Chronic mucocutaneous candidiasis disease associated with inborn errors of IL-17 immunity

Satoshi Okada¹, Anne Puel²,³,⁴, Jean-Laurent Casanova²,³,⁴,⁵,⁶ and Masao Kobayashi¹

Chronic mucocutaneous candidiasis (CMC) is characterized by recurrent or persistent infections affecting the nails, skin and oral and genital mucosae caused by *Candida* spp., mainly *Candida albicans*. CMC is an infectious phenotype in patients with inherited or acquired T-cell deficiency. Patients with autosomal-dominant (AD) hyper IgE syndrome (HIES), AD signal transducer and activator of transcription 1 (STAT1) gain-of-function, autosomal-recessive (AR) deficiencies in interleukin (IL)-12 receptor β1 (IL-12Rβ1), IL-12p40, caspase recruitment domain-containing protein 9 (CARD9) or retinoic acid-related orphan receptor γT (RORγT) or AR autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED) develop CMC as a major infectious phenotype that is categorized as Syndromic CMC. In contrast, CMC disease (CMCD) is typically defined as CMC in patients in the absence of any other prominent clinical signs. This definition is not strict; thus, CMC is currently used to refer to patients presenting with CMC as the main clinical phenotype. The etiology of CMCD is not related to genes that cause severe combined immunodeficiency or combined immunodeficiency, nor to genes responsible for Syndromic CMC. Four genetic etiologies, AR IL-17 receptor A, IL-17 receptor C and ACT1 deficiencies, and AD IL-17F deficiency, are reported to underlie CMCD. Each of these gene defects directly has an impact on IL-17 signaling, suggesting their nonredundant role in host mucosal immunity to *Candida*. Here, we review current knowledge focusing on IL-17 signaling and the genetic etiologies responsible for, and associated with, CMC.

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INTRODUCTION

*Candida albicans* is a ubiquitous fungus and commensal yeast in humans. It can occasionally be pathogenic causing oral thrush, intertrigo and genital candidiasis in healthy populations. However, in immunocompromised hosts, *Candida* can cause chronic mucocutaneous or invasive infections. Chronic mucocutaneous candidiasis (CMC) is characterized by recurrent or persistent infections affecting the nails, skin and oral and genital mucosae caused by *Candida* spp., often *C. albicans*.¹,² CMC is one of the infectious phenotypes in patients with inherited or acquired T-cell deficiencies.³,⁴ These clinical observations demonstrate the pivotal role of T-cell immunity in host defense against superficial *Candida* infections. Recent studies have revealed that Th17 cells, together with other cells expressing retinoic acid-related orphan receptor γT (RORγT), such as γδT cells and group 3 innate lymphoid cells, produce interleukin (IL)-17 and have an essential role in host defense against mucocutaneous *Candida* infections in mice and humans.²,⁵,⁶ In contrast, invasive fungal infections are also observed in patients with quantitative and/or qualitative disorders of neutrophils, such as chronic granulomatous disease (CGD), autosomal-recessive (AR) caspase recruitment domain-containing protein 9 (CARD9) deficiency and neurogenic conditions.⁷,⁸

