

Letter to the Editor

Exome sequencing reveals a signal transducer and activator of transcription 1 (*STAT1*) mutation in a child with recalcitrant cutaneous fusariosis

To the Editor:

Fusarium species are saprophytic organisms that are widely distributed in soil and plants. They can cause superficial, invasive, or disseminated fusariosis in immunocompromised and immunocompetent subjects.¹ Cutaneous fusariosis is characterized by papulopustular lesions with abscesses, ulcerations, and even necrosis. Most immunocompetent patients with cutaneous fusariosis respond well to antifungal therapy.²

Here we report the case of a 7-year-old girl with cutaneous fusariosis recalcitrant to therapy. Using exome sequencing for this patient, we identified a *de novo* missense mutation in the signal transducer and activator of transcription 1 (*STAT1*) gene, the mutation of which was previously known to cause autosomal dominant chronic mucocutaneous candidiasis (CMC).³

A 7-year-old Han Chinese girl presented with progressive red verrucous plaques and nodules with ulcerations, exudates, and coarse crusts predominating on her nose, cheeks, right hand, and the inner side of her right knee for more than 6 years (Fig 1, A and B). The lesions were first noticed around her right knee and cheeks after she fell on the floor when she was 11 months old and then involved her right hand 3 years later without traumatic injury.

The patient was of full-term normal delivery, with nonconsanguineous marriage of her parents. Family history revealed no members with relevant fungal infectious diseases or immunodeficiencies. She had mild malnutrition and developed normal intelligence. The results of all laboratory examinations, including complete blood count, lymphocyte subsets, serum immunoglobulin levels, and serum complement levels, were normal. Histopathology of the lesions revealed mixed inflammatory cells infiltrating throughout the dermis. Numerous branching hyphae were noted in the stratum corneum with periodic acid–Schiff staining (Fig 1, C). *Fusarium solani* was isolated from the tissue cultures and identified based on morphologic features (Fig 1, D), and this was further supported by internal transcribed spacer region nucleotide sequencing. On the basis of all the above findings, we made a diagnosis of cutaneous fusariosis caused by *F solani*.

The patient had received different systemic antifungal treatments in the past 5 years, including fluconazol, itraconazole and terbinafine, amphotericin B, and voriconazole. In addition, intramuscular injection of thymopentin, topical antifungal agents, and local heat therapy were also applied since 1.5 years ago, but the lesions were extremely intractable with slow progression.

Because of the early onset of the disease and the resistance to antifungal treatment, a genetic defect concerning immune response to fungal infections was hypothesized. Written informed consent was obtained from the parents for molecular genetic studies according to the rules from the Clinical Research Ethics Committee of the Peking University First Hospital.

We applied a genome-wide approach and sequenced the exome of the patient (Beijing Genomic Institute, Shenzhen, China). Exome capture was carried out with the SureSelect Human All

Exon Kit (Agilent, Santa Clara, Calif), according to the manufacturer's protocols, and then sequenced with the HiSeq2000 platform (Illumina, San Diego, Calif). Single nucleotide variations of the patient were filtered by using the dbSNP134, 1000 Genomes Project, and HapMap8 databases, with 1006 variants left, involving 772 genes. When we compared the data with all the genes reported to be related to fungal infections (see Table E1 in this article's Online Repository at www.jacionline.org),⁴ only 1 heterozygous missense mutation c.604A>G (p.M202V) in the *STAT1* gene was noted. Sanger sequencing confirmed the *STAT1* mutation in the patient. The same variation was not found in her parents, which indicated a *de novo* mutation (see Fig E1 in this article's Online Repository at www.jacionline.org). This mutation was not detected in 200 ethnically matched healthy control subjects, and the parentage of the patient-parent trio was confirmed by using a panel of microsatellite markers. On the basis of the rarity of *de novo* mutations (<1 per exome)⁵ and the previous report of c.604A>G mutation in 3 cases of CMC from 2 kindreds,³ this variant was most likely to be the genetic defect underlying the fusariosis in this patient.

