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Human genetic susceptibility to *Candida* infections

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Abstract

Infections with *Candida* spp. have different manifestations in humans, ranging from mucosal to bloodstream and deep-seated disseminated infections. Immunocompromised patients have increased susceptibility to these types of infections, due to reduced capacity to elicit effective innate or adaptive immunity. In addition, rare and common genetic variants in the human genome have been identified that influence susceptibility to *Candida* infections. Genetic determinants of primary immunodeficiencies leading to chronic mucocutaneous candidiasis have been reported, and polymorphisms in genes that are known to be involved in anti-*Candida* host defense are associated with increased susceptibility to systemic infection. These findings have greatly increased our understanding of pathways important for anti-*Candida* defense in humans, and patterns of prevalence of *Candida* infections. In addition, these pathways may offer novel therapeutic targets for treatment. This review provides an overview of the current insights in genetic susceptibility to *Candida* infections and their consequences for the immune response against *Candida*.

Keywords

Candida; genetic susceptibility; chronic mucocutaneous candidiasis; candidemia; cytokines; immunity

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Introduction

Candida is a dimorphic fungal pathogen that colonizes the mucosal surfaces of approximately 30% of healthy individuals at any given moment [1]. In immunocompetent hosts, the colonization by *Candida* does not cause disease, but during a breach of the anatomical barriers or in immunocompromised hosts, important clinical consequences may ensue. The spectrum of clinical diseases caused by *Candida* spp. comprises clinical syndromes ranging from mucocutaneous infections of the oral and vaginal mucosae, to candidemia and deep-seated infections that are often associated with a septic syndrome [2 – 4]. Although *C. albicans* is still the most prevalent species causing infection, the recent years have witnessed a trend towards an increased prevalence of non-*C. albicans Candida* species such as *C. glabrata* and *C. krusei* [5,6]. Furthermore, increasing reports of resistance to antifungal azoles have occurred, which may be in part promoted by the frequent use of antifungal prophylaxis, preemptive therapeutic strategies in high-risk patients, or alteration of host status [7,8]. Clinical observations have taught us that mucocutaneous candidiasis develops when either T cell immunity is defective (as probably best exemplified in HIV infection), whereas invasive infections tend to occur when phagocytic function falls short or innate immunity is compromised (such as in neutropenia and neutrophil disorders). In recent years the insight in host defense against candidiasis has been greatly augmented and this gain in knowledge has started to be applied to clinical medicine.

The first step in mounting a protective immune response is the recognition of the fungal pathogens by pattern recognition receptors (PRRs), followed by activation of a protective inflammatory reaction. In this early response, neutrophil influx and macrophage activation come into play, followed by the initiation of adaptive immunity through Th1 or Th17 responses. The host-*Candida* interaction results either in the elimination of the pathogen in the immunocompetent host, or in persistence of infection such as observed in chronic mucocutaneous candidiasis (CMC), candidemia and/or persistent disseminated candidiasis in immunocompromised individuals. Here, we describe the current understanding of the molecular mechanisms involved in the recognition of *Candida* spp. and activation of host defense by cells of the innate immune system, and we present the recent insights in the genetic defects of innate and adaptive immunity that can lead to an increased susceptibility to *Candida* infections.

Pattern recognition and host defense mechanisms against *Candida* infections

Host defense against pathogenic microorganisms, fungi in particular, relies on rapid (hours to days) activation of an acute inflammatory response after the encounter with the fungal pathogen. This is followed by an incremental stimulation of specific immune responses mediated by T-lymphocytes (cellular immunity) or B-lymphocytes (humoral immunity), including production of T cell-dependent cytokines such as IFN-γ and IL-17 [9,10]. The first step in the initiation of an immune response is the recognition of conserved structures of the pathogen named pathogen-associated molecular patterns (PAMPs) by PRRs [11,12]. This recognition is followed by induction of intracellular signals leading to phagocytosis and

killing of the fungus, production of proinflammatory cytokines, and the induction of specific adaptive immune responses.