Patients with autosomal-dominant (AD) hyper IgE syndrome (HIES), AD signal transducer and activator of transcription 1 (STAT1) gain-of-function (GOF), AR autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED), or AR CARD9, IL-12 receptor β1 (IL-12Rβ1), IL-12p40 or RORγT deficiencies, develop CMC as one of the major infectious phenotypes associated with the other clinical and infectious manifestations.²,⁴,⁶-¹⁸ These specific conditions are designated as Syndromic CMC (Table 1) and occur in association with impaired IL-17 immunity (Figure 1). Patients with AD HIES develop CMC and staphylococcal infections associated with other clinical manifestations, such as elevated serum IgE, characteristic facial features, panniculitis and retained primary teeth. These patients have severely decreased frequencies of circulating IL-17A- and IL-22-producing T cells, probably associated with impaired STAT3-dependent signaling downstream of IL-6, IL-21 and/or IL-23.¹⁵,¹⁷,¹⁹,²⁰ The presence of CMC is also identified in one patient with AR HIES with TYK2 mutation.²¹ However, a follow-up study reported that the core clinical phenotype of TYK2 deficiency is...
mycobacterial and/or viral infections, with an association of CMC.22 Patients with APECED present with CMC in addition to polyendocrinopathy and ectodermal dysplasia.23,24 These patients produce neutralizing autoantibodies against IL-17A, IL-17F and/or IL-22, leading to development of CMC.9,13,25 Neutralizing antibodies against these Th17-produced cytokines are also identified in patients with thymoma who develop CMC.9 Patients with AR CARD9 deficiency develop CMC in this review.35,36 However, recent studies revealed that patients with GOF mutations in STAT1 present with broad clinical manifestations, including bacterial, viral, mycobacterial and invasive fungal infections, autoimmune diseases, aneurysms and tumors.34,35 Patients with AR CARD9 deficiency develop CMC, deep dermatophytosis and invasive fungal infections.7,8,26 They present with decreased frequency of circulating IL-17-producing T cells and impaired neutrophil-killing of C. albicans.7,8,26 Patients with AR IL-12p40 or IL-12β1 deficiency develop Mendelian susceptibility to mycobacterial disease (MSMD), a primary immunodeficiency with selective host susceptibility to intracellular bacteria such as Mycobacterium bovis BCG, environmental mycobacteria and Salmonella that is associated with impaired IL-12-induced interferon gamma (IFN-γ) signaling.27–29 These patients occasionally develop mild CMC and show decreased frequencies of circulating IL-17A- and IL-22-producing T cells as a result of impaired IL-23 responses.10,16,17

In 2011, AD STAT1-GOF was found to be responsible for CMC disease (CMCD), typically defined as CMC in patients without any other prominent clinical signs.30,31 Subsequent studies revealed that AD STAT1-GOF is the major genetic etiology of CMCD, explaining more than half of all CMCD cases.32–34 In the classification of primary immunodeficiency compiled by the Primary Immunodeficiency Expert Committee of the International Union of Immunological Societies, AD STAT1-GOF, together with four genetic etiologies directly related to defective IL-17 signaling, is categorized as CMC, which is often referred to as CMCD.35,36 However, recent studies revealed that patients with GOF mutations in STAT1 present with broad clinical manifestations, including bacterial, viral, mycobacterial and invasive fungal infections, autoimmune diseases, aneurysms and tumors.34,35 Therefore, AD STAT1-GOF is categorized as Syndromic CMC in this review.

Recently, a new primary immunodeficiency due to biallelic mutations in RORC, encoding RORγ and RORγT, was identified (designated as AR RORγT deficiency).12 RORγT is a master

| Disease | Frequency of CMC | Other infections | Associated symptoms | Immunological phenotype | Gene | Inheritance | Refs |
|---------|-----------------|-----------------|--------------------|------------------------|------|-------------|------|
| Syndromic CMC |  | | | | | |
| HIES | 85% | Staphylococcus, Aspergillus | Eczema, scoliosis, pneumatocele, hyperextensibility, dysmorphic facial features, retention of primary teeth | Increased serum IgE, eosinophilia, decreased IL-17-producing T cells | STAT3 | AD | 14,17,19,20,78 |
| APECED | 70–98% | Mycobacterium, Salmonella | Ectodermal dysplasia, autoimmune dysfunction of parathyroid and adrenal glands, alopecia | Neutralizing antibodies against IL-17A, IL-17F and/or IL-22 | AIRE | AR | 9,23–25 |
| CARD9 deficiency | 35–86% | Dermatophytes, Candida, brain abscess | Decreased IL-17-producing T cells, impairment of C. albicans-killing by neutrophils | CARD9 | AR | 7,8,18,26 |
| IL-12Rβ1 and IL-12p40 deficiency | 6–25% | Mycobacterium, Salmonella | Decreased IL-17-producing T cells, impaired IL-12 signaling | IL12RB1, IL12B | AR | 10,11,16,27–29 |
| STAT1 gain-of-function | 98% | Bacteria, viruses, fungi, mycobacteria | Decreased IL-17-producing T cells, decreased switched memory B cells | STAT1 | AD | 30–34,52,66 |
| RORγT deficiency | 6/7 (86%) | Mycobacterium | Defect of MAIT, type 1 NKT, IL-17-producing T cells, impaired antigen-specific IFN-γ production | RORC | AR | 12 |
| CMCD | | | | | | |
| IL-17RA deficiency | 3/3 (100%) | Staphylococcus | No response to IL-17A, IL-17E and IL-17F | IL17RA | AR | 38,72 |
| IL-17RC deficiency | 3/3 (100%) | | No response to IL-17A and IL-17F | IL17RC | AR | 40 |
| IL-17F deficiency | 5/7 (70%) | | Impaired IL-17F and IL-17AF function | IL17F | AD | 38,71 |
| ACT1 deficiency | 2/2 (100%) | Staphylococcus | No response to IL-17A, IL-17E, and IL-17F | TRAF3IP2 | AR | 39 |

