IFIH1 gene

interferon induced with helicase C domain 1

Normal Function

The *IFIH1* gene provides instructions for making the MDA5 protein, which plays an important role in innate immunity, the body's early, nonspecific response to foreign invaders (pathogens) such as viruses and bacteria. In particular, the MDA5 protein recognizes a molecule called double-stranded RNA (a chemical cousin of DNA), which certain viruses, including rhinovirus (the virus that causes the common cold), respiratory syncytial virus (RSV), and the influenza (flu) virus, have as their genetic material or produce when they infect cells and copy (replicate) themselves. (Another subset of viruses has DNA as the genetic material.)

When pieces of viral RNA are present inside a cell, multiple MDA5 proteins attach to it, one after another, forming a filament. Filament formation stimulates signals that turn on the production of immune system proteins called interferons. Interferons control the activity of genes that help block the viruses from replicating themselves and stimulate the activity of certain immune system cells to fight infection. Interferons also help regulate inflammation, which is another part of the body's innate immune response.

Health Conditions Related to Genetic Changes

Aicardi-Goutières syndrome

At least 12 *IFIH1* gene mutations have been found in people with Aicardi-Goutières syndrome. This disorder is characterized by abnormalities of the immune system, skin, and brain, including calcium deposits in parts of the brain.

The *IFIH1* gene mutations involved in Aicardi-Goutières syndrome are described as " gain-of-function" because they lead to production of an MDA5 protein with enhanced activity. The altered protein may more readily attach to RNA, even pieces of RNA that are not from viruses, or to other MDA5 proteins to form filaments. Alternatively, filaments containing the altered protein may not be broken down when immune signaling is no longer needed. As a result of these changes, interferon production is abnormally turned on, leading to excessive immune system activity and inflammation.

Constant inflammation is thought to disrupt the way calcium is handled in the body, leading to calcium deposits in people with Aicardi-Goutières syndrome. Excessive

inflammation is also thought to damage cells in the brain and skin, leading to the abnormalities in these tissues characteristic of this disorder.

MDA5 deficiency

At least four genetic changes in the *IFIH1* gene have been found to cause MDA5 deficiency, an immune system disorder (immunodeficiency) that leads to recurrent, severe viral infections in the lungs and airways (respiratory tract). Infections are most commonly caused by rhinovirus, RSV, and the flu virus. The changes in the *IFIH1* gene that cause this condition are described as "loss-of-function" mutations because they lead to an altered version of the MDA5 protein that cannot function. Studies suggest that the altered protein is unable to attach to viral RNA or to other MDA5 proteins to form filaments. As a result, interferon production is not turned on. A lack of the important early immune response stimulated by interferons leads to severe viral infections in infants with MDA5 deficiency.

Other disorders

IFIH1 gene mutations have also been found to cause Singleton-Merten syndrome. A feature of Singleton-Merten syndrome is calcium deposits in the large vessel that carries blood from the heart to the rest of the body (the aorta) and in certain valves in the heart. Other signs and symptoms include tooth abnormalities, low bone density (osteopenia), and other bone problems. Some people with *IFIH1* gene mutations have signs and symptoms of both Singleton-Merten syndrome and Aicardi-Goutières syndrome (described above), suggesting that these two conditions may be part of a spectrum caused by *IFIH1* gene mutations.

As in Aicardi-Goutières syndrome, the *IFIH1* gene mutations involved in Singleton-Merten syndrome are described as "gain-of-function" and lead to excessive immune system activity and inflammation, disrupting calcium handling in the body. It is unclear why people with gain-of-function mutations in the *IFIH1* gene develop signs and symptoms of one condition or the other.

Singleton-Merten syndrome and Aicardi-Goutières syndrome both have autoimmune features, which occur when the immune system malfunctions and damages the body's own tissues and organs. Common variations (polymorphisms) in the *IFIH1* gene have been associated with other autoimmune disorders. It is thought that polymorphisms that enhance the activity of the MDA5 protein increase the risk of certain autoimmune disorders, while polymorphisms that reduce the activity of the MDA5 protein help protect against others.

Other Names for This Gene

- AGS7
- CADM-140 autoantigen
- clinically amyopathic dermatomyositis autoantigen 140 kDa
- DEAD/H (Asp-Glu-Ala-Asp/His) box polypeptide

- helicard
- helicase with 2 CARD domains
- Hlcd
- IDDM19
- interferon-induced helicase C domain-containing protein 1
- MDA-5
- MDA5
- melanoma differentiation-associated gene 5
- melanoma differentiation-associated protein 5
- murabutide down-regulated protein
- RIG-I-like receptor 2
- RLR-2
- RNA helicase-DEAD box protein 116
- SGMRT1

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of IFIH1 (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=64135[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28%28IFIH1%5BTIAB%5D%29+OR+%28interferon+induced+with+helicase+C+domain+1%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+1080+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- SINGLETON-MERTEN SYNDROME 1; SGMRT1 (https://omim.org/entry/182250)
- INTERFERON-INDUCED HELICASE C DOMAIN-CONTAINING PROTEIN 1; IFIH1 (https://omim.org/entry/606951)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/64135)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=IFIH1[gene])

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Genomic Location

The *IFIH1* gene is found on chromosome 2 (https://medlineplus.gov/genetics/chromosome/2/).

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