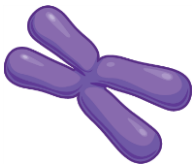
WHAT IS GENETIC DISEASE? WHAT CAUSES IT?

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, sickle cell disease, and metachromatic leukodystrophy, 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 dietary 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.

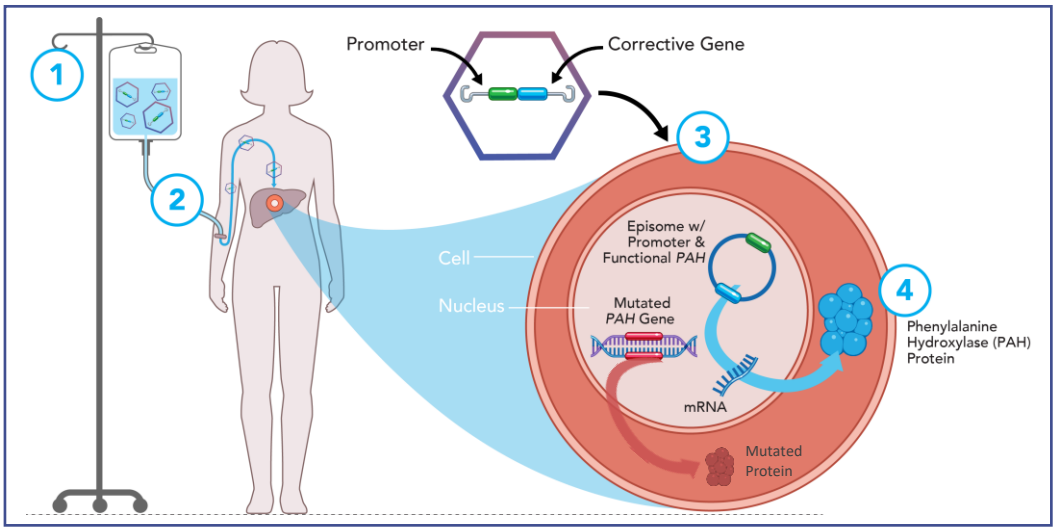
Some treatments are available to address symptoms or to slow the progression of genetic diseases, while another option is to directly address the causative gene mutations.

WHAT IS GENE THERAPY?

Gene therapy involves introducing a functional copy of a gene into a patient's cells where there is a missing or mutated gene. The functional gene exists inside the cell with a set of instructions to create the needed protein.

Gene therapies can be made in different ways. Gene therapies are most commonly delivered using an adeno-associated virus (AAV) vector, which is a virus that will not cause disease.

At right is an illustration of how a potential gene therapy could be delivered to an adult with PKU. Currently, all potential gene therapies 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 the PKU gene therapy. This could include AAV vectors with a copy of the functional *PAH* gene.

Step 2: The gene therapy could target the cells in the liver, where PAH activity is required to metabolize Phe normally.

Step 3: The gene therapy could enter the liver cell, where it would deliver the functional gene and promoter, which will help "activate" the gene.

Step 4: The functional *PAH* gene contains the instructions necessary to create functional PAH protein that metabolizes dietary Phe, potentially restoring the normal biochemical pathway.

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

HOMOLOGY Medicines, Inc.

Homology Medicines is developing the gene therapy candidate HMI-102 for the treatment of adults with PKU.