Abbreviations: AD, autosomal-dominant; APECED, autoimmune polyendocrinopathy-candidiasis-ectodermal dysplasia; AR, autosomal-recessive; CARD9, caspase recruitment domain-containing protein 9; CMC, chronic mucocutaneous candidiasis; CMCD, CMC disease; HIES, hyper IgE syndrome; IFN-γ, interferon gamma; IL, interleukin; RORγ, retinoic acid-related orphan receptor γT.
transcription factor of Th17 cells; thus, these patients showed a markedly decreased frequency of circulating IL-17A- and IL-22-producing T cells, which probably underlies the CMC seen in these patients. Surprisingly, all RORγT-deficient patients also developed MSMD, probably because of the impairment of IFN-γ production associated with mycobacterial infections. AD STAT1 gain-of-function was originally identified as a genetic etiology of CMC. However, it can be categorized as Syndromic CMC based on its broad clinical manifestations. The majority of patients with GOF-STAT1 display a decreased frequency of IL-17-producing cells. Defects in four genes (encoding IL-17F, IL-17RA, IL-17RC and ACT1) that are directly involved in IL-17 signaling have been identified in patients with CMC. Blue: Syndromic CMC-related molecules and neutralizing antibodies (APECED). Magenta: CMCD-related molecules.

**Figure 1** Inborn errors of IL-17 immunity. Phagocytes recognize *C. albicans* via pattern recognition receptors and produce proinflammatory cytokines, such as IL-6 and IL-23. These proinflammatory cytokines activate T cells via STAT3 and upregulate RORγT expression, leading to production of IL-17A, IL-17F and IL-22. Impairment in IL-23-induced STAT3-mediated signaling in AD Hyper IgE Syndrome (HIES) and AR IL-12Rβ1 and IL-12p40 deficiencies cause Syndromic CMC. Neutralizing autoantibodies against IL-17A, IL-17F and IL-22 in patients with APECED impair IL-17 signaling, underlying Syndromic CMC. Patients with AR RORγT deficiency show developmental defects of Th17 cells, resulting in Syndromic CMC. They also develop MSMD, probably caused by impairment of IFN-γ production associated with mycobacterial infections. AD STAT1 gain-of-function was originally identified as a genetic etiology of CMCD. However, it can be categorized as Syndromic CMC based on its broad clinical manifestations. The majority of patients with GOF-STAT1 display a decreased frequency of IL-17-producing cells. Defects in four genes (encoding IL-17F, IL-17RA, IL-17RC and ACT1) that are directly involved in IL-17 signaling have been identified in patients with CMC. Blue: Syndromic CMC-related molecules and neutralizing antibodies (APECED). Magenta: CMCD-related molecules.

