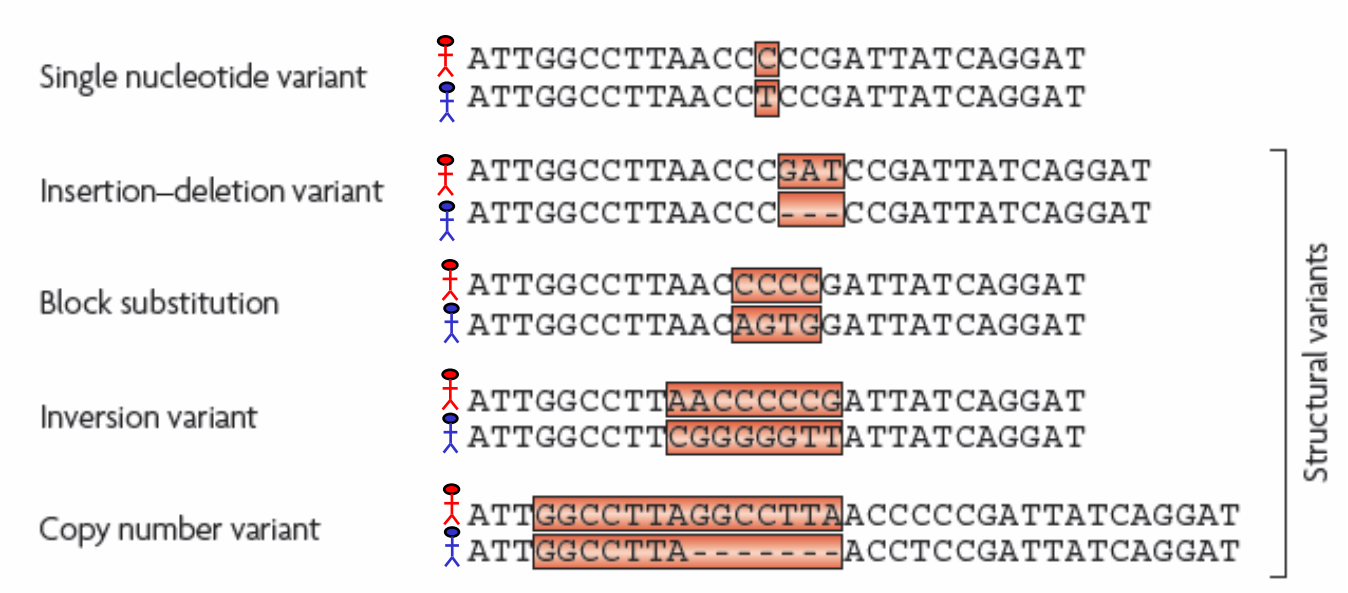


Individual A



Individual B

Different types of DNA polymorphisms



Terminology

- Allele
- Genotype

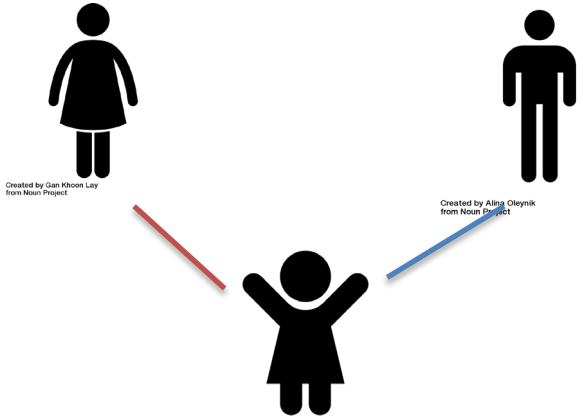
NTNU
K.G. Jebsen Center for Genetic Epidemiology