Pattern recognition of Candida

The cell wall of *Candida albicans* consists of an internal skeleton of chitin and β-glucans that confers the necessary rigidity; this layer is covered by a heavily mannosylated layer of mannoproteins at the surface. Mannans and mannoproteins are recognized by specific PRRs [13–15], as are β-glucans and chitin structures [16,17]. These PAMPs are recognized by receptors grouped in three major families: the Toll-like receptors (TLRs), the C-type lectin receptors (CLRs), and the nucleotide binding domain leucine-rich repeat-containing receptors (NLRs). The fourth major family of PRRs, the retinoic acid-inducible gene-I (RIG-I) receptors (RLRs), is believed to mediate especially the immune responses to viruses [13].

Toll-like receptors

The first suggestion of a fundamental role of TLRs in anti-fungal host defense was made by Lemaitre and colleagues, who observed that *Drosophila* deficient in the Toll receptor succumbed rapidly to *Aspergillus fumigatus* infection [18]. Subsequently, mammalian orthologs have been identified that have a leucine-rich repeats extracellular domain that recognizes PAMPs, and a cytoplasmic Toll/IL-1 receptor (TIR) domain responsible for transducing intracellular signals [19]. Ligand recognition by TLRs and subsequent transduction of intracellular signals by several adaptor proteins such as myeloid differentiation factor 88 (MyD88)/Mal and the TRIF/TRAM pathway activates a kinase cascade, followed by nuclear translocation of transcription factors such as NF-κB, AP-1 and IRF3, and production of chemokines and cytokines [13].

Several TLRs, including TLR2, TLR4 and TLR9, have been reported to mediate recognition of components of *Candida* [20–23]. TLR2 on myeloid cells recognizes the phospholipomannan component of the *Candida* cell wall [21], while a limited role for TLR1 and especially TLR6, two receptors known for forming heterodimers with TLR2, has been recently reported to play a role in *C. albicans* recognition in a mouse model of invasive candidiasis [24]. TLR4 recognizes mannans from *Saccharomyces cerevisiae* and *C. albicans* [25], and another study found that short linear *O*-bound mannans of *C. albicans* are recognized by TLR4 and induce proinflammatory cytokines such as TNFα [26]. Both TLR2 and TLR4 influence susceptibility to murine disseminated candidiasis [20,22,27,28]. TLR7 has been shown to recognize fungal RNA in the autophagosome, which is required for IFN-β release and is associated with prolonged infection by *C. glabrata* [29]. Unmethylated CpG sequences of DNA are the natural ligands for TLR9. Indeed, TLR9 is able to recognize fungal DNA from *C. albicans*, and upon recognition induces stimulation of cytokines in dendritic cells [30]. Bellochio *et al.* have reported that TLR9 knockout mice produced less IL-12 and more IL-4 and IL-10, but this had little effect on the overall mortality of the animals [20,31]. In conclusion, most of the data available at this time suggest a role for TLR9 for the recognition of fungal DNA, but the magnitude of this effect for the overall antifungal defense seems to be overshadowed by redundant signals induced by other PRRs.

C-type lectin receptors

Although TLRs are clearly involved in the recognition of *Candida* spp., the potent residual production of cytokines in mice with genetic defects in TLRs or MyD88 clearly demonstrates that a second major route of pattern recognition must be involved. CLRs are a large family of PRRs including the mannose receptor (MR), dectin-1, dectin-2, DC-SIGN, Mincle, and circulating mannose-binding lectin (MBL). These receptors share one or more carbohydrate recognition domains that were originally found in MBL [32], and are involved in the recognition of polysaccharide structures from both microorganisms and endogenous ligands [33]. Importantly, over the recent years these receptors have been shown to be central for fungal recognition and induction of the innate immune response.