**Classification of Syndromic CMC**

**AD Hyper IgE Syndrome**

HIES is a primary immunodeficiency disease, which is characterized by elevated serum IgE levels, recurrent staphylococcal skin abscesses, eczema and pulmonary infections. It was first described in 1966 and was originally named Job’s syndrome. HIES has either a dominant or recessive pattern of autosomal inheritance, with the rare AR HIES largely shown to be caused by mutations in *DOCK8* (OMIM ID: 606581).
Figure 2 IL-17 and IL-17 receptor family. The IL-17 cytokine family consists of six members (IL-17A, IL-17B, IL-17C, IL-17D, IL-17E and IL-17F), whereas the IL-17R family consists of five members (IL-17RA, IL-17RB, IL-17RC, IL-17RD and IL-17RE). IL-17 cytokines form disulfide-linked homodimers, whereas IL-17A and IL-17F can form heterodimers. Functional receptors for IL-17 family cytokines are thought to consist of homodimers or heterodimers. Upon stimulation, ACT1 is recruited to IL-17RA, IL-17RB and/or IL-17RC (and probably IL-17RE) by homotypic dimerization of two SEFIR domains, and activates IL-17A and IL-17F can form heterodimers. Functional receptors for IL-17 family cytokines are thought to consist of homodimers or heterodimers. Upon stimulation, ACT1 is recruited to IL-17RA, IL-17RB and/or IL-17RC (and probably IL-17RE) by homotypic dimerization of two SEFIR domains, and activates IL-17A/F-induced, IL-17RA/RC-mediated signaling, and mutations in IL17RA and IL17RC have been identified in patients with CMCD. These mutations are directly related to IL-17A/F-induced, IL-17RA/RC-mediated signaling, and mutations in IL17RA and IL17RC also affect IL-17E-induced, IL-17RA/IL-17RB-mediated signaling. Thus, effective host mucocutaneous immunity against *Candida* in humans is critically dependent on functional and effective IL-17A/F-induced, IL-17RA/RC-mediated signaling. Magenta: CMCD-related molecules.

AR CARD9 deficiency
CARD9 is an intracellular adaptor molecule that, together with its binding partners BCL10, MALT1 and NEMO, mediates signals from C-type lectin-like receptors, Dectin-1 and Dectin-2, to induce transcription and production of proinflammatory cytokines via nuclear factor-xB (NFxB) signaling. In 2009, a primary immunodeficiency, which associates with a genetic defect of CARD9, was identified in the patients who suffer from CMC and invasive fungal infections (OMIM ID:212050). A homozygous mutation, Q295X, in CARD9 was identified in those patients. Subsequent studies revealed that patients with AR CARD9 deficiency also suffer from deep dermatomyositis, invasive *Exophiala dermatitidis*, subcutaneous Phaeohyphomycosis and *Candida*-species meningoencephalitis and/or colitis, and are thus considered Syndromic CMC. There are several reports describing a decreased frequency of
circulating IL-17-producing cells in CARD9-deficient patients, probably explaining the clinical phenotype of CMC.\(^7^,18,45\) On the other hand, several studies also report that the frequency of circulating IL-17-producing cells in CARD9-deficient patients is equivalent to healthy controls.\(^44^,66\) Therefore, there is some controversy regarding the frequency of circulating IL-17-producing cells in CARD9-deficient patients. Neutrophils kill both serum-opsonized and unopsonized \(C.\ albicans\) via distinct mechanisms; reactive oxygen species production by the NADPH oxidase system has an important role for neutrophil-killing of serum-opsonized \(Candida\), whereas neutrophil-killing of unopsonized \(Candida\) requires complement receptor type 3 (CR3) and CARD9.\(^47\) Neutrophils from CARD9-deficient patients show a selective \(C.\ albicans\)-killing defect that is CR3- and CARD9-dependent, but NADPH oxidase-independent.\(^8\) Furthermore, patients with AR CARD9 deficiency are particularly predisposed to meningoencephalitis caused by \(Candida\) species.\(^18\) This might be explained by the enhanced requirement of CR3- and CARD9-dependent neutrophil-killing in the limited access of plasma proteins that is required for opsonization in cerebrospinal fluids,\(^8\) as well as the finding that neutrophils from CARD9-deficient patients normally inhibit germination of \(Aspergillus\ fumigatus\), consistent with the clinical observation that no CARD9-deficient patients were reported to have \(Aspergillus\) species infection.\(^8,18\)