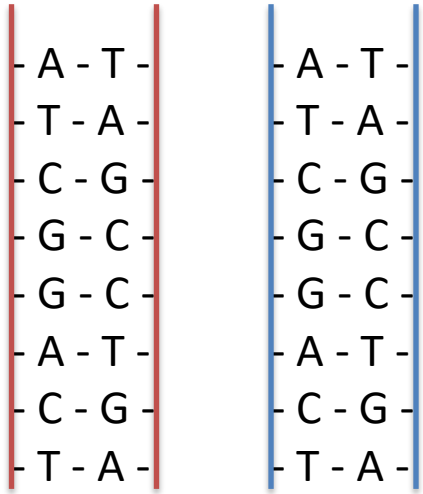
STIFTELSEN KRISTIAN GERHARD JEBSEN

Allele

A T C G G A C T

A T C G T A C T

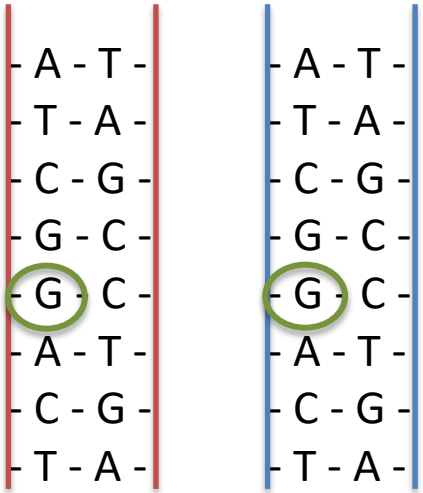

Created by Gan Khoon Lay
from Noun Project
Created by Alina Oleynik
from Noun Project
Created by Musmellow
from Noun Project


- A - T -
- T - A -
- C - G -
- G - C -
- G - C -
- A - T -
- C - G -
- T - A -
- A - T -
- T - A -
- C - G -
- G - C -
- G - C -
- A - T -
- C - G -
- T - A -

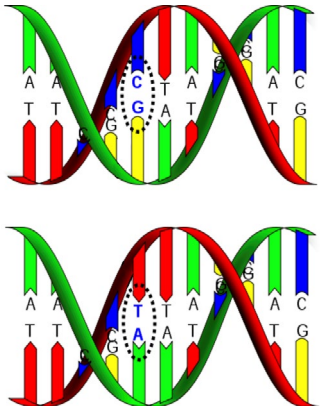
Created by Gan Khoon Lay
from Noun Project

