Published in final edited form as:

Curr Opin Pediatr. 2013 December ; 25(6): 736–747. doi:10.1097/MOP.0000000000000031.

Primary immunodeficiencies underlying fungal infections

Fanny Lanternier^{1,2,3}, Sophie Cypowyj⁴, Capucine Picard^{1,5}, Jacinta Bustamante^{1,5}, Olivier Lortholary^{2,3}, Jean-Laurent Casanova^{1,4,6}, and Anne Puel¹

¹Laboratory of Human Genetics of Infectious Diseases, Necker Branch, INSERM U980 Necker Medical School, Imagine Foundation and Paris Descartes University, Sorbonne Paris Cité, Paris, France, EU

²Infectious Diseases and Tropical Medicine Unit, Necker-Enfants Malades Hospital, AP-HP and Paris Descartes University, Paris, France, EU

³Pasteur Institute, National Reference Center of Invasive Mycoses and Antifungals, Paris, France, EU

⁴St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, The Rockefeller University, New York, USA

⁵Study Center for Immunodeficiency, Necker Enfants-Malades Hospital, AP-HP, Paris, France, EU

⁶Pediatric Hematology-Immunology Unit, Necker Enfants-Malades Hospital, AP-HP, and Paris Descartes University, Paris, France, EU

Abstract

Purpose of review—We review the primary immunodeficiencies underlying an increasing variety of superficial and invasive fungal infections. We also stress that the occurrence of such fungal infections should lead physicians to search for the corresponding single-gene inborn errors of immunity. Finally, we suggest that other fungal infections may also result from hitherto unknown inborn errors of immunity, at least in some patients with no known risk factors.

Recent findings—An increasing number of primary immunodeficiencies are being shown to underlie fungal infectious diseases in children and young adults. Inborn errors of the phagocyte NADPH oxidase complex (chronic granulomatous disease), severe congenital neutropenia and leukocyte adhesion deficiency type I confer a predisposition to invasive aspergillosis and candidiasis. More rarely, inborn errors of IFN- γ immunity underlie endemic mycoses. Inborn errors of IL-17 immunity have recently been shown to underlie chronic mucocutaneous candidiasis, whereas inborn errors of CARD9 immunity underlie deep dermatophytosis and invasive candidiasis.

Summary—Chronic mucocutaneous candidiasis, invasive candidiasis, invasive aspergillosis, deep dermatophytosis, pneumocystosis, and endemic mycoses can all be caused by primary immunodeficiencies. Each type of infection is highly suggestive of a specific type of primary

Correspondence to AP: anne.puel@inserm.fr, Laboratory of Human Genetics of Infectious Diseases, Necker Branch, Institut National de la Santé et de la Recherche Médicale INSERM U980 Necker Medical School, Imagine Foundation and University Paris Descartes, Sorbonne Paris Cité, 156 rue de Vaugirard, 75015 Paris, France, EU, phone: 00 33 1 72 60 65 28, fax: 00 33 1 72 60 65 29.

immunodeficiency. In the absence of overt risk factors, single-gene inborn errors of immunity should be sought in children and young adults with these and other fungal diseases.

Keywords

primary immunodeficiencies (PIDs); superficial and invasive fungal diseases; chronic mucocutaneous candidiasis; invasive aspergillosis; candidiasis; *Candida* central nervous system infection; deep dermatophytosis; endemic mycosis; pneumocystosis; IL-17; NADPH oxidase complex; CARD9; STAT1; IFN- γ /IL-12; autoantibodies against GM-CSF; autoantibodies against IFN- γ ; X-linked CD40L deficiency

Introduction

Saprophytic and commensal fungi infect billions of people each year [1,2]. Medically important fungi include yeast *Candida* spp., mold *Aspergillus* spp., the atypical fungus *Pneumocystis jirovecii*, dimorphic (*Coccidioides*, *Paracoccidioides* and *Histoplasmosma* spp.) fungi, dermatophytes (e.g. *Trichophyton* spp.), and encapsulated yeast *Cryptococcus* spp. Invasive fungal diseases (IFDs), such as candidiasis, aspergillosis, pneumocystosis and cryptococcosis in particular, have become a major health problem [3,4]. The acquired immunodeficiency syndrome (AIDS) epidemic, the more widespread use of immunosuppressive therapies, the longer survival of immunosuppressed patients, the increased use of intravenous lines and increased movements of patients at risk are the main acquired risk factors contributing to IFDs. Despite advances in treatment, mortality rates for IFDs remain high, at 30 to 50% [5–7]. Superficial fungal diseases, although less severe, can also lead to significant morbidity and mortality [8]. In any case, a number of superficial and invasive fungal diseases are not explained by any of the known risk factors.

It is important to understand the pathogenesis of fungal infections in patients without known risk factors. It is also timely to decipher the cellular and molecular mechanisms of anti-fungal immunity, with a view to developing new tools for treating fungal infections [7,9] and new preventive measures, including vaccines [10]. The study of primary immunodeficiencies (PIDs) conferring a predisposition to fungal infections can serve both purposes, as the elucidation of genetic etiologies of unexplained fungal diseases also improves our understanding of antifungal immunity in other settings [11–14]. In recent years, the genetic dissection of chronic mucocutaneous candidiasis disease (CMCD) has revealed a role for IL-17 in mucocutaneous immunity to *C. albicans* [7,15–18]. Other examples include the role played by CARD9 in IFDs caused by dermatophytes and *Candida* spp., that of IFN- γ in immunity to dimorphic fungi, and that of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex in immunity to *Aspergillus* spp. We review here the PIDs known to confer a predisposition to fungal infections.

Primary immunodeficiencies underlying chronic mucocutaneous candidiasis

Candida spp. are cosmopolite commensal yeasts colonizing the skin (*C. parapsilosis*) and digestive tract (*C. albicans*) of healthy individuals. However, they can lead to superficial mucocutaneous infections, which can occasionally become chronic (chronic mucocutaneous

candidiasis or CMC). CMC is characterized by persistent or recurrent infections of the mouth, esophagus, digestive and genital mucosae, nails and/or skin, mostly with *C. albicans*. CMC is frequent, and associated with other infections caused by a broad spectrum of microorganisms, in the context of acquired conditions (HIV infection, immunosuppressive therapies, prolonged antibiotic therapies, diabetes mellitus) or various inherited primary T-cell immunodeficiencies. Patients with severe combined immunodeficiencies (SCID) and patients with combined immunodeficiencies (CID) develop CMC in infancy due to T-cell deficiency [13,16]. Patients with idiopathic CD4 lymphopenia are also susceptible to CMC. All ($n=6$) known patients with an autosomal dominant (AD) $I\kappa B\alpha$ gain-of-function mutation [19,20] and impaired NF- κ B signaling have developed CMC and other fungal infections [19]. Two thirds of patients with CID and low T-cell counts, such as those with autosomal recessive (AR) DOCK8 deficiency, display CMC [21,22]. Those with CID and impaired T-cell function, caused by AR TCR- α , AR ORAI1, AR MST1/STK4, AR RFXANK or AR CD25 deficiencies, for example, have also been reported to display susceptibility to CMC [19,21–31].

In other PIDs, CMC is one of the main clinical presentations [15,16]. Approximately 85% of patients with AD STAT3 deficiency and hyper-IgE syndrome (AD-HIES) display CMC in addition to severe staphylococcal skin and pulmonary disease [26,32–36], with 64% of these patients displaying oral candidiasis from the neonatal period onwards. CMC has also been reported in 25% of patients with AR IL-12R β 1 or IL-12p40 deficiency, both of which are genetic etiologies of Mendelian susceptibility to mycobacterial disease (MSMD) [37,38]. Six of the seven patients reported in one large consanguineous multiplex kindred with AR CARD9 deficiency displayed CMC in addition to other fungal diseases [39]. In these three PIDs, patients have been shown to have a deficit of IL-17A- and IL-22-producing T cells [36,40–46]. This deficit probably results from impaired STAT3-dependent signaling downstream from IL-6, IL-21 and IL-23, impaired IL-12R β 1-dependent signaling downstream from IL-23 or impaired CARD9-dependent signaling downstream from C-type lectin receptors, respectively, these signaling pathways being involved in IL-17 T-cell development and maintenance [47,48]. Finally, in AR autoimmune polyendocrinopathy syndrome type 1 (APS-1 or APECED), caused by AIRE deficiency [49–51] and resulting in impaired T-cell tolerance, 88% of patients develop CMC at a mean age of 3.7 years [52]. High levels of neutralizing autoantibodies against IL-17A, IL-17F and/or IL-22 have been detected in the sera of APS-1 patients [41,52]. Overall, these studies strongly suggest that human IL-17 immunity plays a critical role in defense against CMC [15–17,53–57], and they paved the way for the identification of the first genetic etiologies of CMC disease (CMCD) [7].

CMCD is defined as CMC in patients with no other prominent clinical signs and with none of the genetic defects mentioned above. Complete AR IL-17RA and partial AD IL17F deficiencies, resulting in impaired IL-17 immunity, were first reported in one CMCD family each [58]. Subsequently, genome-wide approaches led to the discovery of heterozygous *STAT1* missense mutations in patients with CMCD [59,60]. These mutations, unlike the previously reported mono- or biallelic *STAT1* loss-of-function mutations associated with susceptibility to mycobacterial, intracellular bacterial and viral infections [61–63], were

shown to be gain-of-function (GOF). Almost 100 patients with *STAT1* GOF mutations have been reported to date [59,60,64–72]. These patients developed CMCD at a mean age of 1.4 years, mostly affecting the oropharynx (98%), nails (58%), skin (46%) and esophagus (20%). CMCD-causing *STAT1* mutations increase STAT1 responses to IFN- α/β , IFN- γ and IL-27, which repress IL-17 T-cell development, probably accounting for the small numbers of IL-17-producing T cells in these patients and the resulting CMCD [59]. Accordingly, GM-CSF, followed by G-CSF treatment, in one of these patients improved candidiasis and resulted, in parallel, in the restoration of normal IL17-producing T-cell counts and an increase in STAT3 levels [73], confirming the role of IL-17 cytokines in mucosal cutaneous immunity to *Candida* infections. Primary immunodeficiencies associated with chronic mucocutaneous candidiasis are summarized in Table 1. Other extensive superficial fungal infections, such as dermatophytosis [60,65] and recurrent skin fusariosis [81] (caused by an environmental hyalohyphomycete and leading to disseminated infections in neutropenic individuals [82–84]) have been observed in a few patients with *STAT1* GOF mutations.

