A Genetic Outlook on Phenylketonuria

Introduction
In 1934, Dr. Archibald Garrod, a British medical researcher, published a report describing a group of mentally retarded patients who had a peculiar color. It was determined that the color of the urine phenylketones and that these individuals had been suffering from a metabolic disorder known as phenylketonuria (PKU). PKU is a genetic disorder that affects the metabolism of phenylalanine.

Within 20 years of discovery, the management of PKU was understood. Through the use of diet and medication, patients with PKU could live a normal life, and the number of new cases declined significantly. However, PKU remains a significant challenge for medical professionals and families.

Phenylketonuria is a genetic disorder where the body is unable to properly metabolize the amino acid phenylalanine. When this occurs, phenylketones, which are toxic to the brain, accumulate in the blood and can cause mental retardation, seizures, and other serious health problems.

Biochemistry
Classic PKU results from a defect in the gene coding for the enzyme phenylalanine hydroxylase (PAH). PAH is an enzyme that converts phenylalanine into tyrosine, a non-essential amino acid. Without PAH, phenylalanine cannot be metabolized properly, and toxic levels build up in the body.

Phenylalanine is converted into tyrosine in the liver and other tissues. High levels of phenylalanine in the blood can lead to reduced IQ, delays in language development, and other neurological problems. Affected infants may have seizures, difficulty sleeping, or other symptoms.

Phenylketonuria is inherited in an autosomal recessive pattern, meaning that both parents must be carriers of the gene to pass it on to their children. The chance of having a child with PKU is 1 in 40,000 in the general population.

Genetic alteration of PKU locus
Many mutations have been identified in the PAH locus, including snp15, tyrosinase, tyrosine decarboxylase, dopamine, histidine decarboxylase, and other regulatory genes. There are more than 20 mutations within the gene that lead to PKU.

Phenylalanine hydroxylase (PAH)
Genetic testing is available to diagnose PKU. The PAH gene is located on chromosome 12 and is linked to various other genes associated with PKU. There are more than 20 mutations within the gene that lead to PKU.

Genetic Testing
Gene Therapy: Retrovirus Mediated Gene Transfer in Skin Cells
A group of researchers from University of California, San Diego, have used a retrovirus to transfer the PAH gene into skin cells to treat PKU. The retrovirus contains the PAH gene, which is then incorporated into the skin cells, allowing them to produce phenylalanine hydroxylase. This treatment has been successful in animal models, but more research is needed to confirm its effectiveness in humans.

Phenylalanine hydroxylase (PAH) mutation map
Fig: speck unnatural amino acid located near 48811099 in the PAH gene.

Prenatal Testing
Currently, the only way to screen for PKU is through prenatal testing. This can be done through several methods, including amniocentesis and chorionic villus sampling. These tests evaluate the enzymes involved in the metabolism of phenylalanine and can detect early signs of the disease.

Exon splicing at the q24-q24.1 of PAH base on chromosome 12. Introduction by the numbered color boxes, score the black letters separating boxes. Mutations that affect splicing of the gene are shown below the gene diagram; all shown are above the exon. The position of the black numbers in section 5.1 reflects the importance of these domain to correct protein function. Mutation map from the Pahent database.

Improving Identification
PAH-1 is a genetically identifiable test that can be done through the Nuch Test, but the Nuch Test offers weak genetic identification for skin or blood for phenylketonuria using an array of molecular genetics, including linkage and genetic mapping.

Phenylketonuria is a genetic disease that affects the metabolism of the amino acid phenylalanine. It is inherited in an autosomal recessive pattern, meaning that both parents must be carriers of the gene to pass it on to their children. The chance of having a child with PKU is 1 in 40,000 in the general population.

Fig: A, Shaffer siblings with PKU, B) cutaneous reactive cells in the fibroblasts seen in PKU.

Treatment Today
Conventional treatment for PKU is a controlled diet, but the diet is extremely restrictive and patients need to be very diligent in following it. In recent years, there has been progress in developing new treatments, including gene therapy and enzyme replacement therapy. These treatments aim to improve the quality of life for individuals with PKU.

Gene Therapy: Bone Marrow
Bone marrow is a rich source of stem cells that can be used to replace damaged cells in the body. In PKU, bone marrow stem cells are used to produce new liver cells that can carry out the function of phenylalanine hydroxylase. This treatment has been successful in animal models, but more research is needed to confirm its effectiveness in humans.

Fig: A, the bone marrow of PKU patients shows a higher number of bone marrow cells in the bone marrow of PKU patients

In the Works: Gene Therapy
Several research groups are exploring the potential of gene therapy. The geneticist looking to improve gene therapy is looking to improve gene therapy. The geneticist looking to improve gene therapy is looking to improve gene therapy. The geneticist looking to improve gene therapy is looking to improve gene therapy.

Gene therapy involves inserting a functional copy of a gene into a patient's cells. This can be done through several methods, including viral vectors and non-viral vectors. The gene is then expressed in the patient's cells, allowing them to produce the protein or enzyme that is missing.

Gene Therapy: Liver Studies
Liver cells are a promising target for gene therapy because they are easily accessible and can be widely used to produce proteins. However, there are several challenges in delivering genes to the liver, including immune responses and the lack of a stable delivery system.

Fig: A, Retrovirus-labeled PKU gene DNA into the genome of host cells, opening the possibility of directly delivering phenylalanine to mutated tissues.

Future Areas of Research
Researchers have successfully substituted a liver-damaged gene in mice, which has the potential to treat PKU. The gene was transferred into a recombinant adenovirus-infected mouse, resulting in the gradual improvement of phenylalanine metabolism in mice.

In conclusion, the development of new treatments for PKU is a promising area of research. Continued efforts to improve gene therapy and other treatments will be crucial in improving the quality of life for individuals with PKU.

Fig: A, CD34+ hematopoietic progenitor cell line isolated from the bone marrow of PKU patients.

Further Reading

More research is needed in order to fully understand the mechanisms of PKU and to develop more effective treatments.

Fig: A, A, retrovirus-labeled PKU gene DNA into the genome of host cells, opening the possibility of directly delivering phenylalanine to mutated tissues.

Non-Facial PAH gene

More research is needed in order to fully understand the mechanisms of PKU and to develop more effective treatments.