Host genetics of invasive *Aspergillus* and *Candida* infections

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Abstract Invasive candidiasis and aspergillosis are major complications in surgical and onco-hematological patients, and still associated with an important morbidity and mortality. A large number of studies highlighted the potential role of host genetic polymorphisms that may influence susceptibility to fungal pathogens, but many were limited by insufficient statistical power, problematic design, and/or lack of replication. However, some relevant polymorphisms are now emerging from well-conducted studies whose associations have been replicated and/or are supported by strong biological evidence. Such polymorphisms together with other biomarkers may play a role in the prediction, diagnosis, and management of severe fungal infections in high-risk patients in the coming years.

Keywords Innate immunity · Single-nucleotide polymorphism · Genetic susceptibility · Invasive *Candida* infection · Invasive aspergillosis

Invasive fungal infections

Candida and *Aspergillus* are the two most common causes of invasive fungal infections [1, 2]. *Candida* species are among the top 10 bloodstream pathogens among hospitalized patients, with an incidence of ~0.5 cases per 10,000 patient days [1, 3]. Non-candidemic forms of the infection include intra-abdominal candidiasis in patients with complicated

gastrointestinal tract surgery [4–6] and hepatosplenic candidiasis in hematological patients with prolonged neutropenia and severe gastrointestinal tract mucositis [7]. Invasive aspergillosis (IA) occurs almost exclusively in immunocompromised patients, including those with hematological malignancies and/or hematopoietic stem cell transplant (HSCT) recipients (incidence 3–5 % [2, 8]) or solid organ transplant (SOT) recipients (incidence 1–3 % [2, 9, 10,]). Despite recent improvement in the prevention, diagnosis, and management of these infections, the mortality associated with both invasive candidiasis and aspergillosis still ranges 30–60 % [2, 3, 11–13].

The development of severe bacterial and fungal infections can be associated with several risk factors, including patient age, comorbid conditions, and/or immunosuppressive drugs [5]. Yet, it is still difficult to predict why certain individuals develop severe infections, while others, under similar conditions, do not. Since the prognosis of invasive fungal infections is severe, prophylactic and empirical anti-fungal agents are increasingly used, exposing patients to the potential development of resistance and/or unnecessary side effects. Therefore, better risk stratification may improve the use anti-fungal drugs. Over the last years, an increasing number of studies were analyzed whether genetic polymorphisms influence susceptibility to or severity of invasive fungal infections. Most studies so far used a candidate gene approach strategy, focused on one or several genes selected for their role in immune responses against fungal pathogens.

Immune responses to fungal infections

The innate immune system is composed of physical barriers (skin and mucous membranes), cellular elements (monocytes, macrophages, neutrophils, dendritic cells (DCs), mast cells, natural killer (NK) cells), and soluble factors (cytokines,

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chemokines, and others), which all contribute to contain the spread of infection. The interaction of fungal pathogens with innate immune cells triggers subsequent adaptive immune mechanisms, including T cell responses and B cell differentiation [14].

At the molecular level, detection of fungal pathogens by innate immune cells is mediated by a series of pattern recognition receptors (PRRs). PRRs detect specific molecular patterns from microorganisms as well as biological components of the self, jointly called “pathogen- or danger-associated molecular patterns” (PAMPs or DAMPs), and mediate subsequent responses through the activation of their downstream signaling pathways. At least three families of PRRs have been shown to be involved in fungal detection, including the Toll-like receptors (TLRs), the C-type lectin receptors (CLRs, such as Dectin-1, Dectin-2, DC-specific ICAM3 grabbing non-integrin (DC-SIGN)), and NOD-like receptors (NLRs such as NLR family pyrin domain containing 3 (NALP3, reviewed in [15, 16]). Among TLRs, fungal recognition is mediated by TLR4 (*O*-linked mannan [17]) and TLR2 (phospholipomannan [18]), a receptor that forms heterodimers with either TLR1 or TLR6. Among CLRs, Dectin-1 was shown to detect β -glucan (β -(1,3)-D-glucan), a key component of *Candida* and *Aspergillus* cell wall [19–21]. The role NLRs in immunity to fungal pathogens has been recently suggested by in vitro and in vivo studies. In human monocytes, NALP3 was shown to be involved in response to *Aspergillus* hyphae by Dectin-1-dependent inflammasome formation leading to interleukin-1 beta (IL-1 β) cleavage and release [22]. Sensing diverse fungal components Dectin-1, TLRs, and NLRs mediate responses in a quite distinct way; nevertheless, they can act synergistically to enhance immune reaction [23, 24]. In addition, pentraxin-3 (PTX3) was shown to be an important soluble PRR of fungal pathogens [25]. It has been shown to bind and opsonize *Aspergillus* conidia by recognizing galactomannan, thereby facilitating pathogen recognition, increasing phagocytosis, and killing of this offending pathogen [25].

PRRs located on the surface of antigen-presenting cells activate transcription factors through different signaling pathways, thereby inducing the production of pro- and anti-inflammatory molecules, which play a central role in immune responses to fungal pathogens. The pattern of cytokines and other mediators in response to fungal pathogens determines the differentiation of CD4⁺ T helper cells [15]. T_H1 responses characterized mainly by the production of interferon gamma (IFN- γ) are usually associated with protective immunity against fungal pathogens [15, 26]. The activations of T_H17 cells characterized by the production of IL-17 and IL-22 were shown to ensure mucosal immunity against *Candida albicans* infection [15, 27]. The anti-fungal immune responses can be counterbalanced by the differentiation of T helper cells into T_H2 (IL-4) and Treg cells (IL-10), which can be associated with insufficient responses against fungal pathogens.

Immunogenetics of fungal infections

Over the last decades, increasing evidence highlighted the importance of host genetic factors in susceptibility to human pathogens, including opportunistic and non-invasive fungi [28]. Predisposition to infections is usually considered to segregate into two groups [29]. On the one hand, individuals with primary immunodeficiencies usually present with infections due to common or opportunistic pathogens, resulting from a clear-cut deficit in a single gene (monogenic inheritance). Such immune deficiencies are usually limited to a very small number of individuals or families, but the identification of genetic defects is very informative on immune defense mechanisms. On the other hand, susceptibility to infections in the general population can be influenced by polymorphisms in several genes (polygenic inheritance) [30]. Although the identification of such polymorphisms may be relevant to implement personalized management strategies in certain circumstances (for example, during chemotherapy-induced neutropenia), their specific contribution to the phenotype is often more difficult to establish.

Monogenic inheritance Several well-characterized primary immunodeficiencies can predispose to IA (Table 1). Increased susceptibility to the infection either an insufficient number of phagocytic cells (severe congenital neutropenia (SCN) with mutation in HCLS1-associated protein X-1 or neutrophil elastase [31, 32]), inability for granulocytes to reach the site of infection (leukocyte adhesion deficiency type 1 with autosomal recessive deficiency in CD18 [33]), or impaired phagocytic functions (mainly due to inability to produce reactive oxygen species (ROS) such as in chronic granulomatous disease (reviewed in [34–37])). IA can also occur in patients with hyperimmunoglobulin E syndrome (HIES) characterized by autosomal-dominant *STAT3* deficiency and epithelial lung dysfunction [38, 39] and those with sporadic monocytopenia and mycobacterial infection (MonoMAC) syndrome with DC deficiency and B and NK cell lymphopenia [40, 41]. Some of primary immunodeficiencies associated with IA have been also reported to cause invasive forms of *Candida* infections [42, 43, 32, 31, 33]. Yet, several other types of primary immunodeficiencies are a cause of chronic mucocutaneous candidiasis (CMC), a non-invasive form of candidiasis characterized by persistent or recurrent fungal infection of the skin, oral or genital mucous, and nails. Those are usually classified into three groups: CMC associated with primary T cell deficiency, syndromic CMC defined as CMC infection associated with presence of other clinical manifestation, and CMC disease (CMCD) defined as CMC infection that occurs without other underlying disease (Table 1). In some instances, deficiencies associated with CMC can also predispose to more invasive infections, such as autosomal-dominant point

Table 1 Primary immunodeficiencies associated with *Candida* and *Aspergillus* infections

Gene	Transmission of mutation	Associated disease	Study
Invasive aspergillosis			
CYBB	X-linked	Chronic granulomatous disease	Lionakis, Lilic, Vinh, and Lanternier et al. [34–37]
CYBA	Autosomal recessive	Chronic granulomatous disease	Lionakis, Lilic, Vinh, and Lanternier et al. [34–37]
NCF1, NCF2, NCF4	Autosomal recessive	Chronic granulomatous disease	Lionakis, Lilic, Vinh, and Lanternier et al. [34–37]
STAT3	Autosomal-dominant	Hyperimmunoglobulin E syndrome	Holland et al. and Minegishi et al. [38, 39]
GATA2	Autosomal-dominant	Sporadic monocytopenia and mycobacterial infection	Camargo et al., Vinh et al., and Glocker et al. [40, 41, 85]
HAX1	Autosomal recessive	Severe congenital neutropenia	Klein et al. [32]
ELA2	Autosomal-dominant	Severe congenital neutropenia	Dale et al. [31]
CD18	Autosomal recessive	Leukocyte adhesion deficiency type 1	Fischer et al [33]
CMC associated with T cell deficiency			
DOCK8	Autosomal recessive	Combined immunodeficiencies	Zhang et al. [86]
IKBG	X-linked recessive	Combined immunodeficiencies	Picard et al. [87]
IKBA	Autosomal-dominant, GOF	Combined immunodeficiencies	Schimke et al. [88]
TCRA	Autosomal recessive	Combined immunodeficiencies	Morgan et al. [89]
CRACM1	Autosomal recessive	Combined immunodeficiencies	Feske et al. [90]
MST1/STK4	Autosomal recessive	Combined immunodeficiencies	Abdollahpour et al. and Nehme [91, 92]
IL2RA	Autosomal recessive	Combined immunodeficiencies	Caudy et al. [93]
CIITA, RFXANK, RFXC, RFXAP	Autosomal recessive	Combined immunodeficiencies	Ouederni et al. [94]
UNC119	Autosomal-dominant	Idiopathic CD4 lymphopenia	Gorska et al. [95]
MAGT1	X-linked	Idiopathic CD4 lymphopenia	Li et al. [96]
RAG1	Autosomal recessive	Idiopathic CD4 lymphopenia	Kuijpers et al. [97]
Over 30 genes	Autosomal recessive or X-linked	Severe combined immunodeficiencies	Puck [98]
Syndromic CMC			
STAT3	Autosomal-dominant	Hyperimmunoglobulin E syndrome	Holland et al., Minegishi et al., Chandesris et al., and Woellner et al. [38, 39, 99, 100]
DOCK8	Autosomal recessive	Hyperimmunoglobulin E syndrome	Engelhardt et al. [101]
AIRE	Autosomal recessive	APECED/APS-I	Kisand et al. and Sarkadi et al. [102, 103]
TYK2	Autosomal recessive	Hyperimmunoglobulin E syndrome	Minegishi et al. [104]
IL12RB1	Autosomal recessive	IL-12RB1 deficiency, MSMD	de Beaucoudrey et al. [105]
IL12B	Autosomal recessive	IL-12p40 deficiency	Prando et al. [106]
CMC disease (CMCD)			

