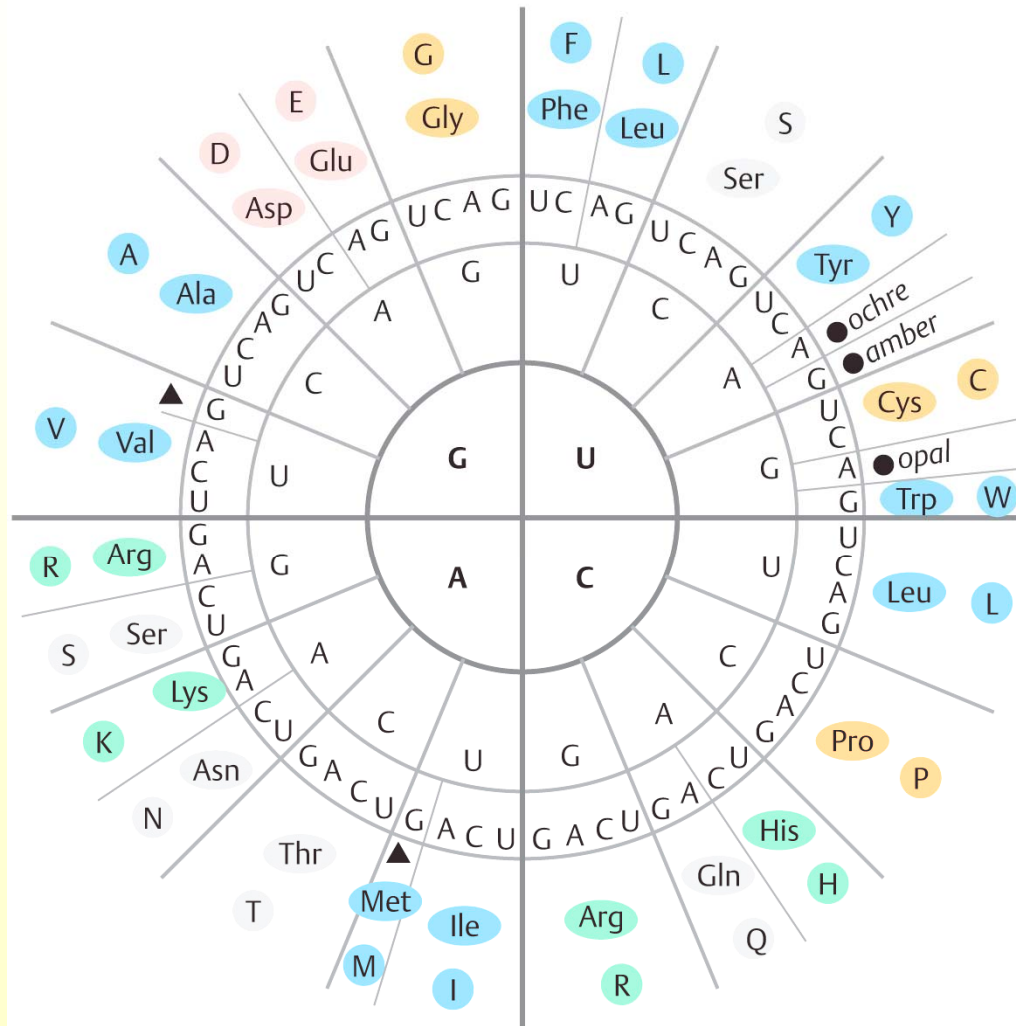


# **Genetic Diseases in Humans**

**Genetic Code and mutation spectrum exemplified by  
the CHARGE syndrome**

EUPRIM-Net  
Dr. med S. Pauli

# Genetic Code



# Classification of mutations

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## **Loss of function mutations:**

the product has reduced or no function

## **Gain of function mutations:**

the product does something positively abnormal  
(e.g. mutations in signaling systems, failing to  
switch a process off when it should)

# Classes of mutations

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## Deletions

**Insertions** including duplications

**Frameshifts:** are produced by deletions, insertions or splicing errors

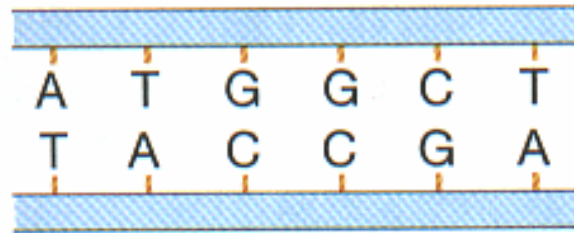
## Single base **substitutions:**

- **missense mutations:** replace one amino acid with another
- **nonsense mutations:** replace an amino acid codon with a stop codon
- **splice site mutations:** create or destroy signals for exon-intron splicing