The MR described by Stahl and Ezekowitz [34] has been implicated in the recognition of C. albicans by both mouse and human monocyte-derived macrophages [15], and recently the role of the MR in the recognition of *C. albicans* has been strengthened by a study showing that it recognizes branched N-bound mannans from *C. albicans* [26]. In line with this, a recent study has demonstrated an important role of MR for the induction of protective Th17 responses by *C. albicans* [35]. MR was found to be recruited to the phagosome relatively late after ingestion of C. albicans; there it mediates intracellular signals leading to cytokine production [36]. Additional CLRs involved in the recognition of *C. albicans* mannans are dectin-2, detected on myeloid cells and maturing inflammatory monocytes recognizing high-mannose structures [37,38], and DC-SIGN and Mincle, primarily expressed on mature DCs, which also recognize mannans [39–41]. Finally, galectin-3 is a receptor mainly expressed by macrophages, and it has been shown to be involved in the recognition of the β–mannosides of *C. albicans*, in close collaboration with TLR2, especially at the level of the intestinal mucosa [42,43].

In contrast to CLRs that recognize mannan structures, dectin-1 is the main receptor on myeloid cells for β-1,3-glucans [44,45]. Dectin-1 signals through the kinase Syk and the adaptor molecule CARD9, and this pathway has been shown to induce IL-2 and IL-10 in DCs. Moreover, it was demonstrated that infection with *C. albicans* induces protective dectin-1/CARD9-dependent Th17 responses that have a role in the antifungal host defense [46]. Although dectin-1 signaling alone may be sufficient to induce responses upon fungal recognition, several studies have emphasized that dectin-1 induces stronger proinflammatory responses in collaboration with other PRRs. Two independent studies have shown that dectin-1 in collaboration with TLR2 triggers proinflammatory responses upon stimulation with *C. albicans* and zymosan [45,47]. Recently, dectin-1 has been found to also amplify TLR4-dependent pathways in both murine and human myeloid cells [48,49].

NLRs and inflammasome activation

In addition to the mainly cell-membrane bound TLRs and CLRs, mammalian host defense has developed a second line of recognition receptors located in the cytoplasm; for the recognition of *C. albicans* these are the receptors of the NLR family. Some NLR family members, such as NLRP3, are part of the inflammasome complex. The inflammasomes are protein platforms composed of a NLR, the linking molecule ASC and caspase-1. Upon recognition of a microbial PAMP or an endogenous danger signal (e.g., ATP or uric acid),

the conformational change in the NLR/ASC complex induces activation of the cysteine protease caspase-1, which in turn processes pro-IL-1β and pro-IL-18 into the bioactive cytokines [50]. IL-1β proved to be important for neutrophil granulocyte recruitment and generation of superoxide [51]. Both IL-1α and IL-1β deficient mice show increased mortality during disseminated candidiasis [51], and NLRP3 and ASC knockout mice have also been reported to be more susceptible to both systemic [52,53] and mucosal [54] *Candida* infections, although conflicting data exist regarding NLRP3 (van de Veerdonk, personal communication). These data underscore the role of this pathway for host defense against *Candida* infections. However, the role of the inflammasome components ASC and NLRP3 for antifungal defense in humans is unclear yet, although genetic variation in NLRP3 has been associated with increased risk for developing recurrent vulvovaginal candidiasis (RVVC) [55].

Primary immunodeficiencies with an increased susceptibility to fungal infections

The *in vitro* and the experimental studies described above provide evidence that PRRs and the mechanisms induced by these receptors are crucial components of the host defense against fungal pathogens. The knowledge regarding the specific roles of PRRs for human antifungal defense has increased during the last few years by the discovery of a number of defects within the innate immune system, and their specific profiles in terms of increased susceptibility to fungal infections.

Recently, Casanova and colleagues have identified patients with defects in the TLR-adaptor molecules IRAK-4 and MyD88 [56,57]. Patients with IRAK-4 or MyD88 deficiency, and thus broad defects in TLR and IL-1 signaling, have a phenotype characterized by increased susceptibility to pus-forming Gram-positive bacteria such as *Streptococcus pneumoniae* and staphylococci, as well as Gram-negative bacteria such as *Pseudomonas* spp. [58]. Interestingly, these patients do not seem to have an increased susceptibility to fungal infections (either invasive or mucocutaneous), suggesting that the MyD88/IRAK-4 pathway may be redundant for human antifungal defense.