**AR IL-12R\(\beta\)1 deficiency and AR IL-12p40 deficiency**

IL-12, IL-23, IL-27 and IL-35 belong to the IL-12 cytokine family. Functional IL-12 (also called IL-12p70) consists of a heterodimer of IL-12p40 and IL-12p40 subunits, each of which has distinct effector functions. IL-12p40 is a common component of both IL-12 and IL-23; IL-12 drives T helper 1 (Th1) differentiation, whereas IL-23 is critical for Th17 survival and expansion. IL-12R\(\beta\)1 combines with IL-12R\(\beta\)2 or IL-23R to form high-affinity receptors for IL-12 or IL-23, respectively. IL-12 binds to the IL-12R complex (IL-12R\(\beta\)1 and IL-12R\(\beta\)2), on T lymphocytes and NK cells, and induces IFN-\(\gamma\) production. IL-23 binds to its receptor complex (IL-12R\(\beta\)1 and IL-23R) on Th17 cells and has an important role in maintenance of Th17 cells and induction of IL-17 and IL-22.

AR-complete IL-12R\(\beta\)1 deficiency (OMIM ID: 614891) is the most common genetic cause of MSMD, explaining 44% of MSMD patients with a known genetic etiology.\(^48\) The first cases of AR-complete IL-12R\(\beta\)1 deficiency were reported in 1998.\(^27,28\) From the first identification, a total of 180 patients from 136 kindreds have since been reported.\(^48\) A large cohort study, collecting 141 patients from 102 kindreds with AR-complete IL-12R\(\beta\)1 deficiency, revealed its heterogeneous clinical manifestations. Mycobacterial disease (83%), Salmonella (43%) and CMC (23%) were the three major infectious phenotypes reported in symptomatic patients.\(^11\) Moreover, 78% of BCG-vaccinated patients developed BCG disease. In contrast, 8 of the 29 genetically affected siblings were asymptomatic (27%), suggesting incomplete penetrance of this disorder.

The first case of AR-complete IL-12p40 deficiency (OMIM ID: 614890) was identified in 1998 in a patient born to consanguineous parents who developed disseminated infection with BCG and \(S.\ enteritidis\).\(^29\) A follow-up study, collecting 49 patients from 30 kindreds, revealed that patients with AR-complete IL-12p40 deficiency develop recurrent infections due to \(Salmonella\) (36.4%) and mycobacteria (25%).\(^10\) Strikingly, BCG disease was observed in 40 of the 41 patients (97.5%) who were vaccinated with BCG. Moreover, CMC was also reported in three patients (6%). The clinical penetrance of IL-12p40 deficiency is incomplete, with 33.3% of genetically affected relatives of index cases showing no symptoms. Therefore, AR-complete IL-12p40 and IL-12R\(\beta\)1 deficiencies are clinical phenocopies that show increased susceptibility to intracellular pathogens and develop CMC.\(^10,11,48\)

Genetic defects in \(IL12B\) or \(IL12RB1\), which encode IL-12p40 or IL-12R\(\beta\)1, respectively, affect both IL-12- and IL-23-induced signaling. Leukocytes from patients with AR-complete IL-12p40 deficiency show a complete absence of IL-12p40, IL-12 and IL-23 proteins.\(^10,17,29\) T-cell blasts from IL-12R\(\beta\)1-deficient patients have undetectable cell surface protein expression of IL-12R\(\beta\)1, and thus a complete lack of cellular responses to IL-12 and IL-23.\(^11\) In both cases, the lack of IL-12 protein itself or cellular response to IL-12 results in poor production of IFN-\(\gamma\) by T and NK cells, and is the pathogenic mechanism responsible for susceptibility to intracellular pathogens, such as mycobacteria and \(Salmonella\). In contrast, the absence of IL-23 protein or defective cellular responses to IL-23 forms the likely molecular cause of CMC in these patients.\(^10,16,17,49,50\) Indeed, patients with AR-complete IL-12p40 or IL-12R\(\beta\)1 deficiencies show decreased frequencies of circulating IL-17-producing cells, albeit a less severe reduction than observed in patients with AD HIES. This difference may explain the disparity in the frequency and severity of CMC between AD HIES and AR IL-12p40/IL-12R\(\beta\)1 deficiencies.\(^10,11,17,43\)