Table 1 (continued)

Gene	Transmission of mutation	Associated disease	Study
CARD9	Autosomal recessive	CMC	Glocker et al. [85]
IL17F	Autosomal-dominant	CMC	Puel et al. [107]
IL17RA	Autosomal recessive	CMC	Puel et al. [107]
STAT1	Autosomal-dominant, GOF	CMC	Liu et al. and van de Veerdonk et al. [108, 109]
ACT1	Missense mutation	CMC	Boisson et al. [110]
Invasive <i>Candida</i> infections			
CARD9	Autosomal recessive	Meningoencephalitis	Lanternier et al. and Drewniak et al. [45, 46]
CYBB	X-linked	Chronic granulomatous disease	Levy et al. and Fleischmann et al. [42, 43]
CYBA, NCF1, NCF2, NCF4	Autosomal recessive	Chronic granulomatous disease	Levy et al. and Fleischmann et al. [42, 43]
CD18	Autosomal recessive	Leukocyte adhesion deficiency type 1	Fischer et al. [33]
ELA2	Autosomal-dominant	Severe congenital neutropenia	Dale et al. [31]
HAX1	Autosomal recessive	Severe congenital neutropenia	Klein et al. [32]

ACT1 nuclear factor- κ B activator 1, *AIRE* autoimmune regulator, *APECED/APS-I* autoimmune polyendocrinopathy candidiasis ectodermal dystrophy /autoimmune polyendocrinopathy syndrome type I, *CARD9* caspase recruitment domain family member 9, *CMC* chronic mucocutaneous candidiasis, *CRACM1* Ca^{2+} channel protein 1, *CYBB* cytochrome B-245 beta polypeptide, *CYBA* cytochrome B-245 alpha polypeptide, *CIITA* class II, major histocompatibility complex transactivator, *DOCK8* dedicator of cytokinesis 8, *ELA2* elastase 2, *GATA2* GATA-binding protein 2, *GOF* gain of function, *HAX1* HCLS1 associated protein X-1, *IKBG* inhibitor of nuclear factor- κ B kinase subunit gamma, *IL* interleukin, *MAGT1* magnesium transporter 1, *MSMD* mendelian susceptibility to mycobacterial diseases, *MST1* mammalian STE20-like kinase, *NCF* neutrophil cytosolic factor, *RAG1* recombination activating gene 1, *RFXANK* regulatory factor X-associated ankyrin-containing protein, *RFXAP* regulatory factor X-associated protein, *STAT* signal transducer and activator of transcription, *STK4* serine/threonine kinase 4, *TCRA* T cell receptor alpha, *TYK* tyrosine kinase 2, *UNC119* unc-119 homolog

mutations in interleukin-12 receptor beta 1 (*IL12RB1*) [44] or inborn deficiency in *CARD9* [45, 46].

Polygenic inheritance Several studies investigated the role of genetic factors in patients at risk to develop invasive fungal infections, such those with hematological malignancies, HSCT recipients with prolonged neutropenia, or ICU surgical patients (Fig. 1, Tables 2 and 3).

Invasive aspergillosis

Pattern recognition receptors Two non-synonymous polymorphisms in *TLR4* (1063A/G (D299G) and 1363C/T (T399I)) in HSCT donors were associated with the risk of IA in the corresponding recipient [47]. This association has been further validated in two independent cohorts of HSCT [48, 47]; however, other studies showed contradictory results in diverse setting [49, 50]. The polymorphisms were initially suggested to impair the detection of LPS (*TLR4* primary ligand [51]), but the exact mechanism by which it influences

immune responses to the fungus has been debated [52]. Polymorphisms in other TLRs (*TLR1/TLR6* [49], *TLR3* [53], and *TLR5* [54]) have also been associated with susceptibility to IA. Although some of these single-nucleotide polymorphisms (SNPs) were shown to influence immune responses to *Aspergillus* species in vitro [55, 54], the genetic associations have not been replicated so far (Table 2). SNPs in *TLR2* (which acts as co-receptor with *TLR1* or *TLR6*) were not associated with susceptibility to IA [50, 47].