The role of CLR-dependent pathways for antifungal host defense is supported by the identification of a family bearing mutations in *CARD9*, an adaptor molecule in the intracellular signaling pathway of dectin-1 and dectin-2, and possibly other CLRs. This family exhibited increased susceptibility to both mucocutaneous and systemic *Candida* infections [59]. The CARD9-deficient patients also displayed almost complete absence of Th17 responses. In addition to CARD9 deficiency, an early stop codon polymorphism Y238X in dectin-1 (*CLEC7A*) has been identified in a family with several individuals suffering from recurrent mucocutaneous fungal infections, including RVVC [60]. Myeloid cells of affected patients showed defective β-glucan recognition and impaired cytokine responses (IL-6, TNFα and IL-17). Neutrophils of patients exhibited normal phagocytosis and killing of opsonized *C. albicans*. This underlines the redundant nature of dectin-1 for the phagocytosis and killing of yeast pathogens by human myeloid cells, explaining the absence of invasive candidiasis in these patients. It is likely that the defective cytokine release of myeloid cells in the patients bearing the Y238X dectin-1 polymorphism, and especially the diminished IL-17 responses, is responsible for the clinical phenotype. However, this genetic

variant is not rare: in the Western world the prevalence of heterozygous individuals ranges from 10–15%, suggesting that it behaves as a susceptibility factor, rather than a true immunodeficiency. Indeed, the role of dectin-1 Y238X as a susceptibility polymorphism for mucosal anti-*Candida* defense has been confirmed in a study showing that individuals heterozygous for the dectin-1 stop polymorphism and undergoing stem cell transplantation are more likely to be colonized with *C. albicans* and need more often antifungal therapy [61]. However, in a study that assessed the role of common genetic variants of dectin-1 (Y238X) and CARD9 (the S12N polymorphism, not the rare mutation leading to immunodeficiency) in systemic *Candida* infection, no association was observed with either susceptibility for or clinical outcome of the infection, suggesting that the β-glucan recognition pathway is redundant in systemic immunity to *C. albicans* [62].

The crucial role of Th17 responses for the host defense against mucosal *Candida* infections is further supported by the discovery of severe IL-17 defects in patients with two major primary immunodeficiencies syndromes, i.e., hyper IgE syndrome (HIES) and chronic mucocutaneous candidiasis (CMC). Patients with these conditions suffer from chronic mucocutaneous fungal infections [63–65]. In the case of HIES, this is most frequently due to mutations in Signal Transducer and Activator of Transcription (STAT) 3, one of the main signaling molecules of the IL-23 receptor. More rarely, HIES is caused by mutations in DOCK8 (dedicator of cytokinesis 8) or TYK2 (Tyrosine Kinase 2), which also predispose to CMC [66,67]. Furthermore, one study has proposed a polymorphism in TLR3 to be associated with infectious manifestations caused by *C. albicans* in CMC patients [68]. However, it is likely that this TLR3 polymorphism represents a susceptibility risk factor rather than a genetic cause of CMC, as this polymorphism is a common variant in the healthy population.

A subgroup of patients with CMC, those with the clinical syndrome named APECED (autoimmune polyendocrinopathy, candidiasis, ectodermal dysplasy) which is due to a defect in the *AIRE* gene (autoimmune regulator), has a propensity for autoimmune phenomena. In these patients, neutralizing autoantibodies against IL-17 and IL-22 have been found [69]. In addition, approximately 20% of patients with defects in IL12Rβ1, a receptor subunit shared by the IL12 receptor and IL-23 receptor, present with *Candida* infections [70].