Primary immunodeficiencies underlying invasive aspergillosis

Aspergillus spp. are present in soils and decaying plant material. Spores are inhaled, and hyphae can grow in the lungs, leading to pulmonary aspergillosis, the most frequent (90%) clinical presentation. Invasive aspergillosis is a life-threatening disease with an incidence of $0.27/10^3$ admissions and a global mortality rate at 3 months close to 45% [5]. The underlying diseases are mostly hematological malignancies and particularly acute myeloblastic leukemia (78%), with prolonged neutropenia, solid organ transplant, solid tumors, systemic inflammatory diseases and chronic respiratory diseases [5]. The prevalence of invasive aspergillosis is particularly high in patients with chronic granulomatous disease (CGD), 17% of whom develop invasive aspergillosis. *A. fumigatus* is the *Aspergillus* spp. most frequently associated with disease, found in approximately 40% of the CGD cases [85,86]. *A. nidulans*, which is encountered almost exclusively in CGD patients, is associated with a high mortality rate [87]. Invasive aspergillosis is mostly pulmonary in CGD patients [85,86]. This disease results from an NADPH oxidase complex defect in phagocytes, mostly due to X-linked (*CYBB*) mutations [88] or biallelic mutations in autosomal (*NCF1*, *NCF2*, *NCF4*, *CYBA*) genes [54–56,85,86,89–94]. Tissue susceptibility to bacteria and fungi is due to a defect in reactive oxygen (ROS) species production by phagocytes, resulting in an inability to kill microorganisms. Studies of patients with mycobacterial but not fungal disease and *CYBB* mutations impairing the respiratory burst in macrophages but not in monocytes or granulocytes [88] have suggested that disruption of the respiratory burst in granulocytes and monocytes underlies pulmonary aspergillosis in CGD patients.

Approximately 20% of AD-HIES patients develop invasive aspergillosis, always secondary to lung lesions (pneumatocyst formation or bronchiectasis), with 17% mortality [36,95]. AD-HIES patients display a normal inhibition of *A. fumigatus* growth by phagocytosis, unlike CGD patients [95]. The susceptibility of AD-HIES patients to IFD therefore results from the presence of pneumatocysts due to repeated bacterial infections of the lungs and defective STAT3-dependent epithelial immunity [95]. The incidence of invasive aspergillosis is also high, at 17%, in patients with AD GATA2 deficiency [55,96], as are the incidences of mycobacterial, papillomavirus and other fungal infections [97,98]. Consistent

with the role of GATA2 as a transcription factor involved in hematopoiesis and maintenance of the stem cell compartment, patients with GATA2 deficiency present a complex phenotype, with monocytopenia, B and NK lymphopenia, low counts of dendritic cells and myelodysplasia [96,97,99–101]. Finally, invasive aspergillosis has been reported in rare cases of AD or AR severe congenital neutropenia (SCN) [102–106] or AR type I leukocyte adhesion deficiency (CD18 deficiency) [107–109].

Primary immunodeficiencies underlying invasive candidiasis

Candida spp. also causes candidiasis, the most frequent presentation of which is as fungemia [110]. Candidiasis is the fourth most important cause of nosocomial blood stream infection [111,112] and the most frequent IFD in Western countries [113], with a mortality rate of 40% [110]. Candidiasis is classically described in neutropenic patients, intensive care unit patients with catheters, treated with broad-spectrum antibiotics and with parenteral nutrition. Invasive candidiasis has occasionally been reported in patients with PIDs: 2% ($n=486$) of the patients from the French SCN registry developed invasive candidiasis, for example [109]. Despite the scarcity of data, AR type 1 leukocyte adhesion deficiency with CD18 deficiency is also known to be complicated with invasive candidiasis [108]. *Candida* spp. infection of the central nervous system (CNS) is mostly reported after neurosurgery or in premature infants [114,115]. It has also been reported in CGD patients [92] and, recently, in patients with AR CARD9 deficiency. So far, at least three (probably four — three from an Iranian kindred and one of Korean origin) individuals have developed *Candida* infections of the CNS, at a mean age of 13 years [39,79], with *Candida* spp. meningoencephalitis reported in three cases. CARD9 is an adaptor molecule expressed in myeloid cells downstream from the C-type lectin receptors (CLR) Dectin-1, Dectin-2 and MINCLE [116–123], which recognize fungal pathogen-associated molecular patterns (PAMPs) [94,124,125]. After coil-coiled domain phosphorylation by PKC- δ [126], activated CARD9 couples with BCL10 and MALT1, resulting in NF- κ B activation, leading to the secretion of proinflammatory cytokines [126–129]. CARD9-deficient peripheral blood mononuclear cells (PBMCs) contain a smaller than normal proportion of IL-17 T cells, but the role of IL-17 immunity in human defense against *Candida* invasive infection remains unclear [39]. In addition, PBMCs and neutrophils display impaired proinflammatory cytokine release in response to *Candida* stimulation [79]. Moreover, an impairment of neutrophil killing of unopsonized *Candida* yeasts has been observed, despite normal levels of NADPH oxidase activity in response to *Candida* stimulation in the patient tested. Nonetheless, it was suggested that the patient's neutrophils displayed an abnormal phagolysosome function in contact with *C. albicans*, on the basis of electron microscopy [79]. The preferential CNS location of *Candida* infection in CARD9- deficient patients may also result from the inability of monocytes, macrophages and/or microglial cells to eliminate *Candida* efficiently at the blood brain barrier [54].

Primary immunodeficiencies underlying deep dermatophytosis

Dermatophytes are cosmopolite filamentous fungi that frequently cause benign infections, such as tinea capitis and corporis and onychomycosis [130]. By contrast, deep dermatophytosis is a rare condition defined by the invasion of the dermis and hypodermis by

dermatophytes, sometimes associated with lymph node, brain, digestive tract or bone involvement [131,132]. Deep dermatophytosis has been reported in immunocompromised patients with HIV infection ($n=3$) or on immunosuppressive therapy ($n=16$) [133]. Sixty-nine cases have been reported in patients without known immunodeficiency [134–144], 45 of whom originated from North Africa. Twenty-four of these patients were from consanguineous families, with 19 familial cases from eight multiplex families. This strongly suggests that predisposition to idiopathic deep dermatophytosis is inherited as an AR trait. Recently, 17 patients from eight kindreds with idiopathic deep dermatophytosis from North Africa (11 previously reported [134,141,145–149]) were shown to display AR CARD9 deficiency [80]. Fifteen Algerian and Tunisian patients carried the same homozygous Q289X allele inherited from a common ancestor living approximately 975 years ago. Whole blood from the patients displayed impaired IL-6 production in response to stimulation with heat-killed *C. albicans* and *S. cerevisiae*, and PBMCs were found to contain a particularly small proportion of circulating IL-17-producing T cells. The only other infectious condition observed was thrush, in 35% of the patients [80]. These data provided evidence for a role of CARD9 in antifungal defense against dermatophytes, broadening the spectrum of IFDs associated with CARD9 deficiency. However, the underlying mechanism remains to be elucidated.

Primary immunodeficiencies underlying dimorphic fungal infections (endemic mycoses)

Dimorphic fungi are present as hyphae in the environment and as yeasts in tissues, the transition between these two forms being triggered by temperature changes. They have a limited geographic distribution. *Coccidioides immitis* or *posadii* is endemic to the South West United States, *Paracoccidioides brasiliensis* is endemic to Latin America and *Histoplasma capsulatum* is endemic to the Midwestern United States [150,151]. Infection occurs by spore inhalation. Disseminated histoplasmosis occurs in patients with immunodeficiency, mostly AIDS, and involves the lymph nodes, liver, spleen, mucosae, bone marrow and brain [152]. Disseminated coccidioidomycosis involves the lungs, central nervous system and bones and occurs in patients without known risk factors in 55% of cases [153]. Patients with mutations affecting the IL-12/IFN- γ circuit and MSMD [37] have been reported with dimorphic fungal infections. Indeed, IL-12R β 1-deficient patients from Arizona, India and Brazil with coccidioidomycosis, ($n=2$) histoplasmosis ($n=1$), and paracoccidioidomycosis ($n=1$) have been reported [37,154,155]. Similarly, two IFN- γ R1-deficient patients, one from Arizona and one from Texas, with disseminated coccidioidomycosis and histoplasmosis, respectively, have been described [156,157]. Salmonellosis and mycobacterial infections were associated with these infections in all but one patient. Patients with disseminated dimorphic infections should therefore be explored for defects of the IFN- γ /IL-12 circuit and patients with deficiencies in the IFN- γ /IL-12 axis should be considered at risk of infection with endemic fungi. Five patients with heterozygous *STAT1* GOF mutations have recently been reported, two with disseminated coccidioidomycosis and three with histoplasmosis [65]. Endemic mycosis occurred in these patients at a mean age of 13 years. Finally, disseminated histoplasmosis has also been

reported in patients with AD GATA2 deficiency [96,98], AR-DOCK8 deficiency [25], idiopathic CD4 lymphopenia [158–161], and X-linked CD40L deficiency [162,163].

Primary immunodeficiencies underlying cryptococcosis

Cryptococcosis is a fungal infection mostly caused by the encapsulated yeast *Cryptococcus neoformans*. The burden of cryptococcosis is high: one million cases are reported each year in Sub-Saharan Africa, with more than 600,000 deaths/year in human immunodeficiency virus (HIV)-infected patients, in whom such infections are the fourth leading cause of death [164]. *Cryptococcus neoformans* is present in the soil. The major route of infection is probably inhalation. The main clinical presentation for *C. neoformans* infections is meningoencephalitis (90% in HIV-positive and 70% in HIV-negative individuals) [165]. Other risk factors include solid organ transplantation, hematological malignancies, diabetes mellitus, cirrhosis, sarcoidosis, CD4 T-cell lymphopenia, prolonged corticosteroid or immunosuppressive treatment. Cryptococcosis has been reported in patients with idiopathic CD4 lymphopenia [166,167], with AD GATA2 deficiency [96], and in a few patients with X-linked CD40L deficiency [168,169]. In addition, cryptococcosis was found in eight patients with neutralizing autoantibodies against IFN- γ [170] and seven patients with neutralizing autoantibodies against GM-CSF [171]. These data suggest, in addition to CD4⁺ T cells, a role for GM-CSF and IFN- γ in defenses against cryptococcosis, at the level of pulmonary macrophages. In patients of East Asian descents with disseminated nontuberculous mycobacterial infections, a genetic origin has recently been demonstrated for the presence of autoantibodies against IFN- γ [172,173]. Genetic defects of the IFN- γ and/or GM-CSF signaling pathways may, therefore, create a predisposition to cryptococcosis. No genetic etiology has yet been identified in patients with unexplained and isolated cryptococcosis.

