GENES AND ENZYMES

Historical: Garrod

1909: Sir Archibald Garrod, an English physician, published a book entitled "Inborn Errors of Metabolism"

One of the diseases Garrod descrobed was ALCAPTONURIA (= ALKAPTONURIA)

Alcaptonuria is inherited as a single gene defect; normals have at least one dominant allele and those affected are homozygous recessive.
LEGEND: A_ = normal
aa = affected (alcaptonuric)

Alcaptonuria is a rare disorder, but it is very easy to detect; it causes the urine to turn black when exposed to air. There are some other symptoms also; as the affected person ages there tend to be yellow deposits in the eye, and often there is a darkening and hardening of cartilage tissues, leading to an arthritis-like condition. Even so, it is not considered a very serious or threatening disease.

When urine from alcaptonurics was analyzed, it was found to contain a chemical compound that was not present in normals. This compound, homogentisic acid, (HA) is the substance that turns black when it is oxidized.

Legend: A_ = normal
aa = affected (alcaptonuric) (accumulate and excrete HA)

Garrod proposed that the reason that normals do not accumulate homogentisic acid is that they convert it to another compound called maleylacetoacetic acid, and furthermore, he suggested that the reason they could do so was that they have an enzyme that is missing in alcaptonuria.

An enzyme is a protein that catalyzes a specific chemical reaction.

A protein is a chain of amino acids, and a catalyst is a substance that causes a reaction to proceed without itself being used up or converted in the reaction.

The names of enzymes usually end in **ase** ie, RNase breaks down RNA, proteases are useful in digestion because they breakdown proteins etc. The name of the enzyme that is present in most people but lacking in alcaptonurics is homogentisic acid oxidase.

Thus we can rewrite the legend:
A_ = normal -- have HA oxidase
aa = affected (alcaptonuric) -- lack HA oxidase

In this case we see that the dominant allele corresponds to the presence of one specific enzyme and that homozygous recessive individuals lack the enzyme, directly leading to the associated phenotype.

When alcaptonurics are fed high protein diets, they excrete more HA. In particular, the levels of two of the amino acids that are present in protein, phenylalanine and tyrosine, seem to correlate to HA production.

This brings us to a much more serious disease called **phenylketonuria or PKU**

PKU is also inherited as a **single gene recessive** character. ie

PKU /_ = normal
pku/pku = affected

It is rare, only about 1 in 11,000 live births is affected in the US

In addition to excretion of phenylketones in the urine, there is a much more serious consequence of this disease. If left untreated, the average IQ of homozygous recessives will be 17!. 96% of untreated PKU patients have an IQ less than 50 and 64% have an IQ below 20. Again, the defect can be traced to the presence or absence of a single enzyme, but in this case, the enzyme is usually found only in the liver. The enzyme phenylalanine hydrolase (**Φ Hase**) is required to convert phenylalanine (phe) to tyrosine (tyr), the first step in getting rid of any excess that may be present in the blood. When excess phe accumulates, it can be converted to phenylketones spontaneously, which are then found at high levels in the urine. Whether the high levels in the blood prevent access of other essential amino acids into the developing brain cells, or intrerfere with a pyruvate kinase required for energy in developing brain cells is a point of contention. In any case, the problem develops very rapidly after birth of an affected infant. Before birth, the mother, who, at least in the past, has always been a PKU/pku heterozygote, has the enzyme and her "filtering system" keeps the level of phe at acceptable levels for normal prenatal development. There is a much higher than normal level of phe in the infants blood at birth though, and this has led to the development of a simple, accurate test which is given to all babies very soon after birth. The test is called the Guthrie test. It consists of a dried filter paper impregnated with bacteria (*B. subtilis*) and a toxic analogue of phe called beta-thienylalanine. When a drop of blood that has lots of phe is applied, the bacteria can grow; otherwise they cannot. Blood samples taken soon after birth are collected, and can be tested for a few cents each. Follow up chemical tests are also needed, since in some cases, especially for small babies, since they tend to have a high level of phe that does not persist as it will with PKU patients.

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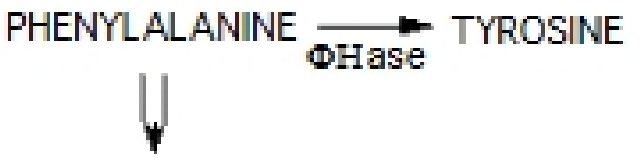

Treatment possibilities: 1) you can't feed a patient the enzyme since they will digest it, 2) you can't inject it since it will probably be recognized as a foreign protein so will induce an immune response, and 3) it needs to function specifically in the liver to be effective. 4) Dietary control of the amount of phe ingested should and does work. Some is needed, since we need Phe to make our own proteins; but if just enough can be given that little accumulates, then there will not be a problem. Of course there needs to be close monitoring, but it seems to be quite effective if the special diet is followed.

It is estimated that 2 potential IQ points are lost for every week an infant goes untreated! The treatment is usually ended by age 6-8. By then, the brain is well developed, and high levels of phenylketones do not seem to have a serious effect. Also, the diet is said to be very bland, and once the child has tasted "pizza", it is virtually impossible to go back to the diet. Some recent studies show that performance on math tests etc. probably drops a bit, but not to the drastic levels seen in untreated cases. There are now special diets for teens and adults so the levels of phe can be maintained all the way through adulthood if desired.

This cure has now been available for some time, and there are pku/pku adults who are of reproductive age. This is especially a problem for females, since they do not have the enzyme, and even if a fetus they are carrying is heterozygous, its enzyme will not function until too late. The first several cases led to death or extreme mental retardation in the infants born to these mothers. I have heard that some have been able to go back onto the diet in order to have babies in the normal range, but it does appear to be a risk and few people have the willpower to succeed.

PKU provides another example where a genetic defect can be absolutely associated with the lack of a specific enzyme in homozygous recessive individuals.

The pigment melanin is derived from tyrosine; at least two steps are required in the conversion. Lets assume that E1 and E2 are two different enzymes needed to make melanin in the pathway as shown: