STAT1 Gene

Subjects: Genetics & Heredity
Contributor: Rui Liu

Signal transducer and activator of transcription 1: The STAT1 gene provides instructions for making a protein that is involved in multiple immune system functions, including the body's defense against a fungus called Candida.

Keywords: genes

1. Normal Function

The *STAT1* gene provides instructions for making a protein that is involved in multiple immune system functions, including the body's defense against a fungus called *Candida*. When the immune system recognizes *Candida*, it generates cells called Th17 cells. These cells produce signaling molecules (cytokines) called the interleukin-17 (IL-17) family as part of an immune process called the IL-17 pathway. The IL-17 pathway creates inflammation, sending other cytokines and white blood cells that fight foreign invaders and promote tissue repair. In addition, the IL-17 pathway promotes the production of certain antimicrobial protein segments (peptides) that control growth of *Candida* on the surface of mucous membranes.

The STAT1 protein helps keep the immune system in balance by controlling the IL-17 pathway. When the STAT1 protein is turned on (activated), it blocks (inhibits) this pathway.

In contrast to its inhibitory role in the IL-17 pathway, the STAT1 protein helps promote other immune processes called the interferon-alpha/beta (IFNA/B) and interferon-gamma (IFNG) signaling pathways. The IFNA/B pathway is important in defense against viruses, and the IFNG pathway helps fight a type of bacteria called mycobacteria, which includes the bacterium that causes tuberculosis.

2. Health Conditions Related to Genetic Changes

2.1. Familial candidiasis

At least 35 *STAT1* gene mutations have been identified in people with familial candidiasis, an inherited tendency to develop infections caused by the *Candida* fungus (commonly called yeast infections). Most people with familial candidiasis have chronic infections of the skin, nails, and mucous membranes such as the lining of the mouth, collectively called chronic mucocutaneous candidiasis, beginning in early childhood. Some people with *STAT1* gene mutations have additional features such as increased susceptibility to other infections and an increased risk of autoimmune disorders, in which the immune system attacks the body's own tissues or organs. This combination of signs and symptoms caused by *STAT1* gene mutations is sometimes called immunodeficiency 31C.

The *STAT1* gene mutations that have been identified in people with familial candidiasis are described as "gain of function" because they increase the amount of activated STAT1 protein in cells. By increasing STAT1's inhibitory effect on the IL-17 pathway, the mutations impair the body's ability to fight *Candida* and result in the chronic infection that occurs in familial candidiasis. The effects of the increase in activated STAT1 protein on other signaling pathways are thought to underlie the variety of features that can occur in immunodeficiency 31C, but the specific mechanisms are not well understood.

2.2. Other disorders

STAT1 gene mutations can also cause other immune system problems called immunodeficiency 31A and immunodeficiency 31B. In contrast with the gain-of-function mutations associated with familial candidiasis (described above), these *STAT1* gene mutations are described as "loss-of-function" mutations because they impair or eliminate the protein's normal action. The *STAT1* gene mutations that cause immunodeficiency 31A impair the STAT1 protein's function in the IFNG pathway, resulting in an increased susceptibility to mycobacteria. In the more severe disorder

immunodeficiency 31B, the *STAT1* gene mutations impair both the IFNG pathway and the IFNA/B pathway, resulting in susceptibility to both viral infections such as herpes simplex and viral encephalitis, and mycobacterial infections such as tuberculosis.

3. Other Names for This Gene

- IMD31A
- IMD31B
- IMD31C
- ISGF-3
- signal transducer and activator of transcription 1, 91kDa
- signal transducer and activator of transcription-1
- STAT91
- transcription factor ISGF-3 components p91/p84