Primary immunodeficiencies underlying *Pneumocystis jirovecii* pneumonia

P. jirovecii is an obligate extracellular fungus [174]. *Pneumocystis* spp. are host-specific and *P. jirovecii* is an exclusively human pathogen [175,176]. This fungus is ubiquitous and seroconversion occurs early in life. *P. jirovecii* is transmitted from individual to individual, through the air. It causes a severe form of interstitial pneumonia in patients with acquired or inherited IDs. Pneumocystosis was the first infection reported in patients with AIDS in the USA, in 1981 [177,178]. Pneumocystis pneumonia remains one of the leading causes of mortality and morbidity in AIDS patients [179], and develops when CD4⁺ T-cell count falls below 200 cell/ μ l [178]. *P. jirovecii* pneumonia is also frequent in patients with severe combined immunodeficiency (SCID), and in patients with idiopathic CD4 lymphopenia [31,158,167], demonstrating the crucial role of CD4 T cells. Patients with impaired NF- κ B signaling, AD I κ B- α gain-of-function mutations [19,20] and X-linked NEMO deficiency [19], AR MHC class II deficiency [180], AR DOCK8 deficiency and X-linked Wiskott-Aldrich syndrome [25,181] also develop pneumocystosis. Finally, *P. jirovecii* pneumonia is common in patients with X-linked CD40L deficiency, associated with recurrent bacterial and cryptosporidium infections. In a series of 79 XHIGM patients, 48% developed *P. jirovecii* pneumonia at a median age of 1.26 years, and this infection was often the revelatory symptom for XHIGM diagnosis [168]. XHIGM is caused by mutations of

CD40L, encoding the CD40 ligand, which is expressed on T cells and necessary for cooperation between T and B lymphocytes and immunoglobulin class switch. Affected patients therefore have deficiencies of IgG, IgA and IgE and high levels of IgM antibodies. CD40L is also required for the maturation of antigen-presenting cells, the stimulation of macrophage effector functions and the antigen priming of T lymphocytes [168]. The T-cell defect is probably the main cause of pneumocystosis in this PID. Primary immunodeficiencies associated with invasive fungal diseases are summarized in Table 2. Main PIDs associated with fungal infections are presented in Table 3.

Conclusion

If the last few years are anything to go by, the near future will bear witness to the discovery of single-gene inborn errors of immunity underlying fungal infections. Progress in this area will be facilitated by technological progress, in deep sequencing in particular, making it possible to decipher genetic etiologies of infectious diseases, including IFDs in particular. The genetic dissection of both superficial and invasive fungal diseases should progressively lead to elucidation of the molecular and cellular mechanisms underlying protective immunity to fungal pathogens. Genetic dissection of the pathogenesis of inherited IFD will shed new light on the pathogenesis of IFD in other settings. The further genetic dissection of patients with no known risk factor displaying IFD should lead to the identification of new genetic etiologies of IFD. These discoveries will improve our knowledge of human antifungal immunity and should pave the way for the development of new, more appropriate treatments.

Acknowledgments

This work was funded by the ANR grant GENCMCD 11-BSV3-005-01 to AP, grant number UL1TR000043 from the National Center for Advancing Translational Sciences, National Institutes of Health Clinical and Translational Science Award (CTSA) program, the Rockefeller University, the St. Giles Foundation, the Rockefeller University, INSERM and Paris Descartes University French Government *Investissement d'Avenir* program, *Laboratoire d'Excellence* "Integrative Biology of Emerging Infectious Diseases" (ANR-10-LABX-62-IBEID). F.L. was supported by a grant from the CMIT (French Faculties College of Infectious Diseases) and INSERM.

References

1. Brown GD, Denning DW, Levitz SM. Tackling human fungal infections. *Science*. 2012; 336:647. [PubMed: 22582229]
2. Brown GD, Denning DW, Gow NA, Levitz SM, Netea MG, White TC. Hidden killers: human fungal infections. *Sci Transl Med*. 2012; 4:165rv113.
3. Lass-Flörl C. The changing face of epidemiology of invasive fungal disease in Europe. *Mycoses*. 2009; 52:197–205. [PubMed: 19391253]
4. Chakrabarti A, Singh R. The emerging epidemiology of mould infections in developing countries. *Curr Opin Infect Dis*. 2011; 24:521–526. [PubMed: 21799406]
5. Lortholary O, Gangneux JP, Sitbon K, Lebeau B, de Monbrison F, Le Strat Y, Coignard B, Dromer F, Bretagne S. Epidemiological trends in invasive aspergillosis in France: the SAIIF network (2005–2007). *Clin Microbiol Infect*. 2011; 17:1882–1889. [PubMed: 21668573]
6. Nivoix Y, Velten M, Letscher-Bru V, Moghaddam A, Natarajan-Ame S, Fohrer C, Lioure B, Bilger K, Lutun P, Marcellin L, et al. Factors associated with overall and attributable mortality in invasive aspergillosis. *Clin Infect Dis*. 2008; 47:1176–1184. [PubMed: 18808352]
7. LeibundGut-Landmann S, Wuthrich M, Hohl TM. Immunity to fungi. *Curr Opin Immunol*. 2012; 24:449–458. [PubMed: 22613091]

8. Kirkpatrick CH, Rich RR, Bennett JE. Chronic mucocutaneous candidiasis: model-building in cellular immunity. *Ann Intern Med.* 1971; 74:955–978. [PubMed: 4931743]
9. Armstrong-James D, Harrison TS. Immunotherapy for fungal infections. *Curr Opin Microbiol.* 2012; 15:434–439. [PubMed: 22884572]
10. Casadevall A, Pirofski LA. Immunoglobulins in defense, pathogenesis, and therapy of fungal diseases. *Cell Host Microbe.* 2012; 11:447–456. [PubMed: 22607798]
11. Parvaneh N, Casanova JL, Notarangelo LD, Conley ME. Primary immunodeficiencies: a rapidly evolving story. *J Allergy Clin Immunol.* 2013; 131:314–323. [PubMed: 23374262]
12. Casanova JL, Abel L. The Genetic Theory of Infectious Diseases: A Brief History and Selected Illustrations. *Annu Rev Genomics Hum Genet.* 2013
13. Casanova JL, Abel L. Primary immunodeficiencies: a field in its infancy. *Science.* 2007; 317:617–619. [PubMed: 17673650]
14. Alcais A, Abel L, Casanova JL. Human genetics of infectious diseases: between proof of principle and paradigm. *J Clin Invest.* 2009; 119:2506–2514. [PubMed: 19729848]
15. Puel A, Picard C, Cypowyj S, Lilic D, Abel L, Casanova JL. Inborn errors of mucocutaneous immunity to *Candida albicans* in humans: a role for IL-17 cytokines? *Curr Opin Immunol.* 2010; 22:467–474. [PubMed: 20674321]
- 16*. Puel A, Cypowyj S, Marodi L, Abel L, Picard C, Casanova JL. Inborn errors of human IL-17 immunity underlie chronic mucocutaneous candidiasis. *Curr Opin Allergy Clin Immunol.* 2012; 12:616–622. A comprehensive review on primary immunodeficiencies (PIDs) with chronic mucocutaneous candidiasis and impaired IL-17 immunity. [PubMed: 23026768]
17. Hernandez-Santos N, Gaffen SL. Th17 cells in immunity to *Candida albicans*. *Cell Host Microbe.* 2012; 11:425–435. [PubMed: 22607796]
- 18*. Sillevs Smitt JH, Kuijpers TW. Cutaneous manifestations of primary immunodeficiency. *Curr Opin Pediatr.* 2013; 25:492–497. A comprehensive review of the main cutaneous signs associated with PIDs. [PubMed: 23744097]
19. Picard C, Casanova JL, Puel A. Infectious diseases in patients with IRAK-4, MyD88, NEMO, or IkappaBalpha deficiency. *Clin Microbiol Rev.* 2011; 24:490–497. [PubMed: 21734245]
20. Schimke LF, Rieber N, Rylaarsdam S, Cabral-Marques O, Hubbard N, Puel A, Kallmann L, Sombke SA, Notheis G, Schwarz HP, et al. A Novel Gain-of-Function IKBA Mutation Underlies Ectodermal Dysplasia with Immunodeficiency and Polyendocrinopathy. *J Clin Immunol.* 2013; 33:1088–1099. [PubMed: 23708964]
21. Zhang Q, Davis JC, Lamborn IT, Freeman AF, Jing H, Favreau AJ, Matthews HF, Davis J, Turner ML, Uzel G, et al. Combined immunodeficiency associated with DOCK8 mutations. *N Engl J Med.* 2009; 361:2046–2055. [PubMed: 19776401]
22. Engelhardt KR, McGhee S, Winkler S, Sassi A, Woellner C, Lopez-Herrera G, Chen A, Kim HS, Lloret MG, Schulze I, et al. Large deletions and point mutations involving the dedicator of cytokinesis 8 (DOCK8) in the autosomal-recessive form of hyper-IgE syndrome. *J Allergy Clin Immunol.* 2009; 124:1289–1302. e1284. [PubMed: 20004785]
23. Caudy AA, Reddy ST, Chatila T, Atkinson JP, Verbsky JW. CD25 deficiency causes an immune dysregulation, polyendocrinopathy, enteropathy, X-linked-like syndrome, and defective IL-10 expression from CD4 lymphocytes. *J Allergy Clin Immunol.* 2007; 119:482–487. [PubMed: 17196245]
24. Sharfe N, Dadi HK, Shahar M, Roifman CM. Human immune disorder arising from mutation of the alpha chain of the interleukin-2 receptor. *Proc Natl Acad Sci U S A.* 1997; 94:3168–3171. [PubMed: 9096364]
25. Su HC, Jing H, Zhang Q. DOCK8 deficiency. *Ann N Y Acad Sci.* 2011; 1246:26–33. [PubMed: 22236427]
26. Minegishi Y, Karasuyama H. Hyperimmunoglobulin E syndrome and tyrosine kinase 2 deficiency. *Curr Opin Allergy Clin Immunol.* 2007; 7:506–509. [PubMed: 17989526]
27. Morgan NV, Goddard S, Cardno TS, McDonald D, Rahman F, Barge D, Ciupek A, Straatman-Iwanowska A, Pasha S, Guckian M, et al. Mutation in the TCRalpha subunit constant gene (TRAC) leads to a human immunodeficiency disorder characterized by a lack of TCRalphabeta+ T cells. *J Clin Invest.* 2011; 121:695–702. [PubMed: 21206088]