STAT1, one of the 7 transcription factors of the STAT family and major signaling components of interferon responses, is activated by tyrosine phosphorylation when interferons bind to their receptors.⁶ By forming a dimer, *STAT1* enters the nucleus and triggers the transcription of its targets, which plays a pivotal role in the defense against pathogens. Different types of *STAT1* mutations underlie different sets of infectious diseases, including complete or partial *STAT1* deficiency with autosomal recessive inheritance in life-threatening or milder intracellular bacterial and viral diseases, autosomal dominant *STAT1* deficiency in Mendelian susceptibility to mycobacterial disease, and autosomal dominant gain of *STAT1* activity in patients with CMC and autoimmunity.⁷ Heterozygous missense mutations in the coiled-coil domain of *STAT1* were first reported in 14 patients with autosomal dominant CMC from 5 families by van de Veerdonk et al,⁸ who subsequently reported 2 other families with CMC harboring known mutations in a latter publication.⁹ They demonstrated that patients had deficiencies in mounting T_H1 and T_H17 responses because of defective IL-12 receptor and IL-23 receptor signaling pathways.

Liu et al³ reported 12 different heterozygous *STAT1* coiled-coil domain missense mutations, including p.M202V, in 47 patients from 20 families with autosomal dominant CMC. All the mutations were shown to be gain-of-function mutations, because of a gain of phosphorylation and a loss of nuclear dephosphorylation. The study found a profound defect in the development of IL-17–producing T cells *ex vivo* and *in vitro*. Our patient had some clinical features similar to the patients with CMC, including opportunistic cutaneous fungal infection since infancy and slowly progressive lesions with unsatisfactory therapeutic effect.

On the basis of all these studies and findings, it is conceivable that the mutant *STAT1* might also function in a dominant-positive manner to predispose our patient to cutaneous fusariosis. It is intriguing that no *Candida* species infection was experienced in our patient despite its ubiquity in human epithelium, which implicates, in addition to genetic predisposition, that other factors might also be involved in the pathogenic mechanisms. To the best of our knowledge, this is the first report of cutaneous fungal

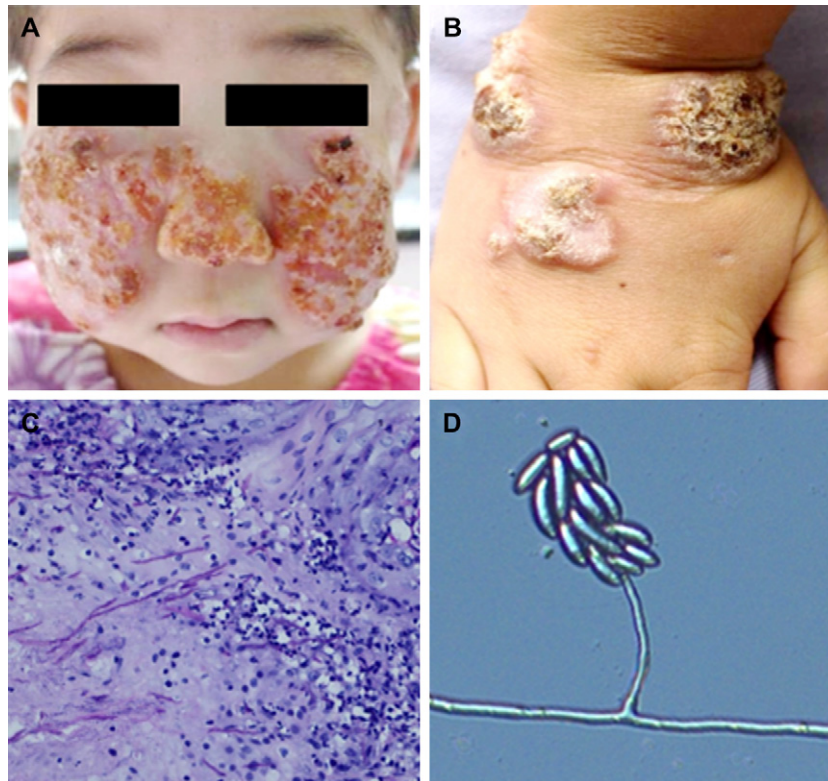


FIG 1. **A** and **B**, Clinical features of the patient: red verrucous plaques on the nose, cheeks, and right hand. **C**, Skin biopsy specimen showing numerous branching hyphae in the stratum corneum (periodic acid-Schiff; original magnification $\times 400$). **D**, Microscopic appearance. Slide culture reveals septate hyaline branching hyphae and fusoid macroconidia (potato dextrose agar, 14 days at 28°C, original magnification $\times 1000$).

infections other than candidiasis related to *STAT1* mutation. Our findings open new doors to understanding genetic predispositions to refractory, early-onset, cutaneous fungal infections.

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9. Smeekens SP, Plantinga TS, van de Veerdonk FL, Heinhuis B, Hoischen A, Joosten LA, et al. *STAT1* hyperphosphorylation and defective IL12R/IL23R signaling underlie defective immunity in autosomal dominant chronic mucocutaneous candidiasis. *PLoS One* 2011;6:e29248.

