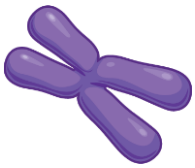
WHAT IS GENETIC DISEASE? WHAT CAUSES IT?

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. Other genetic diseases, such as mucopolysaccharidosis type II (MPS II, or Hunter syndrome), are X-linked conditions, meaning that males inherit an X chromosome with a mutated copy of the gene causing the disease.

Hunter syndrome is an X-linked lysosomal storage disorder caused by mutations in the idurnate-2-sulfatase (*IDS*) gene, which results in the inability to produce the key functional enzyme idurnate-2-sulfatase, or I2S. This leads to toxic lysosomal accumulation of glycosaminoglycans (GAGs), which causes progressive debilitation. In the severe form, Hunter syndrome causes a decline in intellectual function. Hunter syndrome occurs in approximately 1 in 100,000 to 1 in 170,000 males, and the severe form leads to life expectancy of 10 to 20 years.

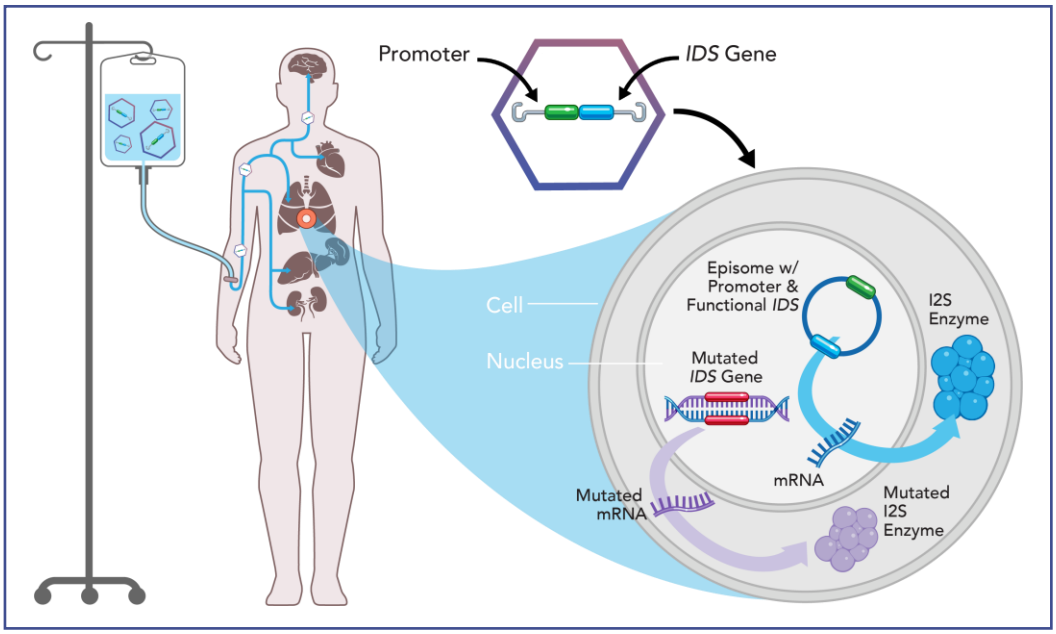
An approved treatment is available to address symptoms or to slow the progression of genetic disease. Other options, including gene therapies, are being investigated to directly address the causative gene mutations.

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 a patient with Hunter syndrome. There are no treatments available to directly address the underlying genetic defect or address both cognitive and peripheral organ manifestations.



Step 1: A patient could receive a one-time intravenous (I.V.) administration of the Hunter syndrome gene therapy.

Step 2: The gene therapy could cross the blood-brain barrier, blood-nerve barrier and reach other peripheral organs where the I2S protein is required to eliminate the build-up of GAGs.

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

Step 4: The gene therapy could result in I2S protein expression, systematic reduction in GAGs and improvements in phenotype.

HOMOLOGY Medicines, Inc.

Homology Medicines plans to initiate a Phase 1/2 dose-escalation trial in 2021 with a gene therapy candidate (HMI-203) for Hunter syndrome.