PIGA gene

phosphatidylinositol glycan anchor biosynthesis class A

Normal Function

The *PIGA* gene provides instructions for making a protein called phosphatidylinositol glycan class A (shortened to PIG-A). The PIG-A protein takes part in a series of steps that produce a molecule called glycophosphatidylinositol (GPI) anchor. Specifically, the PIG-A protein is one piece of a group of proteins (a complex) that performs the first step of the series, which produces an intermediate molecule called N-acetylglucosaminyl phosphatidylinositol, or GlcNAc-PI.

The GPI anchor, the ultimate product of the series of steps, attaches many different proteins to the cell membrane. These proteins are known as GPI-anchored proteins. Anchored proteins have a variety of roles, including sticking cells to one another, relaying signals into cells, and protecting cells from destruction.

Health Conditions Related to Genetic Changes

Paroxysmal nocturnal hemoglobinuria

Variants (also known as mutations) in the *PIGA* gene cause a condition called paroxysmal nocturnal hemoglobinuria (PNH). People with this condition have episodes of blood in the urine (hemoglobinuria) that results from the breakdown of red blood cells. A tendency to develop blood clots (thrombosis) and other blood-cell abnormalities also occur in this condition.

In people with PNH, variants of the *PIGA* gene occur during a person's lifetime and are present only in certain cells. These changes, which are called somatic variants, are not inherited. For the condition to develop, one or more somatic *PIGA* gene variants occur in blood-forming cells called hematopoietic stem cells. Hematopoietic stem cells produce red blood cells, which carry oxygen; white blood cells, which protect the body from infections; and platelets, which are involved in blood clotting. As the abnormal hematopoietic stem cells multiply, populations of abnormal blood cells are formed, alongside normal blood cells produced by normal hematopoietic stem cells that do not have the genetic alteration. The proportion of abnormal blood cells in the body affects the severity of the signs and symptoms of PNH.

Some of the *PIGA* gene variants alter the numbers or types of protein building blocks (

amino acids) in the PIG-A protein, impairing its function. Other variants result in the insertion of a premature stop signal in the genetic instructions for making PIG-A. As a result, an abnormally small protein, which is usually unstable and easily broken down, is produced. A single variant in the *PIGA* gene can severely reduce or eliminate the function of PIG-A, because people have only one active copy of the *PIGA* gene in each cell. (The *PIGA* gene is located on the X-chromosome. Males have only one X chromosome. In females, who have two X chromosomes, a normal process called X-inactivation turns off one copy of the X chromosome, so that females also have only one active copy of the X chromosome in each body cell.)

Cells with little or no functional PIG-A protein do not produce GPI anchors, and therefore are missing GPI-anchored proteins at the surface. Two important GPI-anchored proteins normally found on the surface of red blood cells protect them from being broken down during immune reactions. Without these proteins, the abnormal red blood cells are prematurely destroyed, leading to hemoglobinuria and other features of PNH. It is unclear how changes in the *PIGA* gene affect other types of blood cells.

Other disorders

Inherited (germline) variants in the *PIGA* gene can cause a disorder called PIGA deficiency, which refers to a spectrum of conditions with varied features and severity. Severely affected individuals typically have profound intellectual disability, seizures known as infantile spasms, weak muscle tone (hypotonia), distinctive facial features, and abnormalities of the brain and spinal cord (central nervous system) and other body systems. Less severely affected individuals have mild to moderate intellectual disability, infantile spasms, and other seizures that can typically be treated.

Germline variants are present in every cell of the body (in contrast to somatic variants that cause PNH [described above], which are only found in certain cells). Variants in the *PIGA* gene that cause PIGA deficiency reduce the function of the PIG-A protein in cells. Studies suggest that the amount of remaining PIG-A function determines the severity of the condition: very little PIG-A function causes more severe signs and symptoms. The changes reduce the number of GPI-anchored proteins, possibly on some cells but not others. Researchers suspect that a shortage (deficiency) of PIG-A function impairs the activity of cell structures called mitochondria, which are the energy-producing centers of cells, although the mechanism is not clear. Researchers are still determining how *PIGA* gene variants lead to the features of PIGA deficiency.

Simpson-Golabi-Behmel syndrome

MedlinePlus Genetics provides information about Simpson-Golabi-Behmel syndrome

Other Names for This Gene

- GLCNAC-PI synthesis protein
- GPI anchor biosynthesis
- GPI3

- phosphatidylinositol glycan anchor biosynthesis, class A
- phosphatidylinositol glycan anchor biosynthesis, class A (paroxysmal nocturnal hemoglobinuria)
- phosphatidylinositol glycan, class A (paroxysmal nocturnal hemoglobinuria)
- phosphatidylinositol N-acetylglucosaminyltransferase subunit A
- phosphatidylinositol-glycan biosynthesis, class A protein
- PIG-A
- PIGA_HUMAN

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of PIGA (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=5277[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28PIGA%5BTIAB%5D%29+OR+%28%28GPI3%5BTIAB%5D%29+OR+%28PIG-A%5BTIAB%5D%29+OR+%28GPI+anchor+biosynthesis%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+1440+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- PHOSPHATIDYLINOSITOL GLYCAN ANCHOR BIOSYNTHESIS CLASS A PROTEIN; PIGA (https://omim.org/entry/311770)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/5277)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=PIGA[gene])

References

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Genomic Location

The *PIGA* gene is found on the X chromosome (https://medlineplus.gov/genetics/chromosome/x/).

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