CMC is a relatively heterogeneous immunodeficiency disorder in which several investigators have found strongly decreased IFN-γ and IL-17 production. The availability of next-generation sequencing techniques has allowed for the identification of mutations in the coiled-coil domain of *STAT1* as the genetic cause of the disease in families with autosomal dominant CMC (AD-CMC) [71,72]. The discovery of *STAT1* mutations as cause of AD-CMC was remarkable, as *STAT1* deficiency had been previously reported to be associated with mycobacterial and viral, but not fungal, infections [73,74]. The presence of the AD-CMC mutations in the coiled-coil domain of *STAT1*, rather than in the Src homology 2 (SH2) or DNA-binding domains of the protein as in patients with mycobacterial/viral infections, is believed to explain the difference [71,72]. Functional studies revealed that these mutations lead to a gain-of-function of STAT1, thereby impairing STAT3 and STAT4 signaling which leads to defects in downstream signaling of the IL-12 receptor and the IL-23

receptor. This results in diminished production of IFN-γ, IL-17 and IL-22, crucial cytokines in mucosal antifungal host defense [72,75,76]. Moreover, in a small number of patients with CMC, loss-of-function mutations were detected in the genes encoding IL-17F and IL-17 receptor A, resulting in defective IL-17 signalling [77]. An overview of primary immunodeficiencies associated with increased susceptibility to *Candida* infections is listed in Table 1.

Common genetic variation and susceptibility to Candida infections

The prevalence of bloodstream infections with *Candida* spp. has steadily increased in recent years due to the increased use of invasive procedures, treatment of malignancies and autoimmune diseases with chemotherapy and immunosuppressive drugs, and prolonged ICU stays; the mortality due to this disease remains high at between 30% and 40% [78,79].

Several epidemiological studies have assessed the role of TLR polymorphisms for the susceptibility to disseminated candidiasis. The Asp299Gly *TLR4* polymorphism has been proposed to act as a susceptibility trait for systemic candidiasis [80] and the Asp753Gln *TLR2* polymorphism resulted in an altered cytokine profile in patients with *Candida* sepsis [81]. However, these findings could not be confirmed in a much larger cohort including patients and matched controls [82], suggesting that in the previous studies the cohorts were too small, leading to positive associations likely caused by type I errors. Similarly, no role of *TLR4* polymorphisms in vaginal colonization with *Candida* spp. has been observed [83].

Studies dedicated to identify common genetic variants that predispose to bloodstream infections have revealed a significant role for non-synonymous polymorphisms in *TLR1*, of which three were associated with increased risk of developing candidemia as compared to matched control patients in a hospitalized setting (Plantinga *et al.*, J. Infect Dis in press). These *TLR1* polymorphisms result in loss-of-function of the receptor and consequently decreased cytokine responses induced through the TLR1/TLR2 heterodimer. Although no important role for TLR1 was observed in a mouse model of invasive candidiasis [24], several mechanisms could account for the role of human TLR1 in anti-*Candida* immune responses. The configuration of other TLRs such as TLR2 and TLR6 either as homodimer or heterodimer could be deregulated, that in turn could affect intracellular signaling. Another mechanism through which TLR1 could exert its effect on antifungal host defense is the recent finding that beta-defensin-3 activates immune cells through TLR1/TLR2, with an important lytic activity against *C. albicans* [84,85]. This is complemented by the observation that polymorphisms in beta-defensin-1 are associated with RVVC [86], emphasizing the important role of beta-defensins in antifungal immunity.

In the same invasive candidiasis cohort, persistence of fungemia was shown to be associated with promoter polymorphisms in the cytokine genes *IL-12B* and *IL-10* [87]. These polymorphisms affect cytokine transcription and thereby influence the IL-10 and IL-12 production capacity of innate immune cells [88–92]. The persistence of infection was demonstrated to correlate with decreased IL-12 and increased IL-10 production induced by *Candida*, that likely results in inhibition of the T helper 1 response, known to be crucial for anti-*Candida* systemic immunity [93,94]. In line with this, a decreased production of T

helper 2 cytokines such as IL-4 due to genetic variation in the *IL4* gene leads to protective effects [95,96].

Multiple studies have been dedicated to investigate the role of mannose binding lectin (MBL) deficiency in infections with *Candida* spp., since it was demonstrated that MBL could bind and thereby opsonize fungi to facilitate complement activation and phagocytosis [96,97]. Indeed, genetic associations of MBL deficiency with infection risk were observed in cohorts of patients with candidemia, abdominal infections and RVVC [95,98–100].