References

1. Boisson-Dupuis S, Kong XF, Okada S, Cypowyj S, Puel A, Abel L, Casanova JL.Inborn errors of human STAT1: allelic heterogeneity governs the diversity ofimmunological and infectious phenotypes. Curr Opin Immunol. 2012Aug;24(4):364-78. doi: 10.1016/j.coi.2012.04.011.
2. Depner M, Fuchs S, Raabe J, Frede N, Glocker C, Doffinger R, Gkrania-KlotsasE, Kumararatne D, Atkinson TP, Schroeder HW Jr, Niehues T, Dückers G,Stray-Pedersen A, Baumann U, Schmidt R, Franco JL, Orrego J, Ben-Shoshan M,McCusker C, Jacob CM, Carneiro-Sampaio M, Devlin LA, Edgar JD, Henderson P,Russell RK, Skytte AB, Seneviratne SL, Wanders J, Stauss H, Meyts I, Moens L,Jesenak M, Kobbe R, Borte S, Borte M, Wright DA, Hagin D, Torgerson TR,Grimbacher B. The Extended Clinical Phenotype of 26 Patients with ChronicMucocutaneous Candidiasis due to Gain-of-Function Mutations in STAT1. J ClinImmunol. 2016 Jan;36(1):73-84. doi: 10.1007/s10875-015-0214-9.
3. Liu L, Okada S, Kong XF, Kreins AY, Cypowyj S, Abhyankar A, Toubiana J, ItanY, Audry M, Nitschke P, Masson C, Toth B, Flatot J, Migaud M, Chrabieh M,Kochetkov T, Bolze A, Borghesi A, Toulon A, Hiller J, Eyerich S, Eyerich K,Gulácsy V, Chernyshova L, Chernyshov V, Bondarenko A, Grimaldo RM,Blancas-Galicia L, Beas IM, Roesler J, Magdorf K, Engelhard D, Thumerelle C,Burgel PR, Hoernes M, Drexel B, Seger R, Kusuma T, Jansson AF,Sawalle-Belohradsky J, Belohradsky B, Jouanguy E, Bustamante J, Bué M, Karin N,Wildbaum G, Bodemer C, Lortholary O, Fischer A, Blanche S, Al-Muhsen S,Reichenbach J, Kobayashi M, Rosales FE, Lozano CT, Kilic SS, Oleastro M, Etzioni A, Traidl-Hoffmann C, Renner ED, Abel L, Picard C, Maródi L, Boisson-Dupuis S,Puel A, Casanova JL. Gain-of-function human STAT1 mutations impair IL-17 immunityand underlie chronic mucocutaneous candidiasis. J Exp Med. 2011 Aug1;208(8):1635-48. doi: 10.1084/jem.20110958.
4. Mizoguchi Y, Tsumura M, Okada S, Hirata O, Minegishi S, Imai K, Hyakuna N,Muramatsu H, Kojima S, Ozaki Y, Imai T, Takeda S, Okazaki T, Ito T, Yasunaga S,Takihara Y, Bryant VL, Kong XF, Cypowyj S, Boisson-Dupuis S, Puel A, Casanova JL,Morio T, Kobayashi M. Simple diagnosis of STAT1 gain-of-function alleles inpatients with chronic mucocutaneous candidiasis. J Leukoc Biol. 2014Apr;95(4):667-76. doi: 10.1189/jlb.0513250.
5. Smeekens SP, van de Veerdonk FL, Kullberg BJ, Netea MG. Genetic susceptibilityto Candida infections. EMBO Mol Med. 2013 Jun;5(6):805-13. doi:10.1002/emmm.201201678.
6. Soltész B, Tóth B, Shabashova N, Bondarenko A, Okada S, Cypowyj S, AbhyankarA, Csorba G, Taskó S, Sarkadi AK, Méhes L, Rozsíval P, Neumann D, Chernyshova L, Tulassay Z, Puel A, Casanova JL, Sediva A, Litzman J, Maródi L. New and recurrentgain-of-function STAT1 mutations in patients with chronic mucocutaneouscandidiasis from Eastern and Central Europe. J Med Genet. 2013 Sep;50(9):567-78. doi: 10.1136/jmedgenet-2013-101570.
7. Toubiana J, Okada S, Hiller J, Oleastro M, Lagos Gomez M, Aldave Becerra JC,Ouachée-Chardin M, Fouyssac F, Girisha KM, Etzioni A, Van Montfrans J, Camcioglu Y, Kerns LA, Belohradsky B, Blanche S, Bousfiha A, Rodriguez-Gallego C, Meyts I, Kisand K, Reichenbach J, Renner ED, Rosenzweig S, Grimbacher B, van de VeerdonkFL, Traidl-Hoffmann C, Picard C, Marodi L, Morio T, Kobayashi M, Lilic D, Milner JD, Holland S, Casanova JL, Puel A; International STAT1 Gain-of-Function StudyGroup. Heterozygous STAT1 gain-of-function mutations underlie an unexpectedlybroad clinical phenotype. Blood. 2016 Jun 23;127(25):3154-64. doi:10.1182/blood-2015-11-679902.

8. Yamazaki Y, Yamada M, Kawai T, Morio T, Onodera M, Ueki M, Watanabe N, Takada H, Takezaki S, Chida N, Kobayashi I, Ariga T. Two novel gain-of-functionmutations of STAT1 responsible for chronic mucocutaneous candidiasis disease:impaired production of IL-17A and IL-22, and the presence of anti-IL-17Fautoantibody. J Immunol. 2014 Nov 15;193(10):4880-7. doi:10.4049/jimmunol.1401467.