Created by Alina Oleynik
from Noun Project

Created by Musmellow
from Noun Project

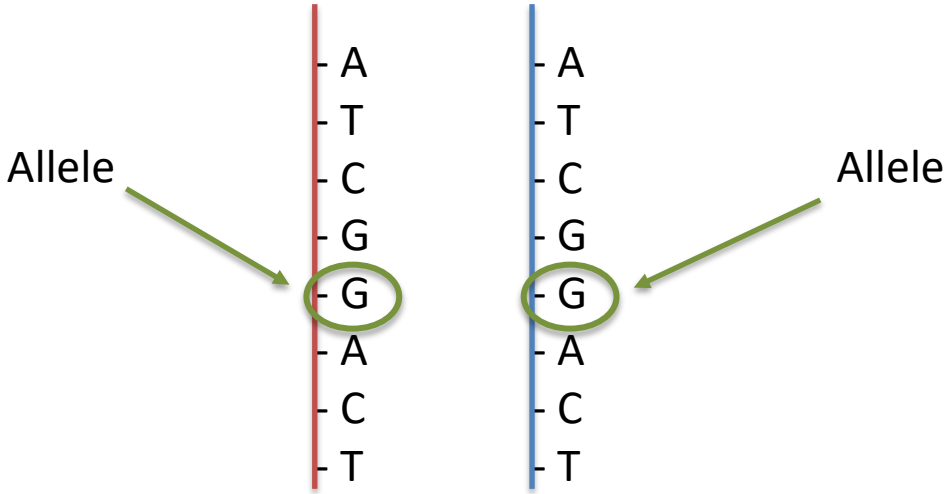


SNP



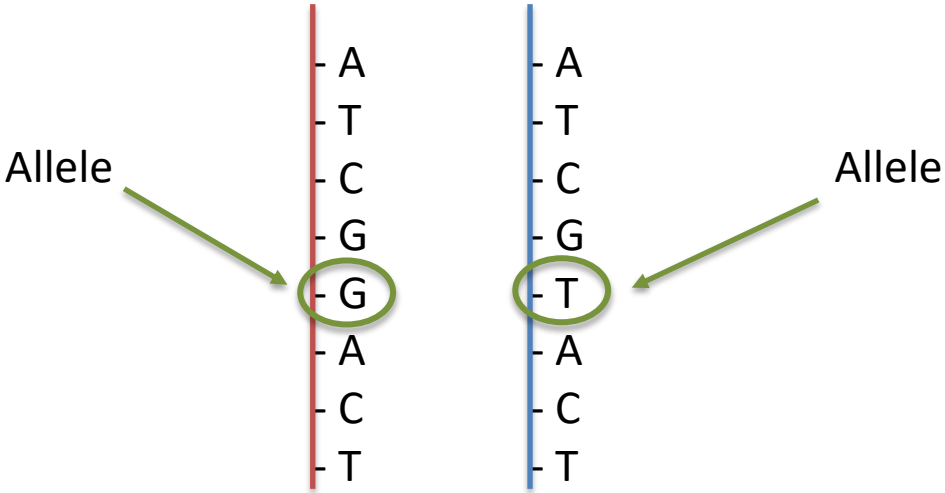
NTNU
K.G. Jebsen Center for
Genetic Epidemiology