A stop codon polymorphism in Dectin-1 (known as *CLEC7A*) in HSCT donor and/or recipient was associated with IA in the recipient [56, 57]. Peripheral blood mononuclear cells (PBMCs) from individuals carrying the 238X risk allele produced lower amounts of IL-1 β , IL-6, IL-17A, and IFN- γ and IL-10 compared to PBMCs in response to *Aspergillus fumigatus* stimulation [56]. Donor and recipient Dectin-1 deficiency also increases susceptibility to *Aspergillus* infection in a mice model of HSCT [56]. These data illustrate the important role of Dectin-1 in immune responses against *Aspergillus* infection. Two other polymorphisms in *CLEC7A* have been associated with IA among patients with

Fig. 1 Candidate gene polymorphisms associated with invasive *Aspergillus* and/or *Candida* infections. *ASC* apoptosis-associated speck-like protein containing a CARD; *BCL10* B cell CLL/lymphoma 10; *CARD9* caspase recruitment domain-9; *CCL8* chemokine C-C motif ligand 8; *CXCL10* CXC chemokine ligand-10; *DC-SIGN* dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin; *DEFB1* β-defensin 1; *IL* interleukin; *IL1RN* interleukin-1 receptor antagonist; *IL23R* interleukin 23 receptor; *MASP2* mannan-binding lectin serine

peptidase 2; *MBL* mannose-binding lectin; *MYD88* myeloid differentiation primary response protein; *NALP3* NACHT, LRR, and PYD domains-containing protein 3; *NF-κB* nuclear factor-κB; *PLG* plasminogen; *PTX3* pentraxin 3; *RAGE* advanced glycosylation end-product-specific receptor; *S100B* S100 calcium-binding protein B; *STAT1* signal transducer and activator of transcription 1; *TNFA* tumor necrosis factor alpha; *TNFR* tumor necrosis factor receptor; *TRIF* TIR-domain-containing adapter-inducing interferon-β; *TLR* Toll-like receptor

hematological malignancies. SNPs in another C-type lectin *CD290* (encoding DC-SIGN) have been associated with IA in patients with hematological malignancies [58]. The latest studies have not yet been validated, and the functional relevance of the polymorphisms still needs to be further explored.

In a recent study, a haplotypic variant in *PTX3* in HSCT donor was associated with an increased risk of IA in the corresponding recipient [59]. This association has been replicated in a cohort of SOT recipients [60]. The variant has been associated with reduced *PTX3* expression or production (either in PBMCs or in broncho-alveolar lavage (BAL) from infected or non-infected patients) as well as reduced phagocytic activity in PBMCs. Furthermore, mice

deficient in *PTX3* have increased susceptibility to IA with defective recognition of *Aspergillus* conidia compared to WT mice [25]. A haplotype determined by three SNPs in the mannose-binding lectin (*MBL*), a complement-related PRR playing an important role in opsonization and lysis of fungal pathogens, has been associated with IA [61]. Presence of this haplotype results in low levels of *MBL* with impaired activity, which could, in part, be responsible for increased susceptibility to invasive infection caused by *Aspergillus*.

Cytokines, chemokines, and their receptors A series of relatively small studies associated SNPs in genes encoding cytokines and chemokines such as *IL10* [62], *IL1B* [63], *IL1A* [63],

