# Genetic diseases & testing

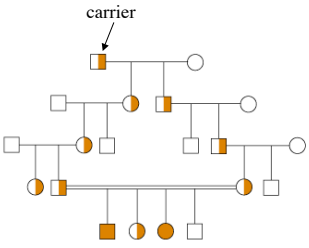
Reading: Chapter 12; and pp 201-202

# Autosomal recessive mutations

# The story of three genetic diseases

## Phenylketonuria
## Sickle-Cell Anemia
## Tay-Sachs Disease

**Phenylketonuria (PKU), Sickle-Cell Anemia and Tay-Sachs Disease are autosomal recessive diseases.**




Disease is expressed in matings between carriers (heterozygotes).

Most affected individuals have unaffected parents.

Increased frequency with inbreeding.

**Frequencies of Sickle-Cell Anemia and Tay-Sachs Disease alleles in different populations.**

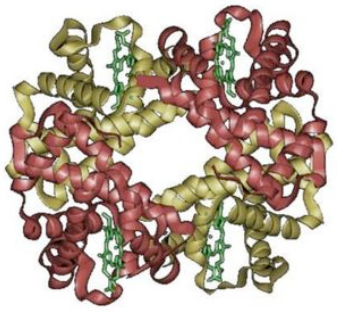
**Sickle-Cell Anemia**
**10-40% of the population in regions of equatorial Africa are carriers**
**<1% of South Africans are carriers**

**Tay-Sachs**
**1/25 American Ashkenazi Jews are carriers**
**1/300 in the general population are carriers**

## Why are the frequencies of some disease alleles so high?

**Explanation #1**
**Heterozygote advantage**

**Explanation #2**
**Founder effect**



## Hemoglobin

Major protein in red blood cells.

Hemoglobin is made of four polypeptide chains--2 alpha and 2 beta chains--and four heme-iron complexes. These complexes bind $O_2$.

Hemoglobin releases $CO_2$ and binds $O_2$ when $CO_2$ concentrations are low. *i.e.,* in the lungs. Hb binds $CO_2$ and releases $O_2$ when $CO_2$ concentrations high.

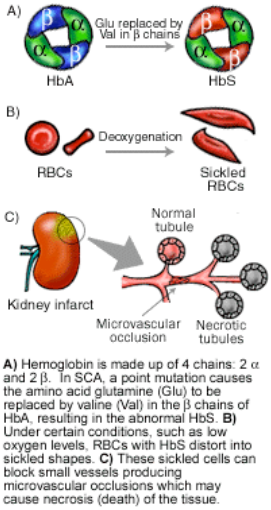
## A single amino acid change in the beta peptide results in sickle cell anemia

**HBB Sequence in Normal Adult Hemoglobin (Hb A):**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Nucleotide | CTG | ACT | CCT | GAG | GAG | AAG | TCT |
| Amino Acid | Leu | Thr | Pro | Glu | Glu | Lys | Ser |
| | 3 | | | 6 | | | 9 |

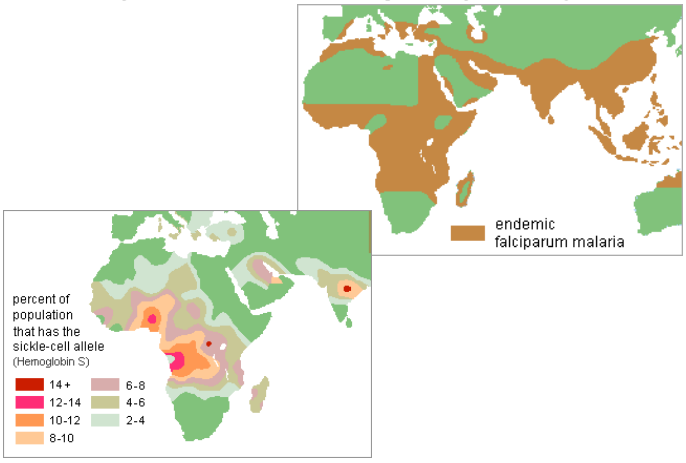
**HBB Sequence in Mutant Adult Hemoglobin (Hb S):**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Nucleotide | CTG | ACT | CCT | GTG | GAG | AAG | TCT |
| Amino Acid | Leu | Thr | Pro | Val | Glu | Lys | Ser |
| | 3 | | | 6 | | | 9 |




**A)** Hemoglobin is made up of 4 chains: 2 α and 2 β. In SCA, a point mutation causes the amino acid glutamine (Glu) to be replaced by valine (Val) in the β chains of HbA, resulting in the abnormal HbS. **B)** Under certain conditions, such as low oxygen levels, RBCs with HbS distort into sickled shapes. **C)** These sickled cells can block small vessels producing microvascular occlusions which may cause necrosis (death) of the tissue.