28. Abdollahpour H, Appaswamy G, Kotlarz D, Diestelhorst J, Beier R, Schaffer AA, Gertz EM, Schambach A, Kreipe HH, Pfeifer D, et al. The phenotype of human STK4 deficiency. *Blood*. 2012; 119:3450–3457. [PubMed: 22294732]
29. Crequer A, Picard C, Patin E, D'Amico A, Abhyankar A, Munzer M, Debre M, Zhang SY, de Saint-Basile G, Fischer A, et al. Inherited MST1 deficiency underlies susceptibility to EV-HPV infections. *PLoS One*. 2012; 7:e44010. [PubMed: 22952854]
30. Ouederni M, Vincent QB, Frange P, Touzot F, Scerra S, Bejaoui M, Bousfiha A, Levy Y, Lisowska-Groszpiere B, Canioni D, et al. Major histocompatibility complex class II expression deficiency caused by a RFXANK founder mutation: a survey of 35 patients. *Blood*. 2011; 118:5108–5118. [PubMed: 21908431]
31. Zonios DI, Falloon J, Bennett JE, Shaw PA, Chaït D, Baseler MW, Adelsberger JW, Metcalf JA, Polis MA, Kovacs SJ, et al. Idiopathic CD4+ lymphocytopenia: natural history and prognostic factors. *Blood*. 2008; 112:287–294. [PubMed: 18456875]
32. Schimke LF, Sawalle-Belohradsky J, Roesler J, Wollenberg A, Rack A, Borte M, Rieber N, Cremer R, Maass E, Dopfer R, et al. Diagnostic approach to the hyper-IgE syndromes: immunologic and clinical key findings to differentiate hyper-IgE syndromes from atopic dermatitis. *J Allergy Clin Immunol*. 2010; 126:611–617. e611. [PubMed: 20816194]
33. Jiao H, Toth B, Erdos M, Fransson I, Rakoczi E, Balogh I, Magyarics Z, Derfalvi B, Csorba G, Szaflarska A, et al. Novel and recurrent STAT3 mutations in hyper-IgE syndrome patients from different ethnic groups. *Mol Immunol*. 2008; 46:202–206. [PubMed: 18706697]
34. Woellner C, Gertz EM, Schaffer AA, Lagos M, Perro M, Glocker EO, Pietrogrande MC, Cossu F, Franco JL, Matamoros N, et al. Mutations in STAT3 and diagnostic guidelines for hyper-IgE syndrome. *J Allergy Clin Immunol*. 2010; 125:424–432. e428. [PubMed: 20159255]
35. Holland SM, DeLeo FR, Elloumi HZ, Hsu AP, Uzel G, Brodsky N, Freeman AF, Demidowich A, Davis J, Turner ML, et al. STAT3 mutations in the hyper-IgE syndrome. *N Engl J Med*. 2007; 357:1608–1619. [PubMed: 17881745]
- 36*. Chandesris MO, Melki I, Natividad A, Puel A, Fieschi C, Yun L, Thumerelle C, Oksenhendler E, Boutboul D, Thomas C, et al. Autosomal dominant STAT3 deficiency and hyper-IgE syndrome: molecular, cellular, and clinical features from a French national survey. *Medicine (Baltimore)*. 2012; 91:e1–19. An extensive clinical, cellular and molecular description of 60 patients with STAT3 deficiency. [PubMed: 22751495]
37. de Beaucoudrey L, Samarina A, Bustamante J, Cobat A, Boisson-Dupuis S, Feinberg J, Al-Muhsen S, Janniere L, Rose Y, de Suremain M, et al. Revisiting human IL-12Rbeta1 deficiency: a survey of 141 patients from 30 countries. *Medicine (Baltimore)*. 2010; 89:381–402. [PubMed: 21057261]
38. Prando C, Samarina A, Bustamante J, Boisson-Dupuis S, Cobat A, Picard C, AlSum Z, Al-Jumaah S, Al-Hajjar S, Frayha H, et al. Inherited IL-12p40 deficiency: genetic, immunologic, and clinical features of 49 patients from 30 kindreds. *Medicine (Baltimore)*. 2013; 92:109–122. [PubMed: 23429356]
39. Glocker EO, Hennigs A, Nabavi M, Schaffer AA, Woellner C, Salzer U, Pfeifer D, Veelken H, Warnatz K, Tahami F, et al. A homozygous CARD9 mutation in a family with susceptibility to fungal infections. *N Engl J Med*. 2009; 361:1727–1735. [PubMed: 19864672]
40. de Beaucoudrey L, Puel A, Filipe-Santos O, Cobat A, Ghandil P, Chrabieh M, Feinberg J, von Bernuth H, Samarina A, Janniere L, et al. Mutations in STAT3 and IL12RB1 impair the development of human IL-17-producing T cells. *J Exp Med*. 2008; 205:1543–1550. [PubMed: 18591412]
41. Kisand K, Boe Wolff AS, Podkrajsek KT, Tserel L, Link M, Kisand KV, Ersvaer E, Perheentupa J, Erichsen MM, Bratanic N, et al. Chronic mucocutaneous candidiasis in APECED or thymoma patients correlates with autoimmunity to Th17-associated cytokines. *J Exp Med*. 2010; 207:299–308. [PubMed: 20123959]
42. Minegishi Y, Saito M, Nagasawa M, Takada H, Hara T, Tsuchiya S, Agematsu K, Yamada M, Kawamura N, Ariga T, et al. Molecular explanation for the contradiction between systemic Th17 defect and localized bacterial infection in hyper-IgE syndrome. *J Exp Med*. 2009; 206:1291–1301. [PubMed: 19487419]

43. Milner JD, Brenchley JM, Laurence A, Freeman AF, Hill BJ, Elias KM, Kanno Y, Spalding C, Elloumi HZ, Paulson ML, et al. Impaired T(H)17 cell differentiation in subjects with autosomal dominant hyper-IgE syndrome. *Nature*. 2008; 452:773–776. [PubMed: 18337720]
44. Ma CS, Chew GY, Simpson N, Priyadarshi A, Wong M, Grimbacher B, Fulcher DA, Tangye SG, Cook MC. Deficiency of Th17 cells in hyper IgE syndrome due to mutations in STAT3. *J Exp Med*. 2008; 205:1551–1557. [PubMed: 18591410]
45. Renner ED, Rylaarsdam S, Anover-Sombke S, Rack AL, Reichenbach J, Carey JC, Zhu Q, Jansson AF, Barboza J, Schimke LF, et al. Novel signal transducer and activator of transcription 3 (STAT3) mutations, reduced T(H)17 cell numbers, and variably defective STAT3 phosphorylation in hyper-IgE syndrome. *J Allergy Clin Immunol*. 2008; 122:181–187. [PubMed: 18602572]
46. Romani L. Immunity to fungal infections. *Nat Rev Immunol*. 2011; 11:275–288. [PubMed: 21394104]
47. Zhou L, Ivanov, Spolski R, Min R, Shenderov K, Egawa T, Levy DE, Leonard WJ, Littman DR. IL-6 programs T(H)-17 cell differentiation by promoting sequential engagement of the IL-21 and IL-23 pathways. *Nat Immunol*. 2007; 8:967–974. [PubMed: 17581537]
48. Bettelli E, Carrier Y, Gao W, Korn T, Strom TB, Oukka M, Weiner HL, Kuchroo VK. Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells. *Nature*. 2006; 441:235–238. [PubMed: 16648838]
49. Notarangelo LD, Gambineri E, Badolato R. Immunodeficiencies with autoimmune consequences. *Adv Immunol*. 2006; 89:321–370. [PubMed: 16682278]
50. Nagamine K, Peterson P, Scott HS, Kudoh J, Minoshima S, Heino M, Krohn KJ, Laloti MD, Mullis PE, Antonarakis SE, et al. Positional cloning of the APECED gene. *Nat Genet*. 1997; 17:393–398. [PubMed: 9398839]
51. Peterson P, Pitkanen J, Sillanpaa N, Krohn K. Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED): a model disease to study molecular aspects of endocrine autoimmunity. *Clin Exp Immunol*. 2004; 135:348–357. [PubMed: 15008965]
52. Puel A, Doffinger R, Natividad A, Chrabieh M, Barcenas-Morales G, Picard C, Cobat A, Ouachee-Chardin M, Toulon A, Bustamante J, et al. Autoantibodies against IL-17A, IL-17F, and IL-22 in patients with chronic mucocutaneous candidiasis and autoimmune polyendocrine syndrome type I. *J Exp Med*. 2010; 207:291–297. [PubMed: 20123958]
- 53*. Cypowyj S, Picard C, Marodi L, Casanova JL, Puel A. Immunity to infection in IL-17-deficient mice and humans. *Eur J Immunol*. 2012; 42:2246–2254. A comprehensive review of the role of IL-17 immunity in mice and humans. [PubMed: 22949323]
54. Vinh DC. Insights into human antifungal immunity from primary immunodeficiencies. *Lancet Infect Dis*. 2011; 11:780–792. [PubMed: 21958581]
- 55*. Lionakis MS. Genetic Susceptibility to Fungal Infections in Humans. *Curr Fungal Infect Rep*. 2012; 6:11–22. A comprehensive review on PIDs and fungal infections. [PubMed: 23087779]
- 56*. Lilic D. Unravelling fungal immunity through primary immune deficiencies. *Curr Opin Microbiol*. 2012; 15:420–426. A comprehensive review on PIDs conferring a predisposition to fungal infections and improvements in antifungal immunity knowledge arising from their study. [PubMed: 22818901]
57. Smeekens SP, van de Veerdonk FL, Kullberg BJ, Netea MG. Genetic susceptibility to *Candida* infections. *EMBO Mol Med*. 2013; 5:805–813. [PubMed: 23629947]
58. Puel A, Cypowyj S, Bustamante J, Wright JF, Liu L, Lim HK, Migaud M, Israel L, Chrabieh M, Audry M, et al. Chronic mucocutaneous candidiasis in humans with inborn errors of interleukin-17 immunity. *Science*. 2011; 332:65–68. [PubMed: 21350122]
59. Liu L, Okada S, Kong XF, Kreins AY, Cypowyj S, Abhyankar A, Toubiana J, Itan Y, Audry M, Nitschke P, et al. Gain-of-function human STAT1 mutations impair IL-17 immunity and underlie chronic mucocutaneous candidiasis. *J Exp Med*. 2011; 208:1635–1648. [PubMed: 21727188]
60. van de Veerdonk FL, Plantinga TS, Hoischen A, Smeekens SP, Joosten LA, Gilissen C, Arts P, Rosentul DC, Carmichael AJ, Smits-van der Graaf CA, et al. STAT1 mutations in autosomal dominant chronic mucocutaneous candidiasis. *N Engl J Med*. 2011; 365:54–61. [PubMed: 21714643]