STIFTELSEN KRISTIAN GERHARD JEBSEN



Genotype: GG

Homozygous



Genotype: GT

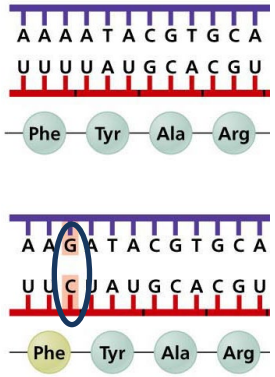
Heterozygous

Consequences of different variants

NTNU
K.G. Jebsen Center for Genetic Epidemiology

STIFTELSEN KRISTIAN GERHARD JEBSEN

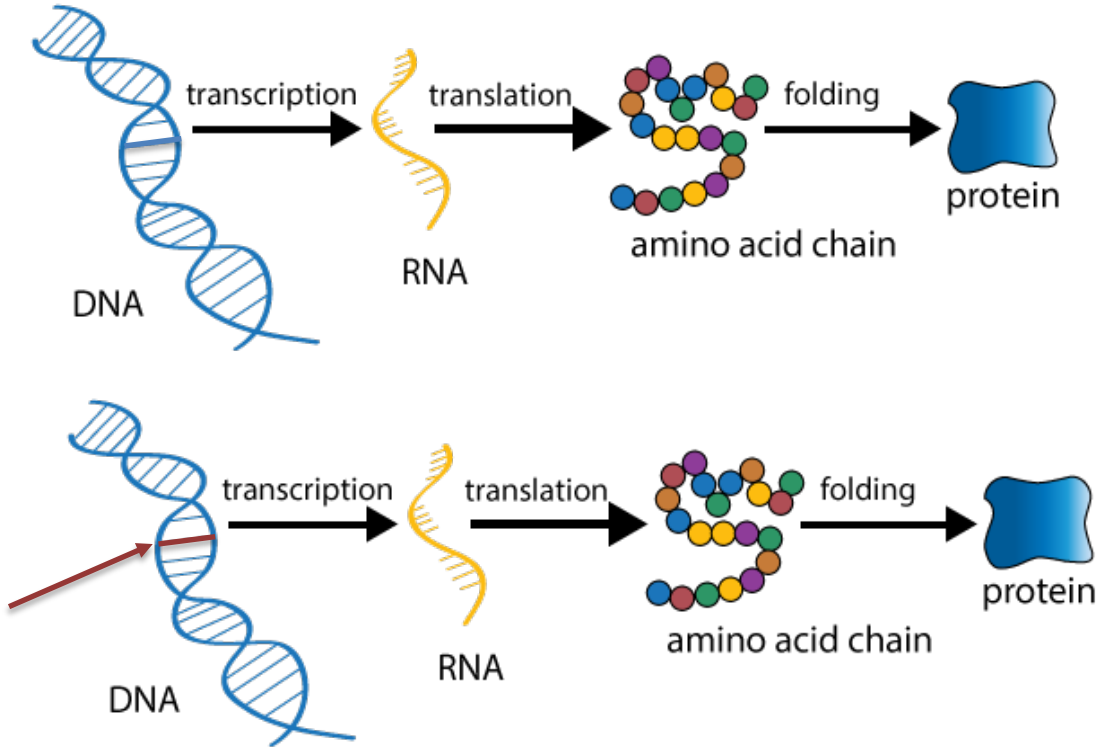
Synonymous SNP



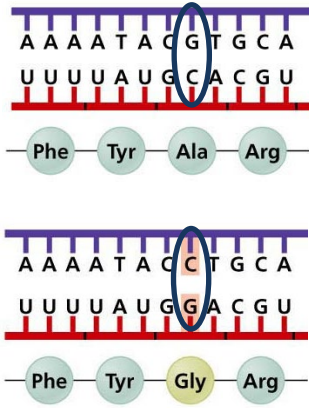
No change in the amino acid sequence

Specialised 

Specialized 


transcription
translation
folding
protein
amino acid chain
RNA
DNA
transcription
translation
folding
protein
amino acid chain
RNA
DNA

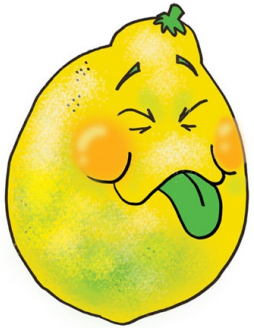
Non-Synonymous SNP (missense)