## Why is the carrier frequency so high?




## Carriers have an advantage in malaria-infested areas

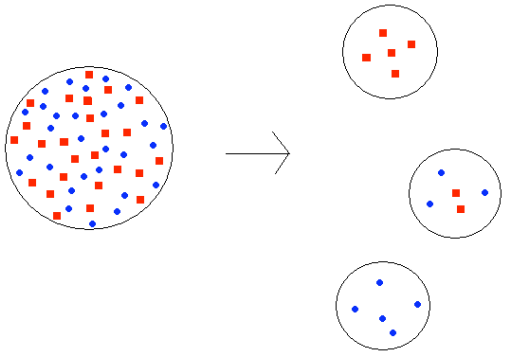
| Genotype | disease | malaria |
|---|---|---|
| HbA/HbA | normal | susceptible |
| HbA/HbS | normal | resistant |

## Tay Sachs

**Progressive disease with an onset in infancy of developmental retardation, followed by paralysis, dementia and blindness. Death occurs in the second or third year of life.**

**Tay-Sachs disease is caused by mutation in the hexosaminidase A gene, which removes fatty substances called gangliosides. When hemosaminidase A is lacking, gangliosides build up in neurons.**

## The Founder Effect



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ARTICLE

## MtDNA evidence for a genetic bottleneck in the early history of the Ashkenazi Jewish population

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# Tay Sachs Disease Testing

**Carriers can be identified by a simple blood test that measures hexosaminidase A activity.**

**In the 1970s, the families of affected children began a program that focused on education of Jewish groups to the risk of Tay Sachs. The community was also instructed on how to seek genetic testing and counseling. Tay Sachs disease is almost never encountered today in Ashkenazi Jews.**

# If left untreated PKU can cause severe mental retardation.

**Mutations in the gene encoding phenylalanine hydroxylase cause PKU. 1/14,000 births**

**Phenylalanine**
**(essential amino acid that we get in our diet).**

↓ **phenylalanine hydroxylase**

**Tyrosine**

# Genetic screening

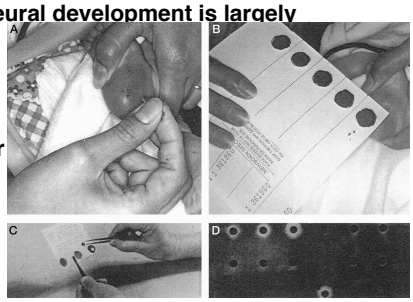
## Infants in all states tested for PKU!

## Mental retardation from PKU has been eliminated in the U.S.

**All newborns are tested for PKU using a simple blood test that measures phenylalanine.**

**Infants with PKU are placed on a phenylalanine restricted diet. Later in life, after neural development is largely completed, PKU individuals can resume a normal diet.**

**PKU is described in your textbook on pp248-252.**




**Tandem Mass Spectrometry has the potential to test for many metabolites in newborns.**

**As the genes for more genetic diseases are isolated, molecular genetic approaches can be used to screen for many genetic diseases. In principle, 100s of genetic traits could be screened in the not so distant future.**

**How many diseases should we test for?**

**Should we be paying for this?**

**Who should get the information?**

# Huntington's Disease (HD) is inherited as an autosomal dominant trait

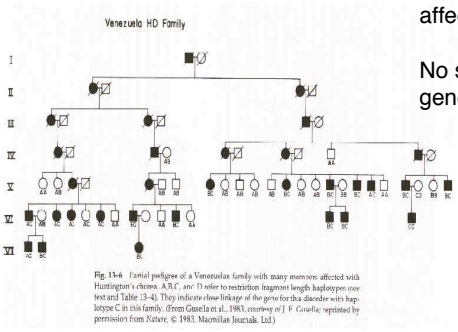



Fig. 13-6 Partial pedigree of a Venezuelan family with many members affected with Huntington's chorea. A,B,C, and D refer to restriction fragment length haplotypes (see text and Table 13-4). They indicate close linkage of the gene for this disorder with haplotype C in this family. (From Gusella et al., 1983, courtesy of J. F. Gusella; reprinted by permission from *Nature*. © 1983, Macmillan Journals Ltd.)