61. Chapgier A, Boisson-Dupuis S, Jouanguy E, Vogt G, Feinberg J, Prochnicka-Chalufour A, Casrouge A, Yang K, Soudais C, Fieschi C, et al. Novel STAT1 alleles in otherwise healthy patients with mycobacterial disease. *PLoS Genet.* 2006; 2:e131. [PubMed: 16934001]
62. 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 of immunological and infectious phenotypes. *Curr Opin Immunol.* 2012; 24:364–378. [PubMed: 22651901]
- 63*. Casanova JL, Holland SM, Notarangelo LD. Inborn errors of human JAKs and STATs. *Immunity.* 2012; 36:515–528. A comprehensive review on inborn errors of the JAK and STAT pathway. [PubMed: 22520845]
64. Soltesz B, Toth B, Shabashova N, Bondarenko A, Okada S, Cypowyj S, Abhyankar A, Csorba G, Tasko S, Sarkadi AK, et al. New and recurrent gain-of-function STAT1 mutations in patients with chronic mucocutaneous candidiasis from Eastern and Central Europe. *J Med Genet.* 2013; 50:567–78. [PubMed: 23709754]
- 65*. Sampaio EP, Hsu AP, Pechacek J, Bax HI, Dias DL, Paulson ML, Chandrasekaran P, Rosen LB, Carvalho DS, Ding L, et al. Signal transducer and activator of transcription 1 (STAT1) gain-of-function mutations and disseminated coccidioidomycosis and histoplasmosis. *J Allergy Clin Immunol.* 2013; 131:1624–1634. e1617. First report of five patients with histoplasmosis or coccidioidomycosis and *STAT1* gain-of-function mutation. [PubMed: 23541320]
66. Al Rushood M, McCusker C, Mazer B, Alizadehfar R, Grimbacher B, Depner M, Ben-Shoshan M. Autosomal dominant cases of chronic mucocutaneous candidiasis segregates with mutations of signal transducer and activator of transcription 1, but not of toll-like receptor 3. *J Pediatr.* 2013; 163:277–279. [PubMed: 23541088]
67. Uzel G, Sampaio EP, Lawrence MG, Hsu AP, Hackett M, Dorsey MJ, Noel RJ, Verbsky JW, Freeman AF, Janssen E, et al. Dominant gain-of-function STAT1 mutations in FOXP3 wild-type immune dysregulation-polyendocrinopathy-enteropathy-X-linked-like syndrome. *J Allergy Clin Immunol.* 2013; 131:1611–1623. e1613. [PubMed: 23534974]
68. Toth B, Mehes L, Tasko S, Szalai Z, Tulassay Z, Cypowyj S, Casanova JL, Puel A, Marodi L. Herpes in STAT1 gain-of-function mutation [corrected]. *Lancet.* 2012; 379:2500. [PubMed: 22748593]
69. Smeekens SP, Plantinga TS, van de Veerdonk FL, Heinhuis B, Hoischen A, Joosten LA, Arkwright PD, Gennery A, Kullberg BJ, Veltman JA, et al. STAT1 hyperphosphorylation and defective IL12R/IL23R signaling underlie defective immunity in autosomal dominant chronic mucocutaneous candidiasis. *PLoS One.* 2013; 6:e29248. [PubMed: 22195034]
70. Takezaki S, Yamada M, Kato M, Park MJ, Maruyama K, Yamazaki Y, Chida N, Ohara O, Kobayashi I, Ariga T. Chronic Mucocutaneous Candidiasis Caused by a Gain-of-Function Mutation in the STAT1 DNA-Binding Domain. *J Immunol.* 2012; 189:1521–1526. [PubMed: 22730530]
71. Romberg N, Morbach H, Lawrence MG, Kim S, Kang I, Holland SM, Milner JD, Meffre E. Gain-of-function STAT1 mutations are associated with PD-L1 overexpression and a defect in B-cell survival. *J Allergy Clin Immunol.* 2013; 131:1691–1693. [PubMed: 23403048]
72. Hori T, Ohnishi H, Teramoto T, Tsubouchi K, Naiki T, Hirose Y, Ohara O, Seishima M, Kaneko H, Fukao T, et al. Autosomal-dominant chronic mucocutaneous candidiasis with STAT1- mutation can be complicated with chronic active hepatitis and hypothyroidism. *J Clin Immunol.* 2012; 32:1213–1220. [PubMed: 22847544]
- 73*. Wildbaum G, Shahar E, Katz R, Karin N, Etzioni A, Pollack S. Continuous G-CSF therapy for isolated chronic mucocutaneous candidiasis: Complete clinical remission with restoration of IL-17 secretion. *J Allergy Clin Immunol.* 2013 Report of a patient with CMCD associated with *STAT1* GOF mutation cured by G-CSF treatment. 10.1016/j.jaci.2013.04.018
74. Puck JM. Neonatal screening for severe combined immunodeficiency. *Curr Opin Pediatr.* 2011; 23:667–673. [PubMed: 22001765]
75. Feske S, Gwack Y, Prakriya M, Srikanth S, Puppel SH, Tanasa B, Hogan PG, Lewis RS, Daly M, Rao A. A mutation in *Orai1* causes immune deficiency by abrogating CRAC channel function. *Nature.* 2006; 441:179–185. [PubMed: 16582901]
76. Gorska MM, Alam R. A mutation in the human Uncoordinated 119 gene impairs TCR signaling and is associated with CD4 lymphopenia. *Blood.* 2012; 119:1399–1406. [PubMed: 22184408]

77. Li FY, Chaigne-Delalande B, Kanellopoulou C, Davis JC, Matthews HF, Douek DC, Cohen JI, Uzel G, Su HC, Lenardo MJ. Second messenger role for Mg²⁺ revealed by human T-cell immunodeficiency. *Nature*. 2011; 475:471–476. [PubMed: 21796205]
78. Kuijpers TW, Ijspeert H, van Leeuwen EM, Jansen MH, Hazenberg MD, Weijer KC, van Lier RA, van der Burg M. Idiopathic CD4⁺ T lymphopenia without autoimmunity or granulomatous disease in the slipstream of RAG mutations. *Blood*. 2011; 117:5892–5896. [PubMed: 21502542]
- 79*. Drewniak A, Gazendam RP, Tool AT, van Houdt M, Jansen MH, van Hamme JL, van Leeuwen EM, Roos D, Scalais E, de Beaufort C, et al. Invasive fungal infection and impaired neutrophil killing in human CARD9 deficiency. *Blood*. 2013; 121:2385–2392. CARD9 deficiency in a patient with *Candida* meningitis associated and a defect of *Candida* killing by polymorphonuclear cells. [PubMed: 23335372]
- 80*. Lanternier F, Pathan S, Vincent Q, Liu L, Cypowij S, Prando C, Migaud M, Taibi L, Ammar-Khodja A, Boudghene Stambouli O, et al. Human deep dermatophytosis and inherited CARD9 deficiency. *N Engl J Med*. 2013 In press. Identification of the first genetic etiology of deep dermatophytosis with CARD9 deficiency reported in 17 patients from North Africa.
81. Wang X, Lin Z, Gao L, Wang A, Wan Z, Chen W, Yang Y, Li R. Exome sequencing reveals a signal transducer and activator of transcription 1 (STAT1) mutation in a child with recalcitrant cutaneous fusariosis. *J Allergy Clin Immunol*. 2013; 131:1242–1243. [PubMed: 23245795]
82. Neji S, Trabelsi H, Cheikhrouhou F, Sellami H, Guidara R, Trigui A, Feki J, Boudaya S, Turki H, Makni F, et al. Fusariosis diagnosed in the laboratory of an UH in Tunisia: Epidemiological, clinical and mycological study. *J Mycol Med*. 2013; 23:130–135. [PubMed: 23725904]
83. Troke P, Obenga G, Gaujoux T, Goldschmidt P, Bienvenu AL, Cornet M, Grenouillet F, Pons D, Ranque S, Sithon K, et al. The efficacy of voriconazole in 24 ocular *Fusarium* infections. *Infection*. 2010; 41:15–20. [PubMed: 22718362]
84. Nkondjo Minkoumou S, Fabrizi V, Papini M. Onychomycosis in Cameroon: a clinical and epidemiological study among dermatological patients. *Int J Dermatol*. 2012; 51:1474–1477. [PubMed: 23171013]
85. Beaute J, Obenga G, Le Mignot L, Mahlaoui N, Bougnoux ME, Mouy R, Gougerot-Pocidalo MA, Barlogis V, Suarez F, Lanternier F, et al. Epidemiology and outcome of invasive fungal diseases in patients with chronic granulomatous disease: a multicenter study in France. *Pediatr Infect Dis J*. 2011; 30:57–62. [PubMed: 20700078]
86. Blumental S, Mouy R, Mahlaoui N, Bougnoux ME, Debre M, Beaute J, Lortholary O, Blanche S, Fischer A. Invasive mold infections in chronic granulomatous disease: a 25-year retrospective survey. *Clin Infect Dis*. 2011; 53:e159–169. [PubMed: 22080130]
87. Segal BH, DeCarlo ES, Kwon-Chung KJ, Malech HL, Gallin JI, Holland SM. *Aspergillus nidulans* infection in chronic granulomatous disease. *Medicine (Baltimore)*. 1998; 77:345–354. [PubMed: 9772923]
88. Bustamante J, Arias AA, Vogt G, Picard C, Galicia LB, Prando C, Grant AV, Marchal CC, Hubeau M, Chapgier A, et al. Germline CYBB mutations that selectively affect macrophages in kindreds with X-linked predisposition to tuberculous mycobacterial disease. *Nat Immunol*. 2011; 12:213–221. [PubMed: 21278736]
89. Kuhns DB, Alvord WG, Heller T, Feld JJ, Pike KM, Marciano BE, Uzel G, DeRavin SS, Priel DA, Soule BP, et al. Residual NADPH oxidase and survival in chronic granulomatous disease. *N Engl J Med*. 2010; 363:2600–2610. [PubMed: 21190454]
90. Matute JD, Arias AA, Wright NA, Wrobel I, Waterhouse CC, Li XJ, Marchal CC, Stull ND, Lewis DB, Steele M, et al. A new genetic subgroup of chronic granulomatous disease with autosomal recessive mutations in p40 phox and selective defects in neutrophil NADPH oxidase activity. *Blood*. 2009; 114:3309–3315. [PubMed: 19692703]
91. Falcone EL, Holland SM. Invasive fungal infection in chronic granulomatous disease: insights into pathogenesis and management. *Curr Opin Infect Dis*. 2012; 25:658–669. [PubMed: 22964947]
92. Winkelstein JA, Marino MC, Johnston RB Jr, Boyle J, Curnutte J, Gallin JI, Malech HL, Holland SM, Ochs H, Quie P, et al. Chronic granulomatous disease. Report on a national registry of 368 patients. *Medicine (Baltimore)*. 2000; 79:155–169. [PubMed: 10844935]

