GNE gene

glucosamine (UDP-N-acetyl)-2-epimerase/N-acetylmannosamine kinase

Normal Function

The *GNE* gene provides instructions for making an enzyme that is found in cells and tissues throughout the body. This enzyme plays a key role in a chemical pathway that produces sialic acid, which is a simple sugar that attaches to the ends of more complex molecules on the surface of cells. By modifying these molecules, sialic acid influences a wide variety of cellular functions, including cell movement (migration), the attachment of cells to one another (adhesion), signaling between cells, and inflammation.

The enzyme produced from the *GNE* gene is responsible for two steps in the formation of sialic acid. It first converts a molecule known as UDP-GlcNAc (UDP-N-acetylglucosamine) to a similar molecule called ManNAc (N-acetylmannosamine). In the next step, the enzyme transfers a cluster of oxygen and phosphorus atoms (a phosphate group) to ManNAc to create ManNAc-6-phosphate. Other enzymes then convert ManNAc-6-phosphate to sialic acid.

Health Conditions Related to Genetic Changes

GNE myopathy

Variants (also called mutations) in the *GNE* gene can cause *GNE* myopathy, a condition that leads to progressive muscle weakness in adults. Many different variants in the gene have been found in people with *GNE* myopathy. Most of these variants change single protein building blocks (amino acids) in several regions of the enzyme. A few variants delete a piece of the enzyme or otherwise alter its structure.

Different *GNE* variants cause *GNE* myopathy in different populations. One variant is more frequent in people of Iranian Jewish heritage; this genetic change replaces the amino acid methionine with the amino acid threonine at position 743 in a region of the enzyme known as the kinase domain (written as Met743Thr or M743T). In the Japanese population, there are three common *GNE* variants that affect amino acids 44, 207, and 603 (written as C44S, D207V, and V603L).

The variants responsible for *GNE* myopathy reduce the activity of the enzyme produced from the *GNE* gene, which decreases the production of sialic acid. As a result, less of this simple sugar is available to attach to molecules on the cell surface. Researchers

are working to determine how a shortage of sialic acid leads to progressive muscle weakness in people with *GNE* myopathy. Sialic acid is important for the normal function of many different cells and tissues, so it is unclear why the signs and symptoms of this disorder appear to be limited to skeletal muscles.

Sialuria

Several variants in the *GNE* gene have been found to cause sialuria. Each of these variants changes a single amino acid in a region of the enzyme known as the allosteric site. This region is critical for the normal regulation of the enzyme.

A feedback system helps control the amount of sialic acid produced in cells. This system shuts off the enzyme produced from the *GNE* gene when no more sialic acid is needed. Variants in the allosteric site can disrupt this feedback mechanism, resulting in an overproduction of sialic acid. This simple sugar builds up within cells and is excreted in urine. Researchers are working to determine how an accumulation of sialic acid in the body interferes with normal development in people with sialuria.

Other Disorders

Some people with *GNE* variants have been found to have a lower number of platelets (thrombocytopenia), a condition called *GNE*-related thrombocytopenia. When variants in the *GNE* gene reduce the function of the enzyme produced by the *GNE* gene, platelets have less sialic acid. This lack of sialic acid causes the liver to remove platelets from the blood more quickly, resulting in a lower number of platelets.

A lower number of platelets may cause bleeding issues in people with *GNE*-related thrombocytopenia. Muscle weakness (myopathy) has also been reported in some individuals.

Other Names for This Gene

- Bifunctional UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase
- DMRV
- GLCNE
- IBM2
- Uae1
- UDP-GlcNAc-2-epimerase/ManAc kinase
- UDP-N-acetylglucosamine 2-epimerase/N-acetylmannosamine kinase

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of GNE (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=10020[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28%28GNE%5BTIAB%5D%29+OR+%28glucosamine-2-epimerase%5BTIAB%5D%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- UDP-N-ACETYLGLUCOSAMINE 2-EPIMERASE/N-ACETYLMANNOSAMINE KINASE; GNE (https://omim.org/entry/603824)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/10020)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=GNE[gene])

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Genomic Location

The *GNE* gene is found on chromosome 9 (https://medlineplus.gov/genetics/chromosome/9/).

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