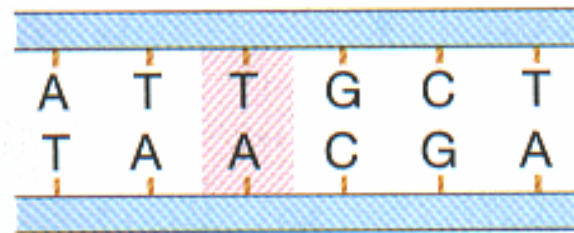
## Dynamic mutations:

are tandem repeats that often change size on transmission to children

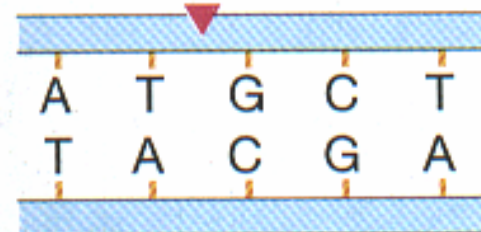
# Classes of mutations



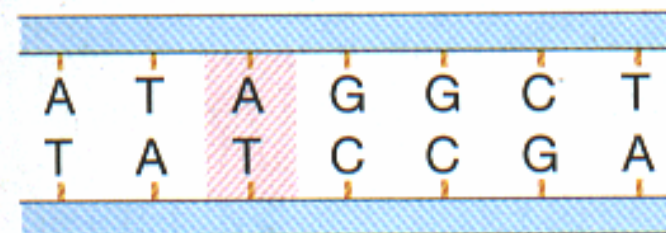
Wildtyp



Substitution

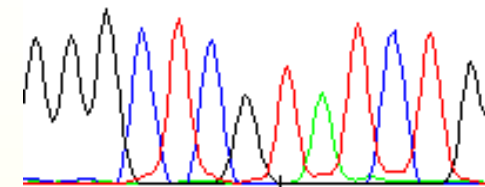


Deletion



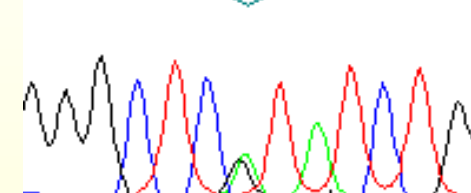
Insertion

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



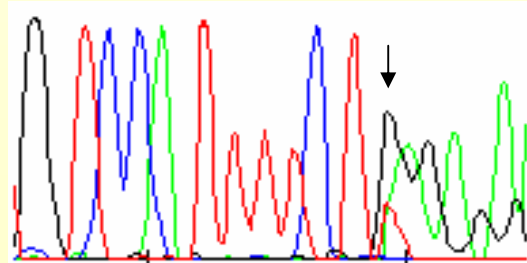
Wildtype

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



Substitution G>A heterozygous

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



Frameshift due to Insertion

# Classes of mutations

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## Different types of substitutions

<b>TTA</b>	<b>CGA</b>	<b>TCT</b>	wild type
<b>Leu</b>	<b>Arg</b>	<b>Ser</b>	amino acid sequence
<b>TTA</b>	<b>CGA</b>	<b>TCA</b>	silent mutation
<b>Leu</b>	<b>Arg</b>	<b>Ser</b>	no amino acid change
<b>TTC</b>	<b>CGA</b>	<b>TCT</b>	missense mutation A>C
<b>Phe</b>	<b>Arg</b>	<b>Ser</b>	amino acid change Leucin>Phenylalanin
<b>TTA</b>	<b>TGA</b>	<b>TCT</b>	nonsense mutation C>T
<b>Leu</b>	<b>Arg</b>	<b>Ser</b>	replacement of an amino acid to a stop codon

## CHARGE syndrome - Introduction

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- phenotypically heterogeneous syndrome
- caused by mutations in the *CHD7* gene
- most cases are sporadic
- autosomal dominant inheritance

**C** = Coloboma/Mikrophtalmia  
**H** = Heart malformations  
**A** = Atresia of the choanae  
**R** = Retardation  
**G** = Genital anomalies  
**E** = Ear anomalies/deafness

→ **CHARGE** acronym  
(was coined by Pagon et al. 1981)

## CASE 1

Clinical features: female,  
cleft lip/palate, coloboma,  
ear abnormality, oedema  
due to heart malformation

Molecular analysis of the *CHD7* gene was performed  
Mutation detection ? what kind of mutation?

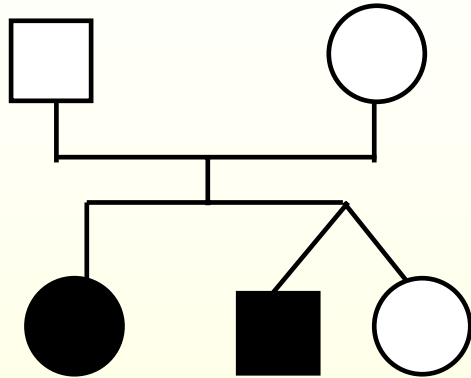
### CASE 2

Clinical features: female, cleft lip/palate, coloboma, ear abnormality, heart malformation

Patient died after few months due to the severe heart defect.

Molecular analysis of the *CHD7* was performed  
Mutation detection ? what kind of mutation?

## CASE 3



### Case history ♀:

6 years, coloboma, ear anomalies., facial nerv palsy, no active speech, mental retardation , brain anomaly

### Case history ♂:

3 years, colobom right eye, deafness, cleft lip and palate, inner organ malformation mental retardation, genital anomaly and brain anomaly

How can you explain the results ?