Table 2 Genetic risk factors for invasive aspergillosis

Gene	Rs no.	Variant	Population	Ethnicity	No. of cases/controls	Association OR (95 %CI), P^a	Effect ^b	Replication	Functional evidence	Study
Pattern recognition receptors										
TLR1	rs5743611	R80T	HSCT	Caucasian	22/105	1.3 (1.1–1.5), $P<0.001$ (R)	↑	–	–	Kesh et al. [49]
	rs4833095	N248S								
TLR6	rs5743810	S249P								
TLR4	rs4986790	D299G	HSCT	Caucasian	33/303 (discovery)	Discovery: 6.2 (2.0–19.3), $P=0.002$ (D) ^c	↑	+	+/-	Bochud et al. [47]
	rs4986791	T399I			103/263 (validation)	Validation: 2.5 (1.2–5.4), $P=0.02$ (D) ^d	↑			
	rs4986790	D299G	HSCT	Caucasian	34/24	0.2 (0.1–0.9), $P=0.03$ (D)	↓	–	+/-	Carvalho et al. [50]
	rs4986791	T399I	HSCT	Caucasian	42/112	D299G; $P=0.006$ (R), $P=0.03$ (D) T399I; $P=0.03$ (R), $P=0.006$ (D)	↑	+	–	Koldehoff et al. [48]
TLR3	rs3775296	-7C/T	HSCT	NS	42/181	HR 2.4 (1.3–4.6), $P=0.007$ (D) ^e	↑	–	+	Carvalho et al. [53]
TLR5	rs5744168	R392X	HSCT	NS	41/130	$P=0.004$ (R)	↑	–	–	Grube et al. [54]
CLEC7A	rs16910526	Y238X	HSCT	Caucasian	71/108	1.8 (0.8–4.2), $P=0.2$ (D + R), not significant	–	+	+	Chai et al. [57]
	rs16910526	Y238X	HSCT	NS	39/166	HR 2.5 (1.0–6.5), $P=0.05$ (D) ^f HR 3.9 (1.5–10.0), $P=0.005$ (D + R) ^f	↑	+	+	Cunha et al. [56]
CD209	rs7309123	375-1404C/G	HM	Caucasian	57/125	5.5 (1.9–16.4), $P=0.001$ ^g	↑	–	+	Sainz et al. [58]
	rs3901533	255 + 813G/T	HM	Caucasian	57/125	6.3 (1.6–25.4), $P=0.007$ ^g	↑	–	–	Sainz et al. [58]
	rs4804800	*2797C/T				2.8 (1.3–6.0), $P=0.009$ ^g	↑			
	rs11465384	341-28C/T				2.7 (1.2–5.9), $P=0.01$ ^g	↑			
	rs7248637	*898T/C				2.4 (1.1–5.2), $P=0.03$ ^g	↑			
	rs7252229	46 + 171C/G				2.1 (1.0–4.2), $P=0.05$ ^g	↑			
MBL	N/A	Low genotype ^h	HSCT	Caucasian	16/105	RR 7.3 (1.9–27.3), $P=0.003$ (D) ⁱ	↑	–	–	Granell et al. [61]
PTX3	rs2305619/	h2h2 ^j	HSCT	Caucasian	51/217 (discovery)	Discovery: HR 3.1 (1.5–6.4), $P=0.003$ (D) ^k	↑	+	+	Cunha et al. [59]
	rs3816527				107/223 (validation)	Validation: HR 2.8 (1.2–8.9), $P=0.03$ (D) ^k	↑			
	rs2305619/	h2h2 ^j	SOT	Caucasian	26/1101	HR 2.7 (1.2–6.1), $P=0.02$ (R) ^l	↑	+	–	Wojtowicz et al. [60]
Cytokines, chemokines, and their receptors										
IL1A	rs1800587	-889C/T	HM	Caucasian	59/51	15.4 (1.4–171.2), $P=0.02$	↑	–	+	Sainz et al. [63]
IL1B	rs1143627	-31T/C								
IL1RN	N/A	82 bp VNTR								
IL10	rs1800896	-1082A/G	HM	Caucasian	59/61	4.5 (1.6–12.9), $P=0.001$	↑	+	–	Sainz et al. [62]
	rs1800896	-1082A/G	HSCT	Asian	9/96	HR 9.3 (1.6–52.8), $P=0.01$ (R) ^m	↑	+	–	Seo et al. [111]
	rs1800871	-819C/T								
	rs1800872	-592A/C								
IL23R	rs11209026	R381Q	HSCT	NS	25/176	$P=0.05$ (D)	↓	–	+/-	Carvalho et al. [65]

Table 2 (continued)

Gene	Rs no.	Variant	Population	Ethnicity	No. of cases/controls	Association OR (95 %CI), P^a	Effect ^b	Replication	Functional evidence	Study
TNFR1	rs4149570	-610T/A	HM	Caucasian	77/67	$P=0.02$	↑	-	+	Sainz et al. [66]
TNFR2	N/A	-322 VNTR	HM	Caucasian	54/48	$P=0.03$	↑	-	-	Sainz et al. [67]
CXCL10	rs3921	1642G/C	HSCT	NS	81/58	2.2 (1.2–3.8), $P=0.007$ (D)	↑	-	+	Mezger et al. [64]
	rs1554013	11101C/T				2.6 (1.4–5.0), $P=0.003$ (D)	↑			
	rs4257674	-1101A/G				2.8 (1.6–5.2), $P=0.001$ (D)	↑			
Others										
MAASP2	rs72550870	D120G	HSCT	Caucasian	16/105	RR 6.4 (2.0–20.6), $P=0.002$ (R) ⁿ	↑	-	-	Granell et al. [61]
RAGE	rs1800624	-388T/A	HSCT	Caucasian	41/182	HR 2.0 (1.0–3.8), $P=0.04$ (D) ^o	↑	-	+	Cunha et al. [68]
						HR 2.0 (1.0–4.1), $P=0.05$ (R) ^o	↑			
S100B	rs9722	*37C/T	HSCT	Caucasian	41/182	HR 3.2 (1.6–6.2), $P<0.001$ (D) ^o	↑	-	+	Cunha et al. [68]
PLG	rs4252125	D472N	HSCT	NS	59/135	HR 3.0 (1.5–6.1), $P<0.001$ (R) ^p	↑	-	+/-	Zaas et al. [69]
						HR 5.6 (1.9–16.5), $P<0.001$ (R) ^p	↑			