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Table E1. Variants associated with susceptibility to fungal infections and diseases

Gene	SNPs or haplotypes	Effect	Disease	References
CARD9	Q295X	Low numbers of TH17 cells	AR- CMC	[1] Glocker EO, Hennigs A, Nabavi M, Schaffer AA, Woellner C, Salzer U, et al. A homozygous CARD9 mutation in a family with susceptibility to fungal infections. N Engl J Med 2009;361:1727-35.
STAT1	R274W	Gain of function, impair the nuclear dephosphorylation of activated STAT1	AD-CMC	[2] Liu L, Okada S, Kong XF, Kreins AY, Cypowyj S, Abhyankar A, et al. Gain-of-function human STAT1 mutations impair IL-17 immunity and underlie chronic mucocutaneous candidiasis. J Exp Med 2011;208:1635-48. [3] Smeekeens SP, Plantinga TS, van de Veerdonk FL, Heinhuis B, Hoischen A, Joosten LA, et al. STAT1 hyperphosphorylation and defective IL12R/IL23R signaling underlie defective immunity in autosomal dominant chronic mucocutaneous candidiasis. PLoS One 2011;6:e29248. [4] van de Veerdonk FL, Plantinga TS, Hoischen A, Smeekeens SP, Joosten LA, Gilissen C, et al. STAT1 mutations in autosomal dominant chronic mucocutaneous candidiasis. N Engl J Med 2011;365:54-61.
	M202V			
	R274Q			
	K286I			
	C174R			
	D165G			
	T288A			
	Y170N			
	D165H			
	M202I			
	A267V			
	Q271P			
STAT3	R382W etc.	failure to mount a TH17 cell response	AD-Hyper-IgE syndrome(oral and mucocutaneous candidiasis)	[5] Minegishi Y, Saito M, Tsuchiya S, Tsuge I, Takada H, Hara T, et al. Dominant-negative mutations in the DNA-binding domain of STAT3 cause hyper-IgE syndrome. Nature 2007;448:1058-62. [6] Holland SM, DeLeo FR, Elloumi HZ, Hsu AP, Uzel G, Brodsky N, et al. STAT3 mutations in the hyper-IgE syndrome. N Engl J Med 2007;357:1608-19. [7] Ma CS, Chew GY, Simpson N, Priyadarshi A, Wong M, Grimbacher B, et al. Deficiency of Th17 cells in hyper IgE syndrome due to mutations in STAT3. J Exp Med 2008;205:1551-7.

IL17F	S65L	inborn errors of IL-17 immunity	AD-CMC	[8] Puel A, Cypowyj S, Bustamante J, Wright JF, Liu L, Lim HK, et al. Chronic mucocutaneous candidiasis in humans with inborn errors of interleukin-17 immunity. Science 2011;332:65-8.
IL17RA	Q284X		AR-CMC	
AIRE	R257X etc.	autoreactive T cells that initiate autoimmunity	APECED(triad of adrenocortical insufficiency, hypoparathyroidism, CMC)	[9] Nagamine K, Peterson P, Scott HS, Kudoh J, Minoshima S, Heino M, et al. Positional cloning of the APECED gene. Nat Genet 1997;17:393-8.
DECTIN1	Y238X	decreased cell surface expression. β -glucan-binding capacity and impaired cytokine production	Chronic mucocutaneous candidiasis, <i>Candida albicans</i> colonization and invasive aspergillosis	[10] Ferwerda B, Ferwerda G, Plantinga TS, Willment JA, van Spruel AB, Venselaar H, et al. Human dectin-1 deficiency and mucocutaneous fungal infections. N Engl J Med 2009;361:1760-7. [11] Cunha C, Di Ianni M, Bozza S, Giovannini G, Zagarella S, Zelante T, et al. Dectin-1 Y238X polymorphism associates with susceptibility to invasive aspergillosis in hematopoietic transplantation through impairment of both recipient- and donor-dependent mechanisms of antifungal immunity. Blood 2010;116:5394-402. [12] Plantinga TS, van der Velden WJ, Ferwerda B, van Spruel AB, Adema G, Feuth T, et al. Early stop polymorphism in human DECTIN-1 is associated with increased candida colonization in hematopoietic stem cell transplant recipients. Clin Infect Dis 2009;49:724-32.
TLR3	L412F	reduced activation of NF- κ B and reduced secretion of IFN- γ in cells stimulated with the TLR3 ligand Poly I:C	CMC, with increased susceptibility to cytomegalovirus, and autoimmunity	[13] Nahum A, Dadi H, Bates A, Roifman CM. The L412F variant of Toll-like receptor 3 (TLR3) is associated with cutaneous candidiasis, increased susceptibility to cytomegalovirus, and autoimmunity. J Allergy Clin Immunol 2011; 127:528-31.

