Genetics& Society
Garriga lecture notes 3/30/09

Genetic diseases and genetic screening

Genetic diseases
Human genetic diseases can be placed into several categories depending on whether the mutations are on an autosome, X chromosome or mitochondrial chromosome and on whether the disease is inherited as a recessive or dominant trait. We will focus on the three recessive autosomal diseases sickle cell disease, Tay-Sachs disease and phenylketonuria (PKU). We will discuss their pattern of inheritance, the effects of the diseases and why the frequency of sickle cell disease and Tay Sachs are prevalent in particular populations.

The diagnosis of a disease having a genetic origin starts with the analysis of a pedigree. Autosomal recessive diseases are characterized by a particular pattern of inheritance. The disease is usually expressed in the progeny resulting from matings between carriers (heterozygotes) that are unaffected. In other words most affected individuals have unaffected parents. The frequency of the disease is increased with inbreeding.

Sickle cell disease
Sickle cell disease is caused by a specific mutation in the hemoglobin A gene. Red blood cells (RBCs) or erythrocytes contain hemoglobin, and carry oxygen (O_2) from your lungs to all of the tissues of your body. The mitochondria of your cells then use the O_2 to generate energy in the form of ATP that the cell can use. As we discussed earlier, the utilization of oxygen to generate energy is caused aerobic metabolism. Aerobic metabolism generates carbon dioxide (CO_2), which the RBCs pick up and carry back to the lungs. Hemoglobin is the molecule in the RBCs that binds O_2 and CO_2.

Hemoglobin is made up of two types of proteins and a heme-iron molecule that binds O_2 and CO_2. When we are born we express two hemoglobin genes: hemoglobin A and hemoglobin B. The hemoglobin A gene encodes the hemoglobin α protein, and hemoglobin B encodes the hemoglobin β protein. These proteins assemble into a tetramer that contains two α peptides and two β peptides that bind four heme-iron complexes.

Sickle cell is caused by a specific mutation in hemoglobin B gene that changes the sixth codon from a GAG to a GTG, and this mutation results in a change of a glutamic acid to a valine in the a protein. The mutant gene is sometimes referred to as HbS to distinguish it from the normal hemoglobin B gene. (The normal situation is sometimes called HbA, which refers to adult hemogrlobin even though the mutation is in the hemoglobin B and not the hemoglobin B gene.) This change causes Hemoglobin to slightly change its structure, especially under lower oxygen tensions. This change results in an alteration of RBC shape, from round to sickle shaped. Abnormal RBCs are removed, resulting in anemia. More problematic is that sickle-shaped RBCs get stuck in capillaries, depriving tissues of oxygen and leading to cell death. This latter consequence leads to pain and organ failure.

Tay-Sachs disease
Tay Sachs is a 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 gene that encodes the enzyme hexosaminidase A. This enzyme removes fatty substances called gangliosides. When hemosaminidase A is lacking, gangliosides build up in neurons of the brain leading to the disease.

PKU
Mutations in the gene encoding phenylalanine hydroxylase cause PKU. Phenylalanine is an essential amino acid that we get in our diet. Phenylalanine is converted into another amino acid, tyrosine, by phenylalanine hydroxylase. In the absence of phenylalanine hydroxylase function, phenalanine builds up to toxic levels that can lead to mental retardation and seizures.

Gene frequencies in specific populations
1/14,000 births in the US result in PKU. This disease frequency is similar in different ethnic and racial groups. The frequencies of sickle-cell disease and Tay-Sachs disease, by contrast, differ in particular groups, For example, 10-40% of the population in regions of equatorial Africa are carriers of sickle-cell disease, whereas <1% of South Africans are carriers. Because of their African origins, 7-10% of African Americans are carriers, which is much higher than the frequency in the general population. Tay-Sachs disease is also overrepresented in a particular group. 1/25 American Ashkenazi Jews are carriers, whereas 1/300 people in the general population carry the disease allele. Why are these diseases so prevalent in a particular group? The explanation is different for the two diseases.

The reason that sickle cell disease allele is so prevalent among equatorial Africans is that being heterozygous for the allele provides protection from malaria. So individuals with that carry the mutant allele have an advantage where malaria is prevalent, and the sickle cell allele is found at high frequencies in areas where malaria is endemic. This effect is referred to as heterozygote advantage. The explanation for the high frequency of the Tay-Sachs allele in Ashkenazi Jews is different. The idea is that there was a bottleneck in the Ashkenazi Jew population, and that the Tay-Sachs allele just happened to be overrepresented when the population of this group was restricted in size. There are several genetic diseases that are overrepresented in Ashkenazi Jews, and analysis of genetic markers, for example, mtDNA differences suggests that the prevalence of these diseases can be explained by a bottleneck in the population when this group of Jews emigrated from the Middle East to Europe.

Genetic screening
Screening for genetic diseases can be done in newborns or prenatally. We will consider newborn screening first. Newborn screening is done for several genetic diseases, but the first was PKU. Before birth, the increased levels of phenylalanine produced by a PKU fetus is removed by the mother, but after birth, the levels in the baby will increase and

cause brain damage if not detected. If a baby is known to have PKU, its diet can be altered to reduce the levels of phenylalanine, and the devastating effects of PKU avoided. When babies are born, a blood sample is taken and assayed for phenylalanine. This simple procedure has eradicated the debilitating effects of PKU from the population. That same blood sample is now used to test for the sickle cell protein in babies. Although these children will still have serious health problems, early detection can help treat the disease. All fifty states now test for these and a few other traits. Because the decision of what traits are screened is determined by the state, different states can test for different genetic diseases. The development of new technologies has revolutionized newborn screening of genetic diseases. Although the testing costs money, the idea is that by reducing future health care costs through effective management of the diseases, screening reduces the cost of the diseases to society.

Genetic diseases can also be assessed before birth. Several approaches are used. Prenatal health is usually assessed using ultrasound, where the developing fetus can be imaged. This approach can identify gross anatomical problems, whether or not they are genetic in origin. As mentioned in an earlier lecture, amniocentesis can be used to look for aneuploidy. Sampling of the placenta can also be used to collect fetal tissue. This latter approach is called chorionic villus sampling (CVS). One advantage of CVS is it can be done earlier in the pregnancy. Amniocentesis, or the sampling of fetal cells from the amniotic sac, can have several applications. Like CVS, amniocentesis can be used to look at the karyotype of the fetus, or the cells can be used for biochemical or genetic tests. Unlike CVS, amniocentesis can be used to test for spina bifida. Spina bifida results from the failure of the neural tube to close during development. High levels of α fetoprotein and acetylcholine esterase in the amniotic fluid are indicative of spina bifida. While there is no cure for spina bifida, early detection can allow surgeons to try to fix the problem in the fetus.

Biochemical or genetic tests of cells obtained by CVS or amniocentesis can be used to determine whether a fetus has a genetic disease. Using a combintion of approaches there is almost no incidence of Tay-Sachs disease in the US Ashkenazi Jewish community. 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. Part of that approach was to identify fetuses that have the disease using a genetic test of fetal cells.

As the genes for more genetic diseases are identified, molecular genetic approaches can also be used to screen for many genetic diseases. In principle, 100s of genetic traits could be screened. This raises several interesting questions. Who will pay for the tests? Who will get the information? Should there be alleles that we should not be screening?