CI confidence interval, CXCL10 CXC chemokine ligand-10, D donor, DEFB1, β -defensin 1, G β HD graft versus host disease, HLA human leukocyte antigen, HM hematologic malignancies, HSC β hematopoietic stem cell transplant, HR hazard ratio, IL interleukin, IL1RN interleukin-1 receptor antagonist, IL23R interleukin 23 receptor, MASP2 mannan-binding lectin serine peptidase 2, NS not specified, OR odds ratio, PLG plasminogen, R recipient, RAGE advanced glycosylation end-product-specific receptor, RR relative risk, S100B S100 calcium-binding protein B, TNFR tumor necrosis factor receptor, CLEC7A C-type lectin domain 7 (known as Dectin-1), MBL mannose-binding lectin, PTX3 pentraxin 3, SOT solid organ transplant recipients, TLR Toll-like receptor

^a P value assessed by univariate analysis otherwise indicated

^b Effect of minor allele on susceptibility to invasive aspergillosis

^c HR adjusted for transplanted dose of CD34⁺ cells and mononuclear cells, source of stem cells, HLA mismatch, conditioning, use of ATG, and GVHD

^d RR adjusted for GVHD

^e HR adjusted for HLA mismatch and GVHD

^f HR adjusted for cell type, HLA mismatch, and category of malignancy

^g OR adjusted for age, gender, hematological malignancy, HSCT, neutropenia, GVHD, and corticoid therapy

^h MBL low genotype (D/B/C) consists of D (R52C, rs5030737), B (G54D, rs1800450), and C (G57E, rs1800451) variants, respectively. This genotype is associated with low serum MBL concentration

ⁱ HR adjusted for HLA matching status, use or non-use of total body irradiation, and anti-fungal prophylaxis

^j PTX3 h2/h2 genotype (G-A/G-A) consists of 281G (rs2305619) and 734A (rs3816527) alleles, respectively

^k RR adjusted for GVHD

^l HR adjusted for recipient age and sex, CMV infection or disease, type of transplanted organ, corticosteroid therapy, and acute cellular rejection

^m OR adjusted for CMV donor and/or recipient serostatus and presence or absence of GVHD

ⁿ OR adjusted for donor and recipient sex, underlying disease, use of anti-fungal prophylaxis, CMV disease, and GVHD

^o HR adjusted for transplantation matching, GVHD, and anti-fungal prophylaxis

^p HR adjusted for age and sex, HLA haplotype-mismatching, and GVHD

and *CXCL10* [64], as well as their receptors (*IL23R* [65], *TNFR1*, and *TNFR2* [66, 67]) or antagonists (interleukin-1 receptor antagonist, *IL1RA* [63]) with susceptibility to IA. Among them, only the association with *IL10* has been validated by independent researchers, yet without biological clarification (Table 2).

Other genes Other investigators pointed out the role of SNPs located in different genes from signaling pathways involved in immune responses to fungi such as mannan-binding lectin serine peptidase 2 (*MASP2*) [61], advanced glycosylation end-product receptor (*RAGE*), alarmin S100 calcium-binding protein B (*S100B*) [68], and plasminogen (*PLG*) [69]. However, most of aforementioned studies were without further validation and/or clear functional relevance, thus require further exploration (Table 2).

Invasive *Candida* infections

Pattern recognition receptors There is also evidence that dysfunction in main PRR sensing fungal cell wall components is associated with susceptibility to invasive *Candida* infections. The *TLR4* D299G and T399I polymorphisms have been associated with candidemia in non-neutropenic patients [70], but this observation was not confirmed in a larger cohort [71]. However, the same SNPs were associated with *Candida* colonization in surgical intensive care unit (ICU) patients, although there was no association with the development of intra-abdominal candidiasis [72]. Again, differences between the studies can be explained by the variation in sample size that was not powerful enough for replication. Nonetheless, *TLR4*-deficient mice have an increased susceptibility to disseminated candidiasis compared to wild-type mice [73]. Three SNPs in *TLR1* (R80T, N248S, and S602I) were associated with candidemia [71] and influenced the production of pro-inflammatory cytokines in PBMCs from affected individuals after stimulation of *TLR1/TLR2* agonists [71]. The R753Q polymorphisms in *TLR2* have been associated with increased risk for septic candidemia in a very small cohort of ICU patients and correlated with diminished IFN- γ and IL-8 plasma levels in patients carrying two copies of mutant allele [74]. However, larger confirmatory cohort would be desired to confirm this association.

Several studies suggest a role for the Dectin-1 Y238X polymorphism in susceptibility to *Candida* infections. The SNP was associated with increased *Candida* colonization in a cohort of HSCT patients [75], but no association could be detected in a case-control study of candidemic patients [76]. This may be due to study limitations, such as the heterogeneity among cases and/or controls and/or insufficient power due to the rare SNP allele frequency. Yet, PBMCs from individuals carrying the SNP produced reduced amounts

of pro-inflammatory cytokines (TNF- α , IL-17) compared to those from WT individuals, after stimulation with *Candida* spp. [75, 76]. Dectin-1 deficiency inconsistently led to increased susceptibility to infection in mice models of *Candida* infection [21, 77]. Besides TLRs and CLRs, polymorphisms in the soluble PRR MBL (i.e., “low MBL haplotypes”) were also associated with abdominal candidiasis [78].

