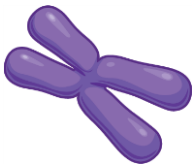
WHAT IS GENETIC DISEASE? WHAT CAUSES IT?

Everyone inherits genetic material from their mother and father.

Genetic material is encoded in 23 chromosomes inherited from each parent.



Chromosomes contain a person's DNA.

DNA makes up genes, which act as instructions to make proteins that are necessary for the body to function normally.

In a genetic disease, a **gene** is either missing or mutated, which means it lacks the instructions to make a normal protein.

Many genetic diseases are caused by mutations in a single gene. Autosomal recessive diseases are those in which someone only develops the disease if they inherit two mutated copies of a gene, one from the mother and one from the father. Examples of autosomal recessive diseases include phenylketonuria (PKU), cystic fibrosis, and sickle cell disease, among others.

In the case of PKU, the *PAH* gene writes the instructions to make phenylalanine hydroxylase (PAH) protein, which is responsible for metabolizing phenylalanine (Phe) that is contained in protein. In people with PKU, mutations in the *PAH* gene result in a loss of function of the PAH protein, which causes toxic levels of Phe to build up in the body and can cause severe neurological problems. Phe metabolism is also required for the production of tyrosine (Tyr) and neurotransmitters.

Some treatments are available to address symptoms or to slow the progression of genetic diseases, while another option is to directly address the causative gene mutations.

WHAT IS GENE EDITING?

Gene editing is designed to make a permanent correction to the genome where there is a missing or mutated gene. Gene editing via homologous recombination, the body's highly precise DNA repair mechanism, does not require DNA cutting (like other methods) and can integrate a whole functional gene into the genome.

Gene editing treatments can be made and delivered in different ways. Homologous recombination-based gene editing treatments are delivered in a single component AAV (adeno-associated virus) system.

At right is an explanation of how a potential gene editing treatment – HMI-103 - could be delivered to an adult with PKU. Currently, all potential gene therapy and gene editing treatments for PKU are investigational, and none have been approved by the FDA.

Step 1:
A patient could receive a one-time intravenous (I.V.) administration of HMI-103 consisting of functional copies of the *PAH* gene surrounded by long DNA sequences homologous to a specific location in the genome (homology arms).

Step 2:
HMI-103 is designed to target the cells in the liver, where PAH activity is required to metabolize Phe normally.

Step 3:
HMI-103 is designed to enter liver cells and deliver the functional *PAH* gene to the nucleus. Through the body's natural DNA repair process of homologous recombination, in some cells the functional *PAH* gene could integrate into the genome to the exact location where it is needed.

Step 4:
The functional *PAH* gene could then create functional PAH protein that metabolizes dietary Phe, potentially restoring the normal biochemical pathway.

This approach is being studied as a potential treatment for people with PKU.

HOMOLOGY Medicines, Inc.

Homology Medicines is developing the gene editing candidate HMI-103 for the treatment of people with PKU.