LYP	R620W	decreased responses to stimulation by anti-CD3 and by anti-IgM as well as decreased numbers of memory B cells	CMC, with recurrent microbial infections as well as gonadal failure and hypothyroidism	[14] Nahum A, Bates A, Sharfe N, Roifman CM. Association of the lymphoid protein tyrosine phosphatase, R620W variant, with chronic mucocutaneous candidiasis. J Allergy Clin Immunol 2008; 122:1220-2.
CXCL10	+11101C/+1642G/-1101A	Reduced chemokine production by DCs exposed to <i>Aspergillus fumigatus</i>	Invasive aspergillosis	[15] Mezger M, Steffens M, Beyer M, Manger C, Eberle J, Toliat MR, et al. Polymorphisms in the chemokine (C-X-C motif) ligand 10 are associated with invasive aspergillosis after allogeneic stem-cell transplantation and influence CXCL10 expression in monocyte-derived dendritic cells. Blood 2008;111:534-6.
IFNG	+874TT	Increased levels of IFN _γ	ABPA, CCPA	[16] Sambatakou H, Pravica V, Hutchinson IV, Denning DW. Cytokine profiling of pulmonary aspergillosis. Int J Immunogenet 2006;33:297-302.
IL1RN IL1A IL1B	VNTR2/-889C/-511T	Increased levels of C-reactive protein	Invasive aspergillosis	[17] Sainz J, Perez E, Gomez-Lopera S, Jurado M. IL1 gene cluster polymorphisms and its haplotypes may predict the risk to develop invasive pulmonary aspergillosis and modulate C-reactive protein level. J Clin Immunol 2008;28:473-85.
IL4	-1098T/-589C/-33C	Unknown	Chronic disseminated candidiasis	[18] Choi EH, Foster CB, Taylor JG, Erichsen HC, Chen RA, Walsh TJ, et al. Association between chronic disseminated candidiasis in adult acute leukemia and common IL4 promoter haplotypes. J Infect Dis 2003;187:1153-6.
	-589T	Increased levels of vaginal IL-4 and reduced levels of nitric oxide and MBL	Recurrent VVC	[19] Babula O, Lazdane G, Kroica J, Linhares IM, Ledger WJ, Witkin SS. Frequency of interleukin-4 (IL-4) -589 gene polymorphism and vaginal concentrations of IL-4, nitric oxide, and mannose-binding lectin in women with recurrent vulvovaginal candidiasis. Clin Infect Dis 2005;40:1258-62.
	-589T	Reduced levels of IL-4	Paracoccidioidomycosis	[20] Bozzi A, Reis BS, Pereira PP, Pedroso EP, Goes AM. Interferon-gamma and interleukin-4 single nucleotide gene polymorphisms in Paracoccidioidomycosis. Cytokine 2009;48:212-7.

IL4R	I75V	Upregulation of CD23 expression	ABPA	[21] Knutsen AP, Kariuki B, Consolino JD, Warriar MR. IL-4 alpha chain receptor (IL-4Ralpha) polymorphisms in allergic bronchopulmonary aspergillosis. Clin Mol Allergy 2006;4:3.
IL10	-1082A	Reduced levels of IL-10	CCPA	[16] Sambatakou H, Pravica V, Hutchinson IV, Denning DW. Cytokine profiling of pulmonary aspergillosis. Int J Immunogenet 2006;33:297-302.
	-1082GG	Increased levels of serum IL-10	ABPA, <i>A. fumigatus</i> colonization	[22] Brouard J, Knauer N, Boelle PY, Corvol H, Henrion-Caude A, Flamant C, et al. Influence of interleukin-10 on Aspergillus fumigatus infection in patients with cystic fibrosis. J Infect Dis 2005;191:1988-91.
IL15	+13689A	Increased levels of IL-15	ABPA, CCPA	[16] Sambatakou H, Pravica V, Hutchinson IV, Denning DW. Cytokine profiling of pulmonary aspergillosis. Int J Immunogenet 2006;33:297-302.
MASP2	D105G	Impaired MBL function	Invasive aspergillosis	[23] Granell M, Urbano-Ispizua A, Suarez B, Rovira M, Fernandez-Aviles F, Martinez C, et al. Mannan-binding lectin pathway deficiencies and invasive fungal infections following allogeneic stem cell transplantation. Exp Hematol 2006;34:1435-41.
MBL2	O/O, A/O	Impaired MBL activity	Invasive aspergillosis, CCPA,VVC	[23] Granell M, Urbano-Ispizua A, Suarez B, Rovira M, Fernandez-Aviles F, Martinez C, et al. Mannan-binding lectin pathway deficiencies and invasive fungal infections following allogeneic stem cell transplantation. Exp Hematol 2006;34:1435-41. [24] Donders GG, Babula O, Bellen G, Linhares IM, Witkin SS. Mannose-binding lectin gene polymorphism and resistance to therapy in women with recurrent vulvovaginal candidiasis. BJOG 2008;115:1225-31.
	LXA/O	Reduced levels of circulating MBL	Invasive aspergillosis	[23] Granell M, Urbano-Ispizua A, Suarez B, Rovira M, Fernandez-Aviles F, Martinez C, et al. Mannan-binding lectin pathway deficiencies and invasive fungal infections following allogeneic stem cell transplantation. Exp Hematol 2006;34:1435-41.