Cytokines, chemokines, and their receptors Several investigators pointed out the role of SNPs located in key cytokines genes, including *TNFA* [72], *IL12B* [79], *IL10* [79], and *IL4* [80], in the susceptibility to *Candida* infections or colonization (Table 3). However, most of this studies were limited by several factors, thus need further validation in larger datasets.

Other genes A SNP in β -defensin 1 gene (*DEFB1*), encoding an anti-microbial peptide that can act against *C. albicans* [81], was associated with decreased *Candida* carriage in diabetic and non-diabetic patients [82]. The same SNP was associated with increased susceptibility to *Candida* infections in ICU surgical patients [72]. However, in the absence of replication and functional evidence, these observations will need further investigations.

Genome-wide approaches Most genetic studies so far used a candidate gene approach, in which the genes were selected for their expected role in host immune responses to the offending pathogen based on the existing literature. Investigators have recently proposed alternative approaches to account for genes that may not be selected by this traditional approach. By analyzing the transcriptional profile of human PBMCs in response to different pathogens, Smeeckens et al. identified the type I IFN pathway as specific transcriptional signature for *Candida* infection. By performing a genetic analysis of 11 candidate genes from this pathway, they identified SNPs in four genes to be associated with candidemia, including a SNP in the signal transducer and activator of transcription 1 (*STAT1*), a SNP nearby the chemokine (C-C motif) ligand 8 (*CCL8*), a SNP in the nuclear body protein *SP110* (known also as IFN-induced protein 41), and a SNP in the proteasome (prosome, macropain) subunit beta type 8 (*PSMB8*) [83]. These novel observations suggest pivotal role of type I IFN signaling also in anti-*Candida* immunity, but biologically, the plausibility of these associations needs be further elucidated. In addition, Kumar et al. by using an immunochip of 118,989 SNPs across 186 loci identify three novel polymorphisms associated with candidemia, including SNP located in *CD56*, SNP between late cornified envelope (LCE) protein 4 A (*LCE4A*) and chromosome 1 open

Table 3 Genetic risk factors for Invasive *Candida* infections

Gene	Rs no.	Variant	Disease	Population	Ethnicity	No. of cases/controls	Association OR (95 %CI), <i>P</i> ^a	Effect ^b	Replication	Functional Study evidence	
Pattern recognition receptors											
TLR1	rs5743611	R80T	Candidemia	Mixed population	Caucasian, African-American	338/351	1.8 (1.1–2.98), <i>P</i> =0.02	↑	–	+	Platinga et al. [71]
	rs4833095	N248S					0.7 (0.5–0.96), <i>P</i> =0.04	↓			
	rs5743618	S602I					0.7 (0.5–0.8), <i>P</i> =0.02	↓			
TLR4	rs4986790	D299G	Candidemia	Non-neutropenic	Caucasian	43/166	3.0 (1.3–6.9), <i>P</i> <0.05	↑	–	+/–	Van der Graaf et al. [70]
	rs4986791	T399I									
TLR2	rs4986790	D299G	<i>Candida</i> colonization	ICU surgical patients	Caucasian	42/47	HR 3.4 (1.5–7.9), <i>P</i> =0.005 ^c	↑	–	–	Wójtowicz et al. [72]
	rs5743708	R753Q	<i>Candida</i> septicemia	ICU septic patients	NS	9/38	NA	↑	–	+	Woehrle et al. [74]
	rs16910526	Y238X	<i>Candida</i> colonization	HM	Caucasian	46/78	11.9 (2.5–56.8), <i>P</i> <0.001	↑	–	+	Platinga et al. [75]
CLEC7A	rs16910526	Y238X	Candidemia	Mixed population	Caucasian, African-American	291/300	Not significant	–	–	+	Rosentul et al. [76]
MBL	Low genotype	N/A	IAC	Non-neutropenic	Caucasian	28/60	39 vs. 16 %, <i>P</i> =0.01	↑	–	+/–	Van Till et al. [78]
Cytokines, chemokines, and their receptors											
IL4	rs2243250	–589T/C	Disseminated candidiasis	Leukemic patients	Caucasian	40/50	2.2 (1.2–4.0), <i>P</i> =0.01	↑	–	–	Choi et al. [80]
	rs2070874	–33T/C									
	rs2243248	–1098G/T									
IL10	rs1800896	–1082A/G	Persistent candidemia	Mixed population	Caucasian, Black	39/259	3.5 (1.3–8.9), <i>P</i> =0.03 ^d	↑	–	+	Johnson et al. [79]
IL12B	rs41292470	–2724ins/del	Persistent candidemia	Mixed population	Caucasian, Black	39/259	5.4 (1.5–19.0), <i>P</i> =0.02 ^d	↑	–	+	Johnson et al. [79]
TNFA	rs1800629	–308G/A	IAC		Caucasian	26/43		↑	–	–	

Table 3 (continued)