93. van den Berg JM, van Koppen E, Ahlin A, Belohradsky BH, Bernatowska E, Corbeel L, Espanol T, Fischer A, Kurenko-Deptuch M, Mouy R, et al. Chronic granulomatous disease: the European experience. *PLoS One*. 2009; 4:e5234. [PubMed: 19381301]
94. Brown GD. Innate antifungal immunity: the key role of phagocytes. *Annu Rev Immunol*. 2011; 29:1–21. [PubMed: 20936972]
95. Vinh DC, Sugui JA, Hsu AP, Freeman AF, Holland SM. Invasive fungal disease in autosomal-dominant hyper-IgE syndrome. *J Allergy Clin Immunol*. 2010; 125:1389–1390. [PubMed: 20392475]
96. Vinh DC, Patel SY, Uzel G, Anderson VL, Freeman AF, Olivier KN, Spalding C, Hughes S, Pittaluga S, Raffeld M, et al. Autosomal dominant and sporadic monocytopenia with susceptibility to mycobacteria, fungi, papillomaviruses, and myelodysplasia. *Blood*. 2010; 115:1519–1529. [PubMed: 20040766]
97. Camargo JF, Lobo SA, Hsu AP, Zerbe CS, Wormser GP, Holland SM. MonoMAC Syndrome in a Patient With a GATA2 Mutation: Case Report and Review of the Literature. *Clin Infect Dis*. 2013
98. Hsu AP, Sampaio EP, Khan J, Calvo KR, Lemieux JE, Patel SY, Frucht DM, Vinh DC, Auth RD, Freeman AF, et al. Mutations in GATA2 are associated with the autosomal dominant and sporadic monocytopenia and mycobacterial infection (MonoMAC) syndrome. *Blood*. 2012; 118:2653–2655. [PubMed: 21670465]
99. Bigley V, Haniffa M, Doulatov S, Wang XN, Dickinson R, McGovern N, Jardine L, Pagan S, Dimmick I, Chua I, et al. The human syndrome of dendritic cell, monocyte, B and NK lymphoid deficiency. *J Exp Med*. 2011; 208:227–234. [PubMed: 21242295]
100. Chu VH, Curry JL, Elghetany MT, Curry CV. MonoMAC versus idiopathic CD4+ lymphocytopenia. *Comment to Haematologica*. 2011;96(8):1221–5. *Haematologica*. 2012; 97:e9–11. author reply e12. [PubMed: 22492293]
101. Ishida H, Imai K, Honma K, Tamura S, Imamura T, Ito M, Nonoyama S. GATA-2 anomaly and clinical phenotype of a sporadic case of lymphedema, dendritic cell, monocyte, B- and NK-cell (DCML) deficiency, and myelodysplasia. *Eur J Pediatr*. 2012; 171:1273–1276. [PubMed: 22430350]
102. Bellanne-Chantelot C, Clauin S, Leblanc T, Cassinat B, Rodrigues-Lima F, Beauvils S, Vaury C, Barkaoui M, Fenneteau O, Maier-Redelsperger M, et al. Mutations in the ELA2 gene correlate with more severe expression of neutropenia: a study of 81 patients from the French Neutropenia Register. *Blood*. 2004; 103:4119–4125. [PubMed: 14962902]
103. Donadieu J, Leblanc T, Bader Meunier B, Barkaoui M, Fenneteau O, Bertrand Y, Maier-Redelsperger M, Mischeau M, Stephan JL, Phillippe N, et al. Analysis of risk factors for myelodysplasias, leukemias and death from infection among patients with congenital neutropenia. Experience of the French Severe Chronic Neutropenia Study Group. *Haematologica*. 2005; 90:45–53. [PubMed: 15642668]
104. Klein C, Grudzien M, Appaswamy G, Germeshausen M, Sandrock I, Schaffer AA, Rathinam C, Boztug K, Schwinzer B, Rezaei N, et al. HAX1 deficiency causes autosomal recessive severe congenital neutropenia (Kostmann disease). *Nat Genet*. 2007; 39:86–92. [PubMed: 17187068]
105. Kostmann R. Infantile genetic agranulocytosis; agranulocytosis infantilis hereditaria. *Acta Paediatr Suppl*. 1956; 45:1–78. [PubMed: 13326376]
106. Dale DC, Person RE, Bolyard AA, Aprikyan AG, Bos C, Bonilla MA, Boxer LA, Kannourakis G, Zeidler C, Welte K, et al. Mutations in the gene encoding neutrophil elastase in congenital and cyclic neutropenia. *Blood*. 2000; 96:2317–2322. [PubMed: 11001877]
107. Harris ES, Weyrich AS, Zimmerman GA. Lessons from rare maladies: leukocyte adhesion deficiency syndromes. *Curr Opin Hematol*. 2013; 20:16–25. [PubMed: 23207660]
108. Fischer A, Lisowska-Grospierre B, Anderson DC, Springer TA. Leukocyte adhesion deficiency: molecular basis and functional consequences. *Immunodef Rev*. 1988; 1:39–54. [PubMed: 3078709]
109. Recommandations sur les prophylaxies anti-infectieuses au cours des déficits immunitaires héréditaires on World Wide Web URL:
110. Leroy O, Gangneux JP, Montravers P, Mira JP, Gouin F, Sollet JP, Carlet J, Reynes J, Rosenheim M, Regnier B, et al. Epidemiology, management, and risk factors for death of invasive *Candida*

- infections in critical care: a multicenter, prospective, observational study in France (2005–2006). *Crit Care Med*. 2009; 37:1612–1618. [PubMed: 19325476]
111. Pfaller MA, Diekema DJ. Epidemiology of invasive candidiasis: a persistent public health problem. *Clin Microbiol Rev*. 2007; 20:133–163. [PubMed: 17223626]
 112. Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. *Clin Infect Dis*. 2004; 39:309–317. [PubMed: 15306996]
 113. Lamagni TL, Evans BG, Shigematsu M, Johnson EM. Emerging trends in the epidemiology of invasive mycoses in England and Wales (1990–9). *Epidemiol Infect*. 2001; 126:397–414. [PubMed: 11467797]
 114. Benjamin DK Jr, Stoll BJ, Fanaroff AA, McDonald SA, Oh W, Higgins RD, Duara S, Poole K, Laptook A, Goldberg R. Neonatal candidiasis among extremely low birth weight infants: risk factors, mortality rates, and neurodevelopmental outcomes at 18 to 22 months. *Pediatrics*. 2006; 117:84–92. [PubMed: 16396864]
 115. O'Brien D, Stevens NT, Lim CH, O'Brien DF, Smyth E, Fitzpatrick F, Humphreys H. Candida infection of the central nervous system following neurosurgery: a 12-year review. *Acta Neurochir (Wien)*. 2011; 153:1347–1350. [PubMed: 21431456]
 - 116*. Roth S, Ruland J. Caspase recruitment domain-containing protein 9 signaling in innate immunity and inflammation. *Trends Immunol*. 2013; 34:243–250. A comprehensive review on CARD9 function. [PubMed: 23523010]
 117. Bertin J, Guo Y, Wang L, Srinivasula SM, Jacobson MD, Poyet JL, Merriam S, Du MQ, Dyer MJ, Robison KE, et al. CARD9 is a novel caspase recruitment domain-containing protein that interacts with BCL10/CLAP and activates NF-kappa B. *J Biol Chem*. 2000; 275:41082–41086. [PubMed: 11053425]
 118. Hsu YM, Zhang Y, You Y, Wang D, Li H, Duramad O, Qin XF, Dong C, Lin X. The adaptor protein CARD9 is required for innate immune responses to intracellular pathogens. *Nat Immunol*. 2007; 8:198–205. [PubMed: 17187069]
 119. Kerrigan AM, Brown GD. Syk-coupled C-type lectins in immunity. *Trends Immunol*. 2011; 32:151–156. [PubMed: 21334257]
 120. Sancho D, Reis e Sousa C. Signaling by myeloid C-type lectin receptors in immunity and homeostasis. *Annu Rev Immunol*. 2012; 30:491–529. [PubMed: 22224766]
 121. Hara H, Saito T. CARD9 versus CARMA1 in innate and adaptive immunity. *Trends Immunol*. 2009; 30:234–242. [PubMed: 19359218]
 122. LeibundGut-Landmann S, Gross O, Robinson MJ, Osorio F, Slack EC, Tsoni SV, Schweighoffer E, Tybulewicz V, Brown GD, Ruland J, et al. Syk- and CARD9-dependent coupling of innate immunity to the induction of T helper cells that produce interleukin 17. *Nat Immunol*. 2007; 8:630–638. [PubMed: 17450144]
 123. Drummond RA, Saijo S, Iwakura Y, Brown GD. The role of Syk/CARD9 coupled C-type lectins in antifungal immunity. *Eur J Immunol*. 2011; 41:276–281. [PubMed: 21267996]
 124. Vautier S, MacCallum DM, Brown GD. C-type lectin receptors and cytokines in fungal immunity. *Cytokine*. 2012; 58:89–99. [PubMed: 21924922]
 125. Hardison SE, Brown GD. C-type lectin receptors orchestrate antifungal immunity. *Nat Immunol*. 2013; 13:817–822. [PubMed: 22910394]
 126. Strasser D, Neumann K, Bergmann H, Marakalala MJ, Guler R, Rojowska A, Hopfner KP, Brombacher F, Urlaub H, Baier G, et al. Syk kinase-coupled C-type lectin receptors engage protein kinase C-sigma to elicit Card9 adaptor-mediated innate immunity. *Immunity*. 2012; 36:32–42. [PubMed: 22265677]
 127. Gross O, Gewies A, Finger K, Schafer M, Sparwasser T, Peschel C, Forster I, Ruland J. Card9 controls a non-TLR signalling pathway for innate anti-fungal immunity. *Nature*. 2006; 442:651–656. [PubMed: 16862125]
 128. Hara H, Ishihara C, Takeuchi A, Xue L, Morris SW, Penninger JM, Yoshida H, Saito T. Cell type-specific regulation of ITAM-mediated NF-kappaB activation by the adaptors, CARMA1 and CARD9. *J Immunol*. 2008; 181:918–930. [PubMed: 18606643]