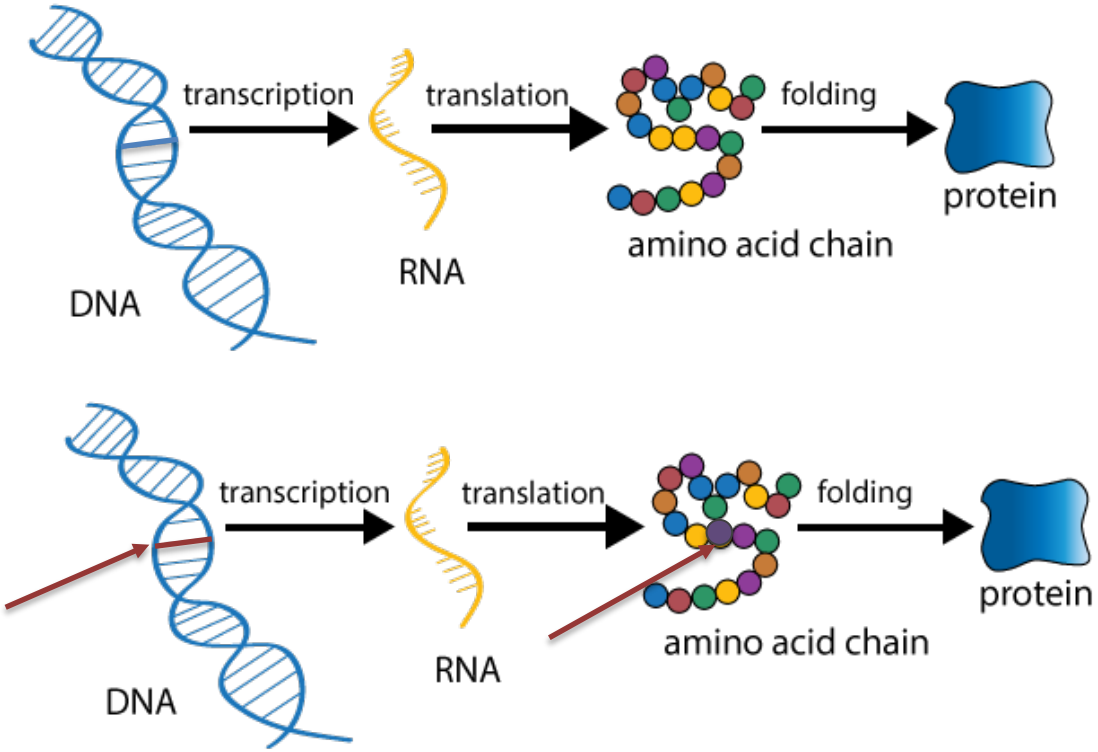
Changes the amino acid

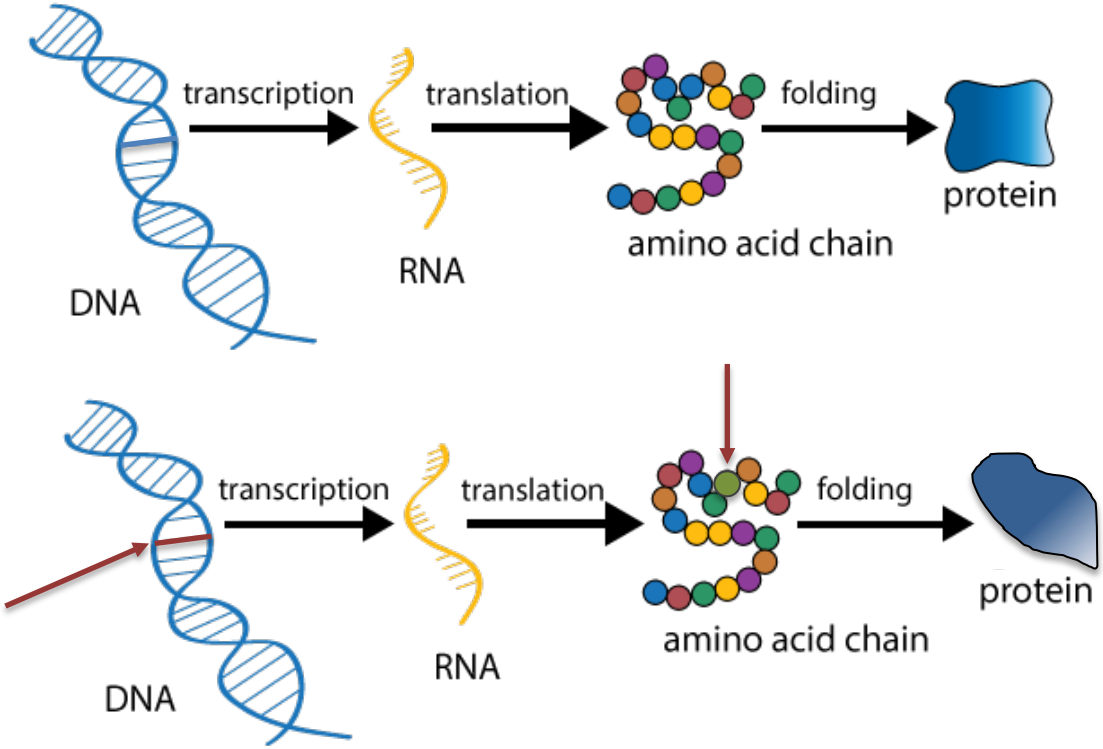
Four

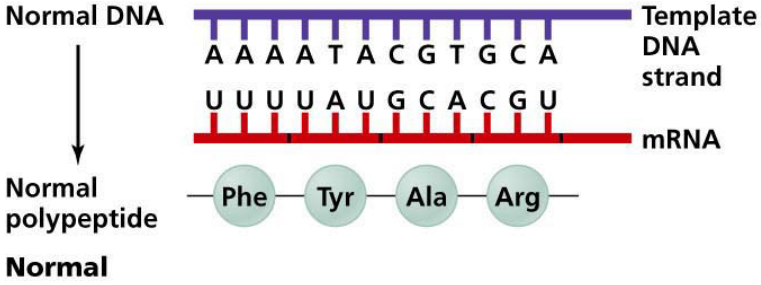
Sour

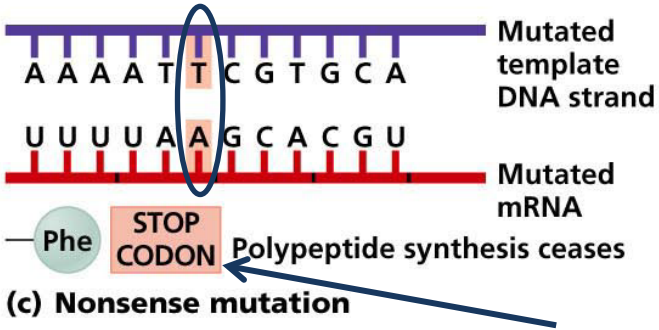


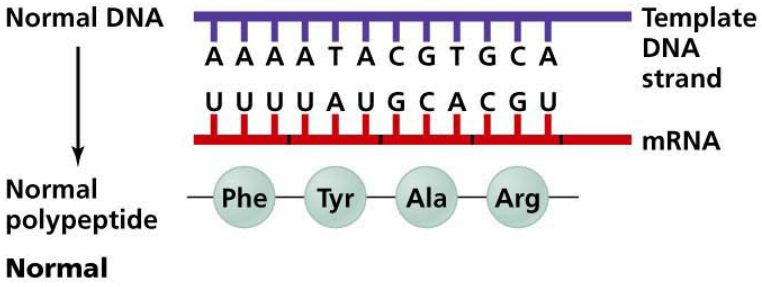
NTNU
K.G. Jebsen Center for Genetic Epidemiology