Gene	Rs no.	Variant	Disease	Population	Ethnicity	No. of cases/controls	Association OR (95 %CI), P^a	Effect ^b	Replication	Functional evidence	Study
CCL8	1kg_17_29697448	N/A	Candidemia	Mixed population	Caucasian, African-American	271/	HR 4.3 (1.9–10.1), $P=0.0007^c$	↑	–	+	Wójtowicz et al. [72]
Others											
DEFB1	rs1800972	–44C/G	<i>Candida</i> carriage	Diabetic	Mixed	43 (19 vs. 24)	Diabetic: $P=0.03$	↓	–	–	Jurevic et al. [82]
	rs1800972	–44C/G	IAC	Non-diabetic	Caucasian	50 (14 vs. 36)	Non-diabetic: $P=0.04$	↑	–	–	Wójtowicz et al. [72]
STAT1	rs16833172	–1-1339C/T	Candidemia	Mixed population	Caucasian, African-American	271/	11'920 $P=0.004$	↑	–	+	Smeekens et al. [83]
SP110	rs3769845	1744 + 425T/C	Candidemia	Mixed population	Caucasian, African-American	271/	$P=0.01$	↑	–	+	Smeekens et al. [83]
PSMB8	rs3198005	*142T/C	Candidemia	Mixed population	Caucasian, African-American	271/	11'920 $P=0.01$	↑	–	+	Smeekens et al. [83]
CD58	rs17035850	N/A	Candidemia	Mixed population	Caucasian, African-American	271/	11'920 4.7 (3.0–7.3), $P=2\times10(-11)$	↑	–	+	Kumar et al. [84]
LCE4A/C1orf68	rs4845320	N/A	Candidemia	Mixed population	Caucasian, African-American	271/	4.2 (2.7–6.6), $P=2\times10(-10)$	↑	–	–	Kumar et al. [84]
TAGAP	rs3127214	N/A	Candidemia	Mixed population	Caucasian, African-American	271/	3.0 (2.0–4.3), $P=2\times10(-8)$	↑	+/-	+	Kumar et al. [84]

C1orf68 chromosome 1 open reading frame 68, *CCL8* chemokine C-C motif ligand 8, *CI* confidence interval, *CLECT7A* C-type lectin domain 7 (known as Dectin-1), *DEFB1* β -defensin 1, *HM*/hematologic malignancies, *HR* hazard ratio, *IAC* intra-abdominal candidiasis, *ICU* intensive care unit, *IL* interleukin, *LCE4A* late cornified envelope (LCE) protein 4 A, *MBL* mannose-binding lectin, *OR* odds ratio, *PSMB8* proteasome (prosome, macropain) subunit beta type 8, *SP110* speckled 110 kDa, *STAT1* signal transducer and activator of transcription 1, *TAGAP* T cell activation RhoGTPase-activating protein, *TNFA* tumor necrosis factor alpha, *TLR* Toll-like receptor

^a P value assessed by univariate analysis otherwise indicated

^b Effect of minor allele on susceptibility to *Candida* infection or colonization

^c HR adjusted for sex and age

^d OR adjusted for dialysis dependence and receipt of total parenteral nutrition

^e HR adjusted for sex, age, and SAPS II score

reading frame 68 (*Clorf68*), and SNP in T cell activation RhoGTPase-activating protein (*TAGAP*) [84] (Table 3).

Summary, limitations, and future perspectives

An increasing number of studies are highlighting a role for genetic polymorphisms in susceptibility to invasive fungal infections. While initial studies usually focused on one of several genes selected for their role in immune response to these pathogens (candidate gene approach), more recent work explored the role of polymorphisms at the genome-wide levels. So far, due to numerous limitations and lack of replication, existing data have not supported the use of genetic polymorphisms for individual risk stratification in the clinical practice. The studies are often limited by small sample size with insufficient power to detect associations, especially for rare variants, or flawed by lack of time-dependent analysis, adjustment for multiple testing (Bonferroni's correction), and/or lack to account for important factors that strongly influence the endpoint. Differences between centers in the use of therapeutic and/or conditioning strategies, e.g., among patients undergoing HSCT, as well as anti-fungal prophylaxis, are another important limiting factor, impeding interpretation of the data. Moreover, some studies were prejudiced due to problematic design, inappropriate control selection for underlying disease, or use of diverse ethnicity in study population. Also, choosing the candidate gene may be subjective and was not always well defined. Aforementioned factors should be taken into account when designing new study or performing validation of existing data.

Despite these limitations, some associations are now emerging. The most consistent findings so far have been the association of polymorphisms in Dectin-1 with both invasive candidiasis as aspergillosis and the association of PTX3 polymorphisms with IA. The validity of these associations relies on the fact that they have been replicated either by the same investigators or by others, that the association is supported by functional evidence of the polymorphism affecting the gene function, and/or by the existence of mutations in the same gene/pathway leading to primary immunodeficiencies causing fungal infections. There is a clear need of well-designed prospective studies including a large number of patients with sufficient power to detect associations with selected markers, clear-cut definitions for the infectious phenotypes, and controls clearly exposed to the same risk as cases. Specific genetic polymorphism used alone or in combination with other biomarkers, together with demographic and clinical data, may be usable in the future to implement individual preventive strategies in patients at risk of fungal infection.

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