129. Hara H, Ishihara C, Takeuchi A, Imanishi T, Xue L, Morris SW, Inui M, Takai T, Shibuya A, Saijo S, et al. The adaptor protein CARD9 is essential for the activation of myeloid cells through ITAM-associated and Toll-like receptors. *Nat Immunol.* 2007; 8:619–629. [PubMed: 17486093]
130. Seebacher C, Bouchara JP, Mignon B. Updates on the epidemiology of dermatophyte infections. *Mycopathologia.* 2008; 166:335–352. [PubMed: 18478365]
131. Hay RJ, Baran R. Deep dermatophytosis: rare infections or common, but unrecognised, complications of lymphatic spread? *Curr Opin Infect Dis.* 2004; 17:77–79. [PubMed: 15021044]
132. Cheikhrouhou F, Makni F, Ayadi A. Dermatophytic disease: literature review. *J Myc Med.* 2010; 2010:61–69.
133. Marconi VC, Kradin R, Marty FM, Hospenthal DR, Kotton CN. Disseminated dermatophytosis in a patient with hereditary hemochromatosis and hepatic cirrhosis: case report and review of the literature. *Med Mycol.* 2010; 48:518–527. [PubMed: 20092423]
134. Cheikhrouhou F, Makni F, Masmoudi A, Sellami A, Turki H, Ayadi A. A fatal case of dermatomycoses with retropharyngeal abscess. *Ann Dermatol Venereol.* 2010; 137:208–211. [PubMed: 20227564]
135. Hadida E, Schousboe A. Dermatophytic disease aspects. *Algérie médicale.* 1959; 63:303–336.
136. Liautaud B, Marill FG. Dermatophytic disease. Recent Algerian observations. *Bull Soc Pathol Exot Filiales.* 1984; 77:637–648. [PubMed: 6525721]
137. Beirana L, Novales J. Tinea universal y granulomatosa por *T. tonsurans*. *Rev Mex Derm.* 1959; 3:4–16.
138. Oliveira H, Trincão R, Leitao A. Tricofotose cutânea generalizada com infecção sistêmica por *T. violaceum*. *J do Medico.* 1960; 41:626–642.
139. Pelevine A, Tchernogouboff N. Mucosal, lymph node and bone dermatophytosis. *Ann Derm Syph.* 1927; 8:403–424.
140. Sequeira. A case of granuloma trichophyticum. *Brit J Derm.* 1912:207.
141. Liautaud, B. Defense mechanisms of dermatophytosis. *Alger; Alger:* 1977.
142. Hironaga M, Okazaki N, Saito K, Watanabe S. *Trichophyton mentagrophytes* granulomas. Unique systemic dissemination to lymph nodes, testes, vertebrae, and brain. *Arch Dermatol.* 1983; 119:482–490. [PubMed: 6859887]
143. Araviysky AN, Araviysky RA, Eschkov GA. Deep generalized trichophytosis. (endothrix in tissues of different origin). *Mycopathologia.* 1975; 56:47–65. [PubMed: 1152975]
144. Tejasvi T, Sharma VK, Sethuraman G, Singh MK, Xess I. Invasive dermatophytosis with lymph node involvement in an immunocompetent patient. *Clin Exp Dermatol.* 2005; 30:506–508. [PubMed: 16045679]
145. Boudghene-Stambouli O, Belbachir A, Bariout A. Dermatophytic disease: 42 years after its description. *Ann Dermatol venereol.* 2002; 129:145–208.
146. Boudghene-Stambouli O, Guelil B, Belbachir A. Tinea: first symptom of dermatophytic disease. *Ann Dermatol Venereol.* 2007; 134:71.
147. Boudghene-Stambouli O, Merad-Boudia A. *Trichophyton rubrum* dermatophytic disease. A new case. *Ann Dermatol Venereol.* 1989; 116:725–727. [PubMed: 2610465]
148. Boudghene-Stambouli O, Merad-Boudia A. Dermatophytic disease in Algeria: new case and literature review. *Ann Dermatol Venereol.* 1991; 118:17–21. [PubMed: 2018301]
149. Boudghene-Stambouli O, Merad-Boudia A. Dermatophytic disease: exuberant hyperkeratosis with cutaneous horns. *Ann Dermatol Venereol.* 1998; 125:705–707. [PubMed: 9835960]
150. Colombo AL, Tobon A, Restrepo A, Queiroz-Telles F, Nucci M. Epidemiology of endemic systemic fungal infections in Latin America. *Med Mycol.* 2011; 49:785–798. [PubMed: 21539506]
151. Hage CA, Knox KS, Wheat LJ. Endemic mycoses: overlooked causes of community acquired pneumonia. *Respir Med.* 2012; 106:769–776. [PubMed: 22386326]
152. Kauffman CA. Histoplasmosis: a clinical and laboratory update. *Clin Microbiol Rev.* 2007; 20:115–132. [PubMed: 17223625]
153. Adam RD, Elliott SP, Taljanovic MS. The spectrum and presentation of disseminated coccidioidomycosis. *Am J Med.* 2009; 122:770–777. [PubMed: 19635278]

154. Moraes-Vasconcelos D, Grumach AS, Yamaguti A, Andrade ME, Fieschi C, de Beaucoudrey L, Casanova JL, Duarte AJ. Paracoccidioides brasiliensis disseminated disease in a patient with inherited deficiency in the beta1 subunit of the interleukin (IL)-12/IL-23 receptor. *Clin Infect Dis*. 2005; 41:e31–37. [PubMed: 16028144]
155. Vinh DC, Schwartz B, Hsu AP, Miranda DJ, Valdez PA, Fink D, Lau KP, Long-Priel D, Kuhns DB, Uzel G, et al. Interleukin-12 receptor beta1 deficiency predisposing to disseminated Coccidioidomycosis. *Clin Infect Dis*. 2011; 52:e99–e102. [PubMed: 21258095]
156. Vinh DC, Masannat F, Dzioba RB, Galgiani JN, Holland SM. Refractory disseminated coccidioidomycosis and mycobacteriosis in interferon-gamma receptor 1 deficiency. *Clin Infect Dis*. 2009; 49:e62–65. [PubMed: 19681704]
157. Zerbe CS, Holland SM. Disseminated histoplasmosis in persons with interferon-gamma receptor 1 deficiency. *Clin Infect Dis*. 2005; 41:e38–41. [PubMed: 16028145]
158. Duncan RA, von Reyn CF, Alliegro GM, Toossi Z, Sugar AM, Levitz SM. Idiopathic CD4+ T-lymphocytopenia-- four patients with opportunistic infections and no evidence of HIV infection. *N Engl J Med*. 1993; 328:393–398. [PubMed: 8093636]
159. Kortsik C, Elmer A, Tamm I. Pleural effusion due to Histoplasma capsulatum and idiopathic CD4 lymphocytopenia. *Respiration*. 2003; 70:118–122. [PubMed: 12584405]
160. Relia N, Kavimandan A, Sinha S, Sharma SK. Disseminated histoplasmosis as the first presentation of idiopathic CD4+ T-lymphocytopenia. *J Postgrad Med*. 2010; 56:39–40. [PubMed: 20393252]
161. Dalal P, Chernin L, Swender D, Tcheurekdjian H, Hostoffer R. Histoplasmosis in the olecranon bursa of a patient with idiopathic CD4 lymphocytopenia. *Ann Allergy Asthma Immunol*. 2011; 107:543–544. [PubMed: 22123388]
162. Tu RK, Peters ME, Gourley GR, Hong R. Esophageal histoplasmosis in a child with immunodeficiency with hyper-IgM. *AJR Am J Roentgenol*. 1991; 157:381–382. [PubMed: 1853826]
163. Hostoffer RW, Berger M, Clark HT, Schreiber JR. Disseminated Histoplasma capsulatum in a patient with hyper IgM immunodeficiency. *Pediatrics*. 1994; 94:234–236. [PubMed: 8036080]
164. Park BJ, Wannemuehler KA, Marston BJ, Govender N, Pappas PG, Chiller TM. Estimation of the current global burden of cryptococcal meningitis among persons living with HIV/AIDS. *Aids*. 2009; 23:525–530. [PubMed: 19182676]
165. Dromer F, Mathoulin-Pelissier S, Launay O, Lortholary O. Determinants of disease presentation and outcome during cryptococcosis: the CryptoA/D study. *PLoS Med*. 2007; 4:e21. [PubMed: 17284154]
166. Zonios DI, Falloon J, Huang CY, Chait D, Bennett JE. Cryptococcosis and idiopathic CD4 lymphocytopenia. *Medicine (Baltimore)*. 2007; 86:78–92. [PubMed: 17435588]
167. Scott-Algara D, Balabanian K, Chakrabarti LA, Mouthon L, Dromer F, Didier C, Arenzana-Seisdedos F, Lortholary O. Idiopathic CD4+ T-cell lymphocytopenia is associated with impaired membrane expression of the chemokine receptor CXCR4. *Blood*. 2010; 115:3708–3717. [PubMed: 20038787]
168. Winkelstein JA, Marino MC, Ochs H, Fuleihan R, Scholl PR, Geha R, Stiehm ER, Conley ME. The X-linked hyper-IgM syndrome: clinical and immunologic features of 79 patients. *Medicine (Baltimore)*. 2003; 82:373–384. [PubMed: 14663287]
169. Iseki M, Anzo M, Yamashita N, Matsuo N. Hyper-IgM immunodeficiency with disseminated cryptococcosis. *Acta Paediatr*. 1994; 83:780–782. [PubMed: 7949815]
170. Browne SK, Burbelo PD, Chetchotisakd P, Suputtamongkol Y, Kiertiburanakul S, Shaw PA, Kirk JL, Jutivorakool K, Zaman R, Ding L, et al. Adult-onset immunodeficiency in Thailand and Taiwan. *N Engl J Med*. 2012; 367:725–734. [PubMed: 22913682]
- 171*. Rosen LB, Freeman AF, Yang LM, Jutivorakool K, Olivier KN, Angkasekwina N, Suputtamongkol Y, Bennett JE, Pyrgos V, Williamson PR, et al. Anti-GM-CSF Autoantibodies in Patients with Cryptococcal Meningitis. *J Immunol*. 2013; 190:3959–3966. A report of seven patients with cryptococcosis and neutralizing anti-GM-CSF autoantibodies. [PubMed: 23509356]
172. Puel A, Casanova JL. Autoantibodies against cytokines: back to human genetics. *Blood*. 2013; 121:1246–1247. [PubMed: 23429982]

173. Chi CY, Chu CC, Liu JP, Lin CH, Ho MW, Lo WJ, Lin PC, Chen HJ, Chou CH, Feng JY, et al. Anti- IFN-gamma autoantibodies in adults with disseminated nontuberculous mycobacterial infections are associated with HLA-DRB1*16:02 and HLA-DQB1*05:02 and the reactivation of latent varicella-zoster virus infection. *Blood*. 2013; 121:1357–1366. [PubMed: 23243276]
174. Catherinot E, Lanternier F, Bougnoux ME, Lecuit M, Couderc LJ, Lortholary O. *Pneumocystis jirovecii* Pneumonia. *Infect Dis Clin North Am*. 2010; 24:107–138. [PubMed: 20171548]
175. Gigliotti F, Wright TW. *Pneumocystis*: where does it live? *PLoS Pathog*. 2012; 8:e1003025. [PubMed: 23209406]
176. Morris A, Norris KA. Colonization by *Pneumocystis jirovecii* and its role in disease. *Clin Microbiol Rev*. 2012; 25:297–317. [PubMed: 22491773]
177. Gottlieb MS, Schroff R, Schanker HM, Weisman JD, Fan PT, Wolf RA, Saxon A. *Pneumocystis carinii* pneumonia and mucosal candidiasis in previously healthy homosexual men: evidence of a new acquired cellular immunodeficiency. *N Engl J Med*. 1981; 305:1425–1431. [PubMed: 6272109]
178. Masur H, Michelis MA, Greene JB, Onorato I, Stouwe RA, Holzman RS, Wormser G, Brettman L, Lange M, Murray HW, et al. An outbreak of community-acquired *Pneumocystis carinii* pneumonia: initial manifestation of cellular immune dysfunction. *N Engl J Med*. 1981; 305:1431–1438. [PubMed: 6975437]
179. HIV/AIDS report CDC. 2009
180. Picard C, Fischer A. Hematopoietic stem cell transplantation and other management strategies for MHC class II deficiency. *Immunol Allergy Clin North Am*. 2010; 30:173–178. [PubMed: 20493394]
181. Imai K, Morio T, Zhu Y, Jin Y, Itoh S, Kajiwarra M, Yata J, Mizutani S, Ochs HD, Nonoyama S. Clinical course of patients with WASP gene mutations. *Blood*. 2004; 103:456–464. [PubMed: 12969986]
182. Minegishi Y, Saito M, Tsuchiya S, Tsuge I, Takada H, Hara T, Kawamura N, Ariga T, Pasic S, Stojkovic O, et al. Dominant-negative mutations in the DNA-binding domain of STAT3 cause hyper-IgE syndrome. *Nature*. 2007; 448:1058–1062. [PubMed: 17676033]
183. Kumar A, Teuber SS, Gershwin ME. Current perspectives on primary immunodeficiency diseases. *Clin Dev Immunol*. 2006; 13:223–259. [PubMed: 17162365]

Key bullets points

Chronic mucocutaneous candidiasis diagnosis should lead to the exploration of IL-17 immunity defects, such as *STAT1* mutations in particular.