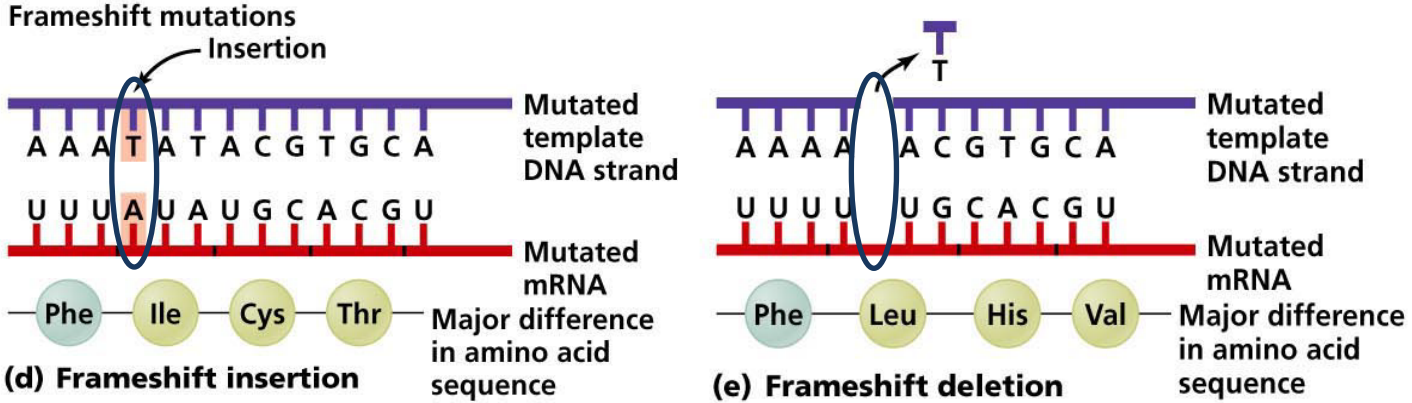

transcription
translation
folding
protein
amino acid chain
RNA
DNA
transcription
translation
folding
protein
amino acid chain
RNA
DNA


transcription
translation
folding
protein
DNA
RNA
amino acid chain
transcription
translation
folding
protein
DNA
RNA
amino acid chain


Normal DNA
A A A A T A C G T G C A
Template DNA strand
U U U U A U G C A C G U
mRNA
Normal polypeptide
Phe
Tyr
Ala
Arg
Normal

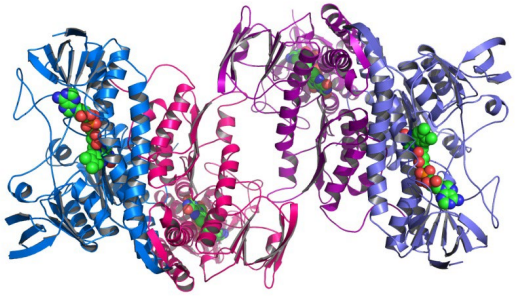

A A A A T T C G T G C A
Mutated template DNA strand
U U U U A A G C A C G U
Mutated mRNA
Phe
STOP CODON
Polypeptide synthesis ceases
(c) Nonsense mutation


Normal DNA
A A A A T A C G T G C A
Template DNA strand
U U U U A U G C A C G U
mRNA
Normal polypeptide
Phe
Tyr
Ala
Arg
Normal


Frameshift mutations
Insertion
A A A T A T A C G T G C A
Mutated template DNA strand
U U U A U A U G C A C G U
Mutated mRNA
Phe
Ile
Cys
Thr
Major difference in amino acid sequence
(d) Frameshift insertion
T
A A A A A C G T G C A
Mutated template DNA strand
U U U U U G C A C G U
Mutated mRNA
Phe
Leu
His
Val
Major difference in amino acid sequence
(e) Frameshift deletion