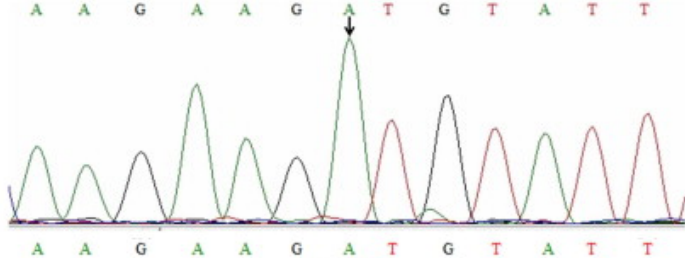
	+1011A	Elevated plasma MBL levels and high peripheral blood eosinophilia	ABPA	[25] Kaur S, Gupta VK, Shah A, Thiel S, Sarma PU, Madan T. Elevated levels of mannan-binding lectin [corrected] (MBL) and eosinophilia in patients of bronchial asthma with allergic rhinitis and allergic bronchopulmonary aspergillosis associate with a novel intronic polymorphism in MBL. Clin Exp Immunol 2006;143:414-9.
NLRP3	Length polymorphism(allele 7)	Impaired production of IL-1 β	Recurrent VVC	[26] Lev-Sagie A, Prus D, Linhares IM, Lavy Y, Ledger WJ, Witkin SS. Polymorphism in a gene coding for the inflammasome component NALP3 and recurrent vulvovaginal candidiasis in women with vulvar vestibulitis syndrome. Am J Obstet Gynecol 2009;200:301-3.
PLG	D472N	Predicted to enhance plasminogen binding to <i>A. fumigatus</i>	Invasive aspergillosis	[27] Zaas AK, Liao G, Chien JW, Weinberg C, Shore D, Giles SS, et al. Plasminogen alleles influence susceptibility to invasive aspergillosis. PLoS Genet 2008;4:e1000101.
SFTPA2	A91P, R94R	Increased levels of total IgE and eosinophilia	ABPA, CCPA	[28] Saxena S, Madan T, Shah A, Muralidhar K, Sarma PU. Association of polymorphisms in the collagen region of SP-A2 with increased levels of total IgE antibodies and eosinophilia in patients with allergic bronchopulmonary aspergillosis. J Allergy Clin Immunol 2003;111:1001-7. [29] Vaid M, Kaur S, Sambatakou H, Madan T, Denning DW, Sarma PU. Distinct alleles of mannose-binding lectin (MBL) and surfactant proteins A (SP-A) in patients with chronic cavitary pulmonary aspergillosis and allergic bronchopulmonary aspergillosis. Clin Chem Lab Med 2007;45:183-6.
TGFB1	+869C	Decreased levels of TGF β	CCPA	[16] Sambatakou H, Pravica V, Hutchinson IV, Denning DW. Cytokine profiling of pulmonary aspergillosis. Int J Immunogenet 2006;33:297-302.
TLR1	R80T, N248S	Unknown	Invasive aspergillosis	[30] Kesh S, Mensah NY, Peterlongo P, Jaffe D, Hsu K, VAN DEN Brink M, et al. TLR1 and TLR6 polymorphisms are associated with susceptibility to invasive aspergillosis after allogeneic stem cell transplantation. Ann N Y Acad Sci 2005;1062:95-103.

