Midterm reminder April 13
Covers lectures 10-18 (this includes Professor Roelink's April 6 lecture)

Office hours this week:
Tu & Th 2-4 PM
No office hours Tu, April 7

Garriga midterm review session
April 12, 5-7 PM 100 GPB

Genetic diseases and genetic screening

Reading: pp 200-202, 316

Outline

Autosomal recessive genetic diseases

Screening

Autosomal recessive mutations

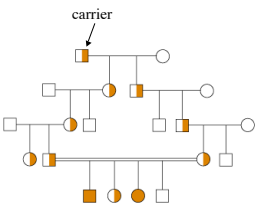
The story of three genetic diseases

Phenylketonuria
Sickle-Cell Disease
Tay-Sachs Disease

Autosomal recessive genetic diseases

-inheritance patterns
-disease phenotype
-prevalence

Phenylketonuria (PKU), Sickle-Cell Disease 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.

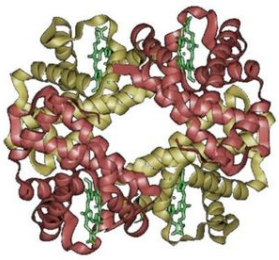
Sickle-Cell Disease
10-40% of the population in regions of equatorial Africa are carriers
7-10% of African Americans are carriers
<1% of South Africans are carriers

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

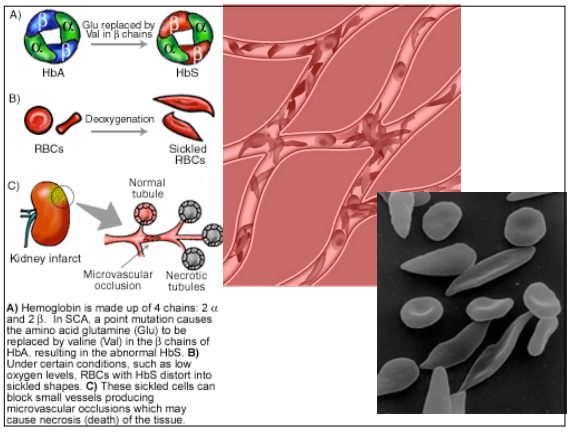
Major protein in red blood cells.

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

	Thr	Pro	Glu	Glu	$beta^A$ chain
...A C T	C C T	G A G	G A G...	$beta^A$ gene
Codon #	4	5	6	7	
...A C T	C C T	G T G	G A G...	$beta^S$ gene
	Thr	Pro	Val	Glu	$beta^S$ chain



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.

Results of RBC sickling

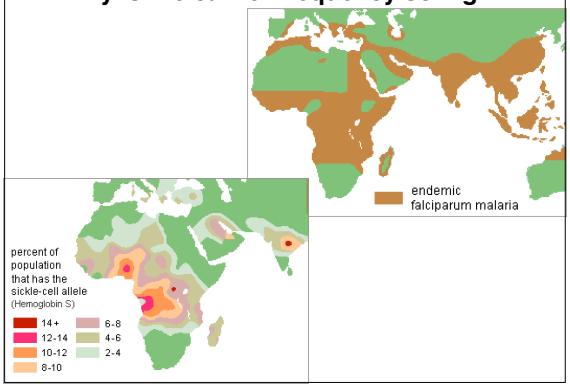
Breakdown of RBC
anemia
Fatigue, shortness of breath
Jaundice

Blood vessel clogging
Organ and joint pain
Organ damage
Stroke

All 50 States, DC, Puerto Rico and the Virgin Islands do a simple blood test for HbS in newborns.

Treatment is effective, and when diagnosed early, sickle cell patients can live beyond 40 years.

Why is the carrier frequency so high?



Carriers have an advantage in malaria-infested areas

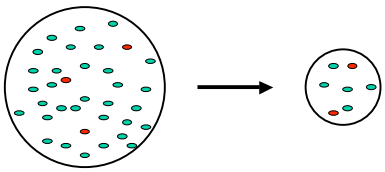
Genotype	disease	malaria
HbB/HbB	normal	susceptible
HbS/HbB	normal	resistant

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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Outline

Autosomal recessive genetic diseases

Screening
-Newborn
-Prenatal

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

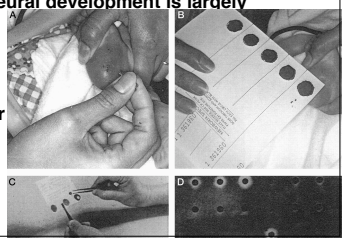
Tyrosine

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.



States decide what genetic diseases are screened in newborns

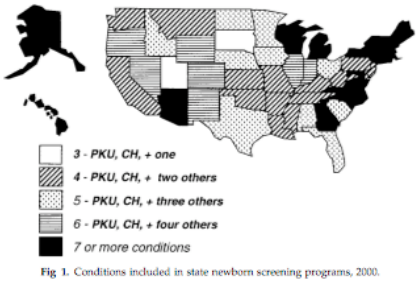


Fig 1. Conditions included in state newborn screening programs, 2000.

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

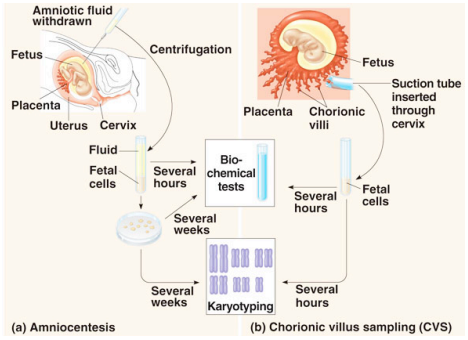
Newborn screening

Infants in all 50 states tested for PKU, sickle cell disease, congenital adrenal hyperplasia and a many others

What about prenatal testing?

Ultrasound
Chorionic villus sampling (CVS)
Amniocentesis

Amniocentesis



Amniocentesis

Aneuploidy
karyotype

Open neural tube defects
Alpha-fetoprotein & acetylcholinesterase

Genetic diseases
PCR

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.

As the genes for more genetic diseases are identified, molecular genetic approaches can be also be used to screen for many genetic diseases. In principle, 100s of genetic traits could be screened.

How many diseases?

Who should pay?

Who should get the information?