Another common *Candida* infection is oropharyngeal candidiasis (OPC), mucosal colonization of the mouth and upper digestive tract that is frequently observed in patients that are infected with human immunodeficiency virus (HIV). About 50–95% of patients encounter this type of candidiasis at least once during their progression to AIDS [101–103]. Hence, occurrence of OPC is associated with decreased numbers of $CD4^+$ T cells. However, also human genetic variation in innate immunity may contribute to the susceptibility for OPC. A recent study addressed the potential role of genetic variants of pattern recognition receptors in susceptibility to OPC in West-African HIV patients, which revealed a potential role for another genetic variant of dectin-1 specific for African populations, I223S [104].

The genetic studies on *Candida* infections described above are variable in terms of size of patient cohorts and statistical power. While some of the studies do have relatively large cohorts, with appropriate statistical analysis done, others are hampered by small cohorts of patients that preclude the drawing of definitive conclusions. On the other hand, some of the reported genetic associations are strengthened by functional studies that provide mechanistic explanations for the increased susceptibility to infection. However, no validation of these genetic associations in replication studies with independent cohorts have been performed so far, which is needed to accumulate the required evidence of true genetic associations. In Table 2, a complete overview of common genetic variants associated with fungal infection is depicted. Fig. 1 illustrates the role and location in human antifungal defense of proteins encoded by susceptibility genes for both rare congenital disorders and for *Candida* infections with population-wide occurrence.

Summary and future directions

Genetic association studies, either on rare monogenic disorders or common fungal infections among immunocompromised patients, have provided fundamental insights into the mechanisms involved in conferring resistance to the fungal pathogen *C. albicans*. Especially cytokines that are crucial in antifungal host defense have been identified, including IFN-γ, IL-17 and IL-22 for mucosal infections, and IL-12 and IFN-γ for systemic infections. These findings have generated the rationale for proposing the treatment with adjuvant immunotherapy in the form of recombinant cytokines for the treatment of *Candida* infections. Indeed, experimental studies [105,106] and anecdotal case reports [107,108] have provided the proof-of-concept for the use of IFN-γ or colony-stimulating factors for the treatment of systemic fungal infections. Future research should extend the studies recently started to deepen the knowledge of the genetic profile that would predispose to candidemia: from assessing an increasing number of candidate genes, to genome wide arrays when large enough cohorts will be available. In addition, it has been suggested that only 10 – 15% of

genetic susceptibility to diseases is to be found in the main effects of the individual common polymorphisms and the rest is most likely hidden in rare genetic variants and complex interactions between genes and the environment. This warrants more detailed assessment of genetic variation by deep-sequencing of candidate genes, pathways and in the future (as assays become more cost-effective) the entire exomes or even genomes of affected patients.

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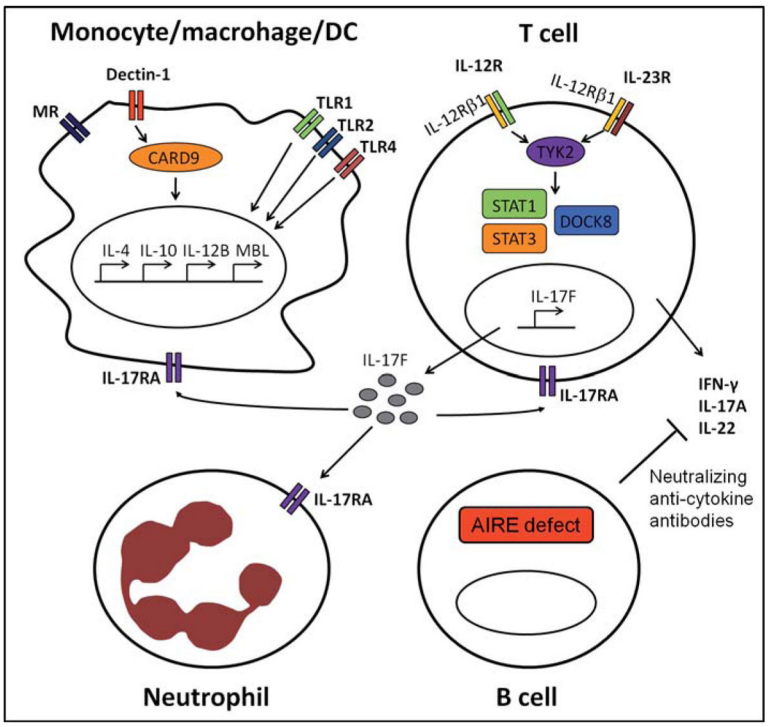

Fig. 1.

