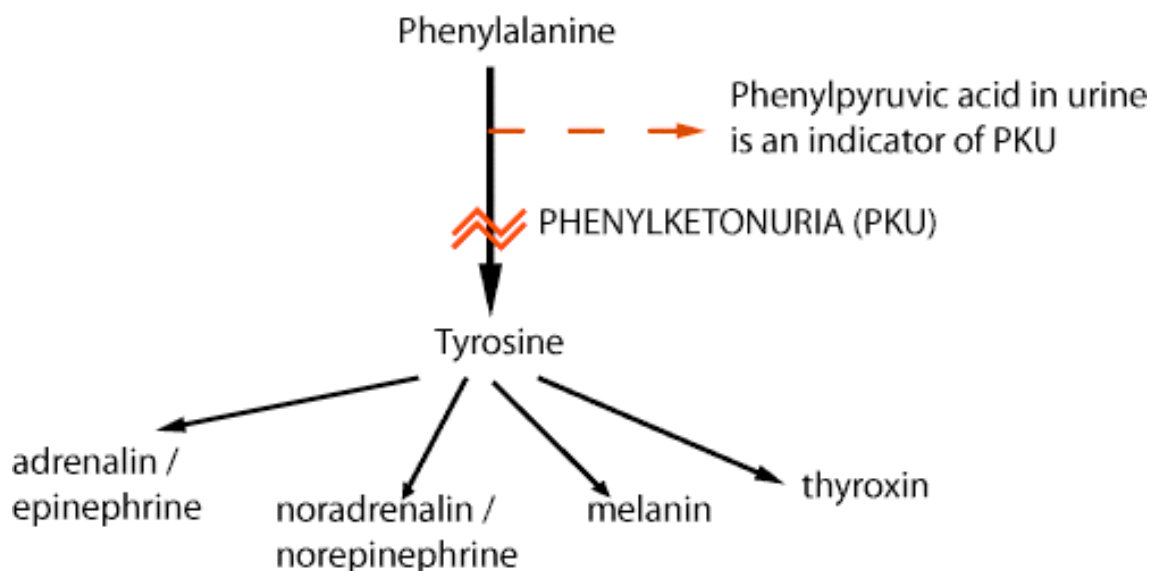


Phenylketonuria (PKU) detection

Mendelian inheritance in humans: single gene disorders, PKU as an example.

There are a number of genetic disorders in humans caused by biochemical defects known as inborn errors of metabolism. Phenylketonuria (PKU), Tay-Sachs disease, cystic fibrosis (CF), and sickle cell anemia are but a few of the hundreds of single gene disorders. These disorders result from defects in individual genes such that the recessive alleles specify inactive enzymes or other essential proteins. Individuals homozygous for the recessive allele cannot produce the normal enzyme or protein. If the product is an enzyme, the immediate result is a blockage of the metabolic pathway in which the enzyme acts, and a build up of the substrate.

Phenylketonuria provides a good example. It is a hereditary human disease that occurs in about 1 in every 15,000 births in the United States. Individuals with this disease are unable to use one particular amino acid, phenylalanine, which is present in all protein foods, and thus have extremely high concentrations of the amino acid in their blood. Normal individuals possess an enzyme that converts excess phenylalanine into tyrosine, which is then further metabolized, but victims of the disease, lacking the enzyme that catalyzes this reaction, accumulate phenylalanine in their bodies. Some of this phenylalanine is converted into phenylpyruvic acid, which accumulates in the cells of the central nervous system, damaging them and causing mental retardation within a few months after birth.



If PKU is diagnosed in the first few months of life, retardation can be prevented by using a special diet that contains a bare minimum of

phenylalanine. Most states, including New York, require a simple blood or urine screening test for PKU in newborn infants. Interestingly, because tyrosine is a precursor to the pigment melanin, children with PKU are always very blond and fair-skinned.



PKU Testing. A Guthrie test is carried out by taking blood samples to screen babies for a rare genetic disease called phenylketonuria (PKU), which affects about 1 in 16000 people. Victims of PKU suffer from a genetic disorder in which the body lacks the enzyme necessary to metabolize phenylalanine into tyrosine. This causes an accumulation of phenylalanine in their blood, which can lead to severe brain damage if not treated. Because phenylalanine is a natural product of protein digestion, babies found to suffer from the condition must be fed a special milk substitute free of phenylalanine. After weaning they are given a very low-protein diet, which they might have to stick to for life. Credit: Garo / © [Photo Researchers, Inc.](#)

Another example is Tay-Sachs disease in which the inborn error is a deficiency of the enzyme hexosaminidase A. Without this enzyme lipids are not metabolized properly and a fatty substance called ganglioside accumulates in the cells of the nervous system, leading to progressive

blindness, mental retardation, paralysis, and death, generally before the age of five. Although the incidence of this allele is low in the general U. S. population, it is considerably higher in Jews of eastern European origin (perhaps as many as one person in 30 in this population may be a carrier).

Single gene disorders show the typical Mendelian pattern of inheritance. These diseases run in families and are often diagnosed through pedigree analysis. For example, among U.S. whites about one person in 20 carries the recessive allele for cystic fibrosis. If two carriers (individuals heterozygous for cystic fibrosis) marry and have children, one-fourth of their children would be expected to have the disease. The metabolic defect in cystic fibrosis involves the lack of a particular membrane protein involved in chloride ion transport. Individuals afflicted with this disease have defective chloride ion transport, which disrupts the normal osmotic concentration of the extracellular fluids. Such individuals have excessive mucus secretions that are unusually thick and sticky, and which clog the ducts of the lungs, pancreas and other mucous secreting organs. Normal function of these organs is impaired, usually leading to death in childhood. Special physical treatments, diet, and antibiotics have enabled many such children to survive past adolescence, but treatment is, at best, palliative.

At present there are no cures for these single gene disorders and treatment, when available at all, is generally directed at alleviating the symptoms. Most inborn errors result in severe debilitating diseases that are incurable and cause much human suffering. Recombinant DNA technology may, in the future, provide the ability to replace the defective gene, but at present the best medical science can do is diagnose the condition in the fetus by amniocentesis or chorionic villi sampling (see figures below) and offer abortion as a means of preventing the birth of an afflicted child.

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