Candida CNS infection diagnosis should lead to explorations of possible chronic granulomatous disease or CARD9 deficiency.

Deep dermatophytosis diagnosis should lead to explorations of possible CARD9 deficiency.

Endemic mycoses and cryptococcosis diagnosis should lead to explorations of the IL-12/IFN- γ axis and evaluations of the presence of plasma autoantibodies against IFN- γ or GM-CSF.

Pneumocystosis diagnosis should lead to the exploration of T-cell disorders, such as SCID and CD40 ligand deficiency in particular.

Table 1

Primary immunodeficiencies associated with chronic mucocutaneous candidiasis

Disease	Associated infections	Immunological phenotype	Gene, transmission
CMC			
SCID	Bacteria, viruses, fungi, mycobacteria	No T cells, with or without B and/or NK cell lymphopenia	>30 genes[74]: <i>IL2RG</i> , XL; <i>JAK3</i> , AR; <i>RAG1</i> , AR; <i>RAG2</i> , AR; <i>ARTEMIS</i> , AR; <i>ADA</i> , AR; <i>CD3</i> , AR...
CID		T-cell defect	
CD25 deficiency	Viruses and bacteria		<i>IL2RA</i> , AR[23]
NEMO or IKBG deficiency	Pyogenic bacteria, mycobacteria, viruses		<i>NEMO</i> , or <i>IKBG</i> X-linked [19]
<i>IKBA</i> GOF mutation			<i>IKBA</i> , AD[19,20]
DOCK8 deficiency	Viruses, bacteria and fungi		<i>DOCK8</i> , AR[21,22,25]
TCR- α deficiency	Viruses and bacteria		<i>TCRA</i> , AR[27]
ORAI1 deficiency	Viruses, mycobacteria, bacteria and fungi		<i>ORAI1</i> , AR[75]
MST1/STK4 deficiency	Viruses and bacteria		<i>MST1/STK4</i> , AR[28,29]
MHC class II deficiency	Viruses, bacteria and fungi		<i>CIITA</i> , <i>RFXANK</i> , <i>RFXC</i> , <i>RFXAP</i> , all AR[30]
Idiopathic CD4 lymphopenia	<i>Pneumocystis</i> , <i>Cryptococcus</i> , virus	CD4 T cells<300/mm ³	<i>UNC119</i> , AD[76], <i>MAGT1</i> , X-linked[77] <i>RAG1</i> , AR[78]
Syndromic CMC			
IL-12R β 1 and IL-12p40 deficiencies	Mycobacteria, <i>Salmonella</i>	Deficit of IL-17 producing T cells	<i>IL12RB1</i> , AR[37] <i>IL12B</i> , AR[38]
STAT3 deficiency (AD-HIES)	<i>Staphylococcus aureus</i> , <i>Aspergillus</i>	Hyper IgE, deficit of IL- 17-producing T cells	<i>STAT3</i> , AD[33,34,35,36]
APECED/APS-1	No	Neutralizing anti-IL- 17A, IL-17F and/or IL- 22 autoantibodies	<i>AIRE</i> , AR[41,52]
CARD9 deficiency	Dermatophytes, <i>Candida</i> brain abscess	Deficit of IL-17- producing T cells	<i>CARD9</i> , AR[39,79,80]
CMCD			
Complete IL-17RA deficiency	<i>S. aureus</i>	No IL-17 response	<i>IL17RA</i> , AR[16]
Partial IL-17F deficiency	<i>S. aureus</i>	Impaired IL-17F, IL- 17A/F function	<i>IL17F</i> , AD[16]
<i>STAT1</i> GOF mutations	Bacteria, viruses, fungi, mycobacteria	Low IL-17 producing T cells	<i>STAT1</i> , AD[59,60,64,65,67- 72,81]

Table 2

Primary immunodeficiencies associated with invasive fungal diseases

Fungal susceptibility	Disease	Associated infections	Immunological phenotype	Gene, transmission
Deep dermatophytosis	CARD9 deficiency	CMC	Deficit of IL-17- producing T cells	CARD9, AR[80]
Aspergillosis	Chronic granulomatous disease	Bacteria, <i>Scedosporium</i>	NADPH oxidase complex defect in phagocytes	CYBB, X-linked or CYBA, NCF1, NCF2, NCF4, AR [54–56,85,86,89–94]
	STAT3 deficiency (AD- HIES) with lung cavities	<i>S. aureus</i>	STAT3 deficiency, epithelial lung dysfunction	STAT3, AD [35,182]
	MonoMAC syndrome	Environmental mycobacteria, viruses, fungi, bacteria	Monocytopenia, deficit of dendritic cells, B and NK cell lymphopenia,	GATA2, AD[96,97,99–101]
	Leukocyte adhesion deficiency type 1	Bacteria	Impaired neutrophil adhesion	CD18, AR
	Severe congenital neutropenia	Bacteria, invasive candidiasis	Neutropenia	ELA2, AD[106] HAX1, AR[104]
Invasive candidiasis	Severe congenital neutropenia	Bacteria, invasive candidiasis	Neutropenia	ELA2, AD[106] HAX1, AR[104]
	Leukocyte adhesion deficiency type 1	Bacteria	Impaired neutrophil adhesion	CD18, AR[108]
Candida CNS infection	Chronic granulomatous disease	Bacteria, <i>Scedosporium</i>	NADPH oxidase complex defect in phagocytes	CYBB, X-linked or autosomal CYBA, NCF1, NCF2, NCF4, AR [54–56,85,86,89–94]
	CARD9 deficiency	Dermatophytes, CMC	Impaired <i>Candida</i> killing by PMN	CARD9, AR[39,79]
Cryptococcosis	Autoantibodies against GM-CSF	No	Neutralizing anti-GM- CSF autoantibodies	Unknown[171]
	Autoantibodies against IFN- γ	Mycobacteria	Neutralizing anti-IFN- γ autoantibodies	
	CD40 ligand deficiency	<i>Pneumocystis</i> , bacteria	Hypo IgG, IgA, High IgM levels, T/B cell cooperation defect	CD40L, X- linked[168,169]
	MonoMAC syndrome	Environmental mycobacteria, viruses, fungi	Monocytopenia, deficit of dendritic cells, B and NK cell lymphopenia,	GATA2, AD[96]
Dimorphic fungal infection				
Coccidioidomycosis	IL-12R β 1 deficiency	Mycobacteria, <i>Salmonella</i>		IL12RB1, AR[155]
	IFN- γ R1 deficiency	Mycobacteria, <i>Salmonella</i>		IFNGR1, AD[156]
	STAT1 GOF mutation	CMC, viruses		STAT1, AD[65]
Histoplasmosis	IFN- γ R1 deficiency	Mycobacteria, <i>Salmonella</i>		IFNGR1, AD[157]
	IL-12R β 1 deficiency	Mycobacteria, <i>Salmonella</i> CMC		IL12RB1, AR[37]
	STAT1 GOF mutation	CMC, viruses	Deficit of IL-17- producing T cells, impaired response to IFN- γ restimulation	STAT1, AD[65]
	Idiopathic CD4 lymphopenia	<i>Pneumocystis</i> , <i>Cryptococcus</i> , viruses	CD4 T cells<300/mm ³	UNC119, AD[76] MAGT1, X-linked[77]

Fungal susceptibility	Disease	Associated infections	Immunological phenotype	Gene, transmission
				RAG1, AR[78]
	DOCK8 deficiency	Viruses and bacteria	T-cell defect	<i>DOCK8</i> , AR[21,22,25]
	X-linked CD40L deficiency	<i>Pneumocystis</i> , bacteria	Hypo IgG, IgA, high IgM levels, T/B cell cooperation defect	<i>CD40L</i> , X-linked[168,169]
	MonoMAC syndrome	Mycobacteria, viruses, fungi	Monocytopenia, deficit of dendritic cells, B and NK cell lymphopenia	<i>GATA2</i> , AD[96]
PCC	IL-12Rβ1 deficiency	Mycobacteria, <i>Salmonella</i>		<i>IL-12RB1</i> , AR[154]
Pneumocystosis	SCID	Bacteria, viruses, fungi, mycobacteria	No T cells, with or without B and NK cell lymphopenia	>30 genes[74]: <i>IL2RG</i> , <i>XL JAK3</i> , AR, <i>RAG1</i> , AR, <i>RAG2</i> , AR, <i>ARTEMIS</i> , AR, <i>ADA</i> , AR, <i>CD3</i> , AR...
	X-linked CD40 ligand deficiency	<i>Pneumocystis</i> , bacteria	Hypo IgG, IgA, high IgM levels, T/B cell cooperation defect	<i>CD40L</i> , X-linked[168,169]
	MHC class II deficiency	Bacteria, viruses, fungi,	T-cell defect	<i>CIITA</i> , <i>REFXANK</i> , <i>REFXC</i> , <i>REFXAP</i> , AR[30]
	NEMO deficiency	Pyogenic bacteria, mycobacteria, viruses	T-cell defect	<i>NEMO</i> , X-linked [19]
	DOCK8 deficiency	Viruses, bacteria	T-cell defect	<i>DOCK8</i> , AR[21,22,25]
	X-linked recessive Wiskott-Aldrich syndrome	Bacteria, viruses	T-cell defect	<i>WASP</i> , X-linked recessive[181,183]

PCC: paracoccidioidomycosis, GOF, gain of function, AR: autosomal recessive, AD: autosomal dominant, CMC: chronic mucocutaneous candidiasis

Table 3

Main genetic etiologies of fungal infections

Fungal susceptibility	Disease
CMC	<i>STAT1</i> GOF mutation (CMCD), <i>STAT3</i> deficiency (AD-HIES), APECED/APS-1
Deep dermatophytosis	CARD9 deficiency
Aspergillosis	Chronic granulomatous disease, <i>STAT3</i> deficiency (AD-HIES) with lung cavities
<i>Candida</i> CNS infection	Chronic granulomatous disease, CARD9 deficiency
Cryptococcosis	Autoantibodies against GM-CSF or against IFN- γ
Dimorphic fungal infection	IL-12R β 1 deficiency, IFN- γ R1 deficiency, <i>STAT1</i> GOF mutation
Pneumocystosis	SCID, X-linked CD40 ligand deficiency