Affected person has an affected parent

No skipping of generations

Huntington's disease (HD) is a late onset, progressive disorder of the central nervous system that affects 1 in 10,000 individuals in the U.S. The disorder usually begins to affect adults between the ages of 30-50 years old. Initial symptoms include irritability, clumsiness, depression and forgetfulness. These progress to more severe mental and physical impairment that leads to death.

Folksinger Woody Guthrie, who died of the disease, was first thought to be an alcoholic and later schizophrenic, before he was properly diagnosed.

## Molecular basis for Huntington's disease

HD is caused by an increase in the number of repeats of three nucleotide bases, CAG, which translates into increases in the amino acid glutamine in the Huntington protein. The normal version of the HD gene has between 6 and 34 copies of CAG. The mutation which causes Huntington's increases the number of repeats to 37 or more. There appears to be a correlation between the number of CAG repeats and the age of disease onset. People with more than 60 repeat can develop HD before age 20. Most people with late adult onset HD have between 37 and 52 repeats.

*Table 11.3* **Some Mutations with Expanded Trinucleotide Repeats**

| Gene | Triplet Repeat | Normal Copy | Copy in Disease | MIM/OMIN Number |
|---|---|---|---|---|
| Spinal and bulbar muscular atrophy | CAG | 12–34 | 40–62 | 313200 |
| Spinocerebellar ataxia type 1 | CAG | 6–39 | 41–81 | 164400 |
| Huntington disease | CAG | 6–37 | 35–121 | 143100 |
| Haw-River syndrome | CAG | 7–34 | 54–70 | 140340 |
| Machado-Joseph disease | CAG | 13–36 | 68–79 | 109150 |
| Fragile-X syndrome | CGG | 5–52 | 230–72,000 | 309550 |
| Myotomic dystrophy | CTG | 5–37 | 50–72,000 | 160900 |
| Friedreich ataxia | GAA | 10–21 | 200–900 | 229300 |

## A hypothetical case

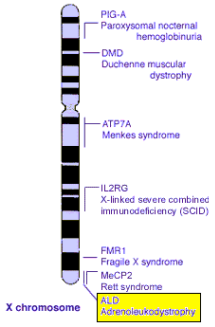
**An airline pilot informs his doctor that his father has just died from HD. It is conceivable that HD could impair his functioning as a pilot.**

**Does the airline pilot have a duty to his passengers to have the PCR test?**

**Does the airline have the right to know?**

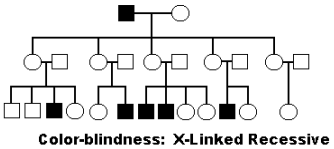
**Does the physician have the right to inform the airline of his patient's father?**

# X-linked diseases



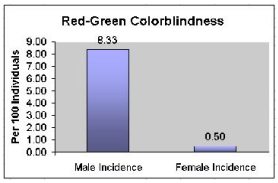

Positions of some genes associated with X-linked inherited diseases.

## Colorblindness is an recessive X-linked trait.



**Color-blindness: X-Linked Recessive**

**Grandfather to Grandson Transmission thru a Female**



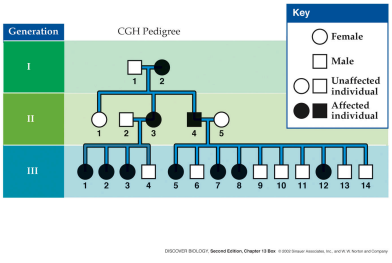

**Trait usually expressed only in males.**

**Sons of carrier females have a 50% chance of being affected.**

**Affected males do not have affected children.**

**Trait skips generations.**

## Congenital Generalized Hypertrichosis is an X-linked dominant trait.




Daughters, but not sons, can inherit the trait from their fathers.

Daughters and sons can inherit the trait from their mothers.

The trait is present in each generation or is lost.

Shao-Lin martial arts master Su Kong Tai Djin.

Congenital Generalized Hypertrichosis is one medical syndrome that could have contributed to the werewolf myth.

Scientists are interested in this atavistic syndrome as its understanding could shed light on how during our evolution we lost hair from parts of our body.