The effect of variants on protein function

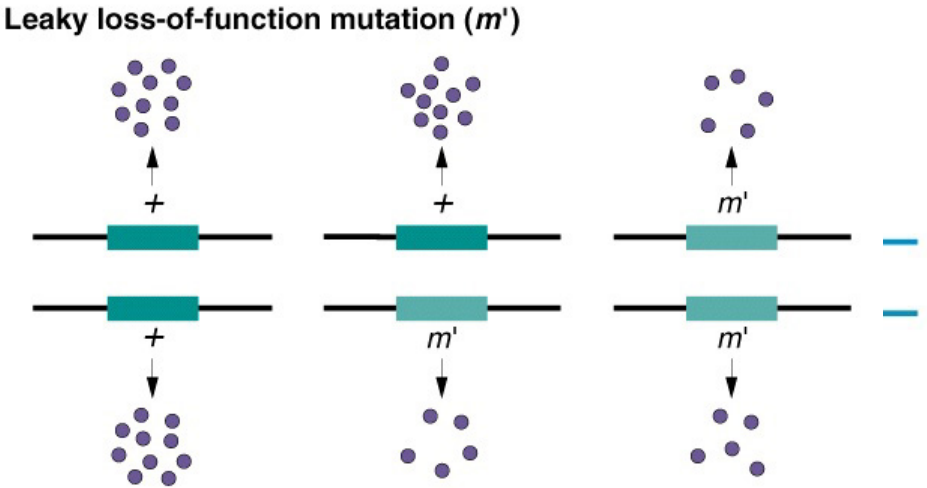
- Loss-of-function
- Gain-of-function
- Novel property
- Abnormal expression of gene at abnormal time or place



Loss-of-function mutations

Consequences:

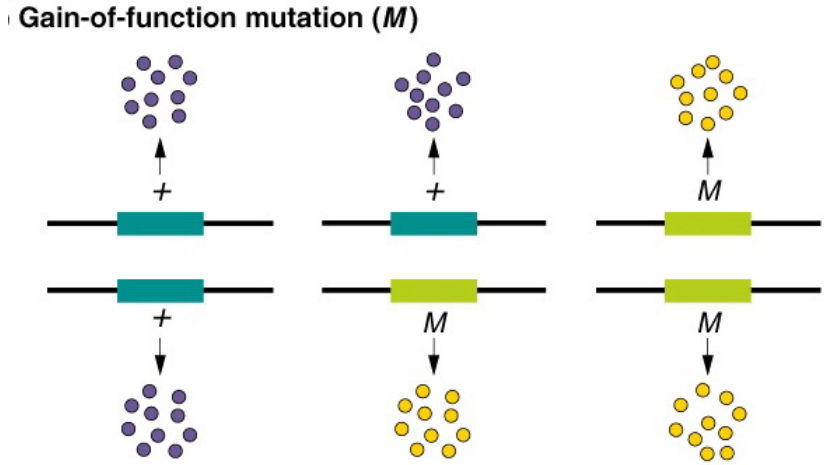
- Complete loss-of-function
- Reduced gene dosage
- Abolished or impaired protein fun
- Instability -> reduced abundance



Gain-of-function

- Variants in the coding region enhancing one normal function of a protein

- Variants increase production of a normal protein
  - Commonly due to increased gene dosage; duplication of part or all of a chromosome, duplication of a gene, somatic mutations in cancer cells



Phenotypic effects of variants

- Many DNA variants do not have a measurable phenotypic effect – ie. not all variation lead to changes in the phenotype
- The effect of genetic variant on the phenotype can vary from slight to large or lethal.
- Many variants can affect several phenotypes: pleiotropy

Summary – key points

- Be familiar with the terms mutation, polymorphism and variant
- Know of causes of mutations
- Know what a SNP is
- Be familiar with the terms allele and genotype
- Understand the consequences some different types of variants including terms like synonymous, non-synonymous, loss and gain or gain of function.

Thank you for listening!

For enquiries,
please contact me at
maiken.e.gabrielsen@ntnu.no

www.ntnu.edu/huntgenes

NTNU
K.G. Jebsen Center for Genetic Epidemiology

STIFTELSEN KRISTIAN GERHARD JEBSEN