Schematic overview of proteins involved in anti-*Candida* host defense of which genetic variants have been identified to increase susceptibility to either mucosal or systemic *Candida* infection. Only those proteins, and the context of these proteins within antifungal immunity, are depicted of which genetic variants in the encoding genes are associated with an increased susceptibility to infection. These proteins have diverse functions, ranging from recognition of *Candida*, cytokine signaling and cellular immunity. TLR, Toll-like receptor; MR, mannose receptor.

Table 1

Primary immunodeficiencies associated with increased susceptibility to *Candida* infections.

Affected gene	Main symptoms	Immune defects	References
STAT1	CMC, hypothyroidism, esophageal cancer	Diminished production of *Candida* induced IFN-γ, IL-17 and IL-22	[71, 72]
STAT3	Serum hyper IgE, *Staphylococcus* and *Candida* infections	Diminished production of *Candida* induced IFN-γ, IL-17 and IL-22	[109, 110]
DOCK8	Serum hyper IgE, *Staphylococcus* and *Candida* infections	Impaired T cell activation, diminished production of *Candida* induced IFN-γ, IL-17 and IL-22	[66]
TYK2	Serum hyper IgE, *Staphylococcus* and *Candida* infections	Defective cytokine signaling	
IL-17RA	CMC	Loss-of-function of IL-17RA	[67]
IL-17F	CMC	Loss-of-function of IL-17F	[77]
CARD9	Mucosal and disseminated *Candida* infections	Diminished production of *Candida* induced IL-17	[77]
IL-12Rβ1	Mycobacterial and *Salmonella* infections and candidiasis	Loss-of-function of IL-12 and IL-23 receptor, diminished production of *Candida* induced IFN-γ and IL-17	[59]
AIRE	CMC, adrenal insufficiency, hypoparathyroidism	Defective thymic negative selection of autoreactive T cells, autoantibodies against IL-17 and IL-22	[111, 112]

Table 2

Common genetic variants associated with increased susceptibility to *Candida* infections.

Affected gene	Polymorphism	Type of infection	Immune defects	References
Dectin-1	Y238X	Recurrent vulvovaginal infections and oral/gastrointestinal colonization	Lack of β-glucan recognition, lower production of *Candida* induced TNFα, IL-6 and IL-17	[60,61]
	I223S	Oropharyngeal candidiasis	Reduced zymosan-binding capacity and IFN-γ production	[104]
TLR1	R80T N248S S602I	Candidemia	Impaired production of pro-inflammatory cytokines induced through TLR1-2 heterodimers	[82]
TLR3	L412F	CMC	Defective TLR3 signaling	[68]
IL-12B	–2724INS/DEL	Persistent candidemia	Lower production of IFN-γ induced by *Candida*	[87]
IL-10	–1082A/G	Persistent candidemia	Higher production of IL-10 induced by *Candida*	[87]
MBL2	Codon 54 and 57	Candidemia, abdominal *Candida* infection, recurrent vulvovaginal candidiasis	Lower MBL serum levels	[95, 98–100]
IL-4	–589T/C	Recurrent vulvovaginal candidiasis	Increased levels of vaginal IL-4 and reduced levels of nitric oxide and MBL	[113]
	–1098T/G –589C/T –33C/T	Chronic disseminated candidiasis	Unknown	[114]
NLRP3	Length polymorphism	Recurrent vulvovaginal candidiasis	Impaired production of IL-1β	[55]
DEFB1	–44C/G	*C. albicans* carriage	Unknown	[86]