TLR4	D299G/T399 I	Predicted to impair the ligand-binding domain	Invasive aspergillosis, <i>A. fumigatus</i> colonization, CCPA, <i>C. albicans</i> systemic infections	[31] Bochud PY, Chien JW, Marr KA, Leisenring WM, Upton A, Janer M, et al. Toll-like receptor 4 polymorphisms and aspergillosis in stem-cell transplantation. <i>N Engl J Med</i> 2008;359:1766-77. [32] Carvalho A, Cunha C, Carotti A, Aloisi T, Guarrera O, Di Ianni M, et al. Polymorphisms in Toll-like receptor genes and susceptibility to infections in allogeneic stem cell transplantation. <i>Exp Hematol</i> 2009;37:1022-9. [33] Carvalho A, Pasqualotto AC, Pitzurra L, Romani L, Denning DW, Rodrigues F. Polymorphisms in toll-like receptor genes and susceptibility to pulmonary aspergillosis. <i>J Infect Dis</i> 2008;197:618-21. [34] Van der Graaf CA, Netea MG, Morre SA, Den Heijer M, Verweij PE, Van der Meer JW, et al. Toll-like receptor 4 Asp299Gly/Thr399Ile polymorphisms are a risk factor for <i>Candida</i> bloodstream infection. <i>Eur Cytokine Netw</i> 2006;17:29-34.
TLR6	S249P	Unknown	Invasive aspergillosis	[30] Kesh S, Mensah NY, Peterlongo P, Jaffe D, Hsu K, VAN DEN Brink M, et al. TLR1 and TLR6 polymorphisms are associated with susceptibility to invasive aspergillosis after allogeneic stem cell transplantation. <i>Ann N Y Acad Sci</i> 2005;1062:95-103.
TLR9	T-1237C	Increased NF-κB binding affinity	ABPA	[33] Carvalho A, Pasqualotto AC, Pitzurra L, Romani L, Denning DW, Rodrigues F. Polymorphisms in toll-like receptor genes and susceptibility to pulmonary aspergillosis. <i>J Infect Dis</i> 2008;197:618-21.
TNF	-308G	Decreased levels of TNF	ABPA, CCPA	[16] Sambatakou H, Pravica V, Hutchinson IV, Denning DW. Cytokine profiling of pulmonary aspergillosis. <i>Int J Immunogenet</i> 2006;33:297-302.
TNFR1	+36G, -609T	Decreased levels of TNFR1 mRNA	Invasive aspergillosis	[35] Sainz J, Salas-Alvarado I, Lopez-Fernandez E, Olmedo C, Comino A, Garcia F, et al. TNFR1 mRNA expression level and TNFR1 gene polymorphisms are predictive markers for susceptibility to develop invasive pulmonary aspergillosis. <i>Int J Immunopathol Pharmacol</i> 2010;23:423-36.

TNFR2	VNTR at -322	Unknown	Invasive aspergillosis	[36] Sainz J, Perez E, Hassan L, Moratalla A, Romero A, Collado MD, et al. Variable number of tandem repeats of TNF receptor type 2 promoter as genetic biomarker of susceptibility to develop invasive pulmonary aspergillosis. Hum Immunol 2007;68:41-50.
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AR, autosomal recessive; AD, autosomal dominant; CMC, chronic mucocutaneous candidiasis; STAT1, signal transducer and activator of transcription factor 1; STAT3, signal transducer and activator of transcription factor 3; AIRE, autoimmune regulator; APECED, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; TLR, Toll-like receptor; LYP, lymphoid protein tyrosine phosphatase; ABPA, allergic bronchopulmonary aspergillosis; CARD9, caspase-recruitment domain family, member 9; CCPA, chronic cavitary pulmonary aspergillosis; CXCL, CXC-chemokine ligand; DC, dendritic cell; DEFB1, β -defensin 1; IFN, interferon; IL, interleukin; IL1RN, IL-1 receptor antagonist; MASP2, mannan-binding lectin serine protease 2; MBL, mannose-binding lectin; NF- κ B, nuclear factor- κ B; NLRP3, NOD-, LRR- and pyrin domain-containing 3; PLG, plasminogen; SFTPA2, surfactant protein A2; SNP, single nucleotide polymorphism; TGF, transforming growth factor; TH17, T helper 17; TNE, tumour necrosis factor; TNFR, TNF receptor; VNTR, variable-number tandem repeat; VVC, vulvovaginal candidiasis.

Parents



Patient