**AD STAT1-GOF**

Germline mutations in \(STAT1\) cause diverse range of primary immunodeficiencies (Figure 3).\(^51\) Patients with biallelic hypomorphic or LOF-STAT1 mutations (AR STAT1 deficiency; OMIM ID: 613796), which partially or completely impair STAT1 protein expression, show susceptibility to viruses and intracellular bacteria.\(^48\) The infectious phenotype observed in patients with AR-partial STAT1 deficiency is milder than in those with AR-complete STAT1 deficiency who require hematopoietic stem cell transplantation to avoid life-threatening infections. Germline monoallelic hypomorphic or LOF-STAT1 mutations are responsible for AD MSMD (AD STAT1 deficiency; OMIM ID: 614892). These \(STAT1\) mutations do not disturb STAT1 protein expression, but exert a dominant-negative effect on IFN-\(\gamma\)-induced STAT1-mediated signaling.\(^48\) In 2011, monoallelic GOF-STAT1 (OMIM ID: 614162) mutations were shown to cause the AD form of CMCD (Table 1).\(^30,31\) These mutations impair dephosphorylation of STAT1, leading to hyperphosphorylation of STAT1 Tyr701 in response to IFN-\(\gamma\), IFN-\(\alpha/\beta\) and IL-27 stimulation. This finding has enabled the development of a simple flow cytometry-based STAT1 functional test to facilitate the diagnosis of CMCD patients with GOF-STAT1 mutations.\(^32\) GOF-STAT1 mutations are preferentially identified in the coiled-coil domain and DNA-binding domain of STAT1, whereas there are no obvious hot spots for LOF-STAT1 mutations (Figure 3).\(^30,31,33,48,51,52\) Moreover, GOF-STAT1 mutations are a major mechanism of molecular pathogenesis of CMCD, and are reported to explain more than half of the cases of this disorder.\(^30,33,35,32\)

Although CMC is the major infectious manifestation among the patients with GOF-STAT1 mutations, some patients develop fungal infections other than candidiasis, or bacterial and viral infections, mycobacterial infections, autoimmune disorders, including IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked-like syndrome) and/or even fatal combined immunodeficiency.\(^53,54,56,60,65,66\) Recently, a large cohort study investigating 274 patients from 167 kindreds reported in detail the clinical manifestations of patients with GOF-STAT1 mutations.\(^34\) In this large cohort, the majority of patients with \(STAT1\) GOF mutations developed CMC (98%), with a median age at onset of 1 year. Many patients also suffered from bacterial infections (74%), mainly due to \(S.\ aureus\) (36%), and viral infections (37%) typically caused by...
Herpes viruses (88%), whereas others/some experienced invasive fungal infections (10%) and mycobacterial diseases (6%). In addition to the infectious phenotypes reported in these patients, over one-third also presented with autoimmune manifestations (37%), such as hypothyroidism (23%), type 1 diabetes (4%) and blood cytopenias (4%), highlighting the broad and devastating clinical symptoms that can be associated with CMC in many patients with GOF-STAT1 mutations. Therefore, based on these broad clinical manifestations, AD STAT1-GOF can be categorized as Syndromic CMC, rather than the original categorization of CMCD. Immunological test also detects CMC and severe mycobacterial infections (OMIM ID: 616622).12 Six of seven patients developed mild mucocutaneous Candida infections, and mycobacterial infection was severe and observed in all patients. Four of the seven patients developed disseminated mycobacterial infection and one died because of BCG meningocerebralitis. The patients presented with mild T-cell lymphopenia, thymic hypoplasia, lack of palpable axillary and cervical lymph nodes, and absence of MAIT and iNKT cells that were consistent with the phenotype of Rorc−/− mice.12 Moreover, Rorc−/− mice were also susceptible to mycobacterial infection, suggesting that host susceptibility to mycobacteria was not a human-specific finding.12

All three homozygous mutations (S17L, Q308* and Q411*) in RORC identified in these patients were LOF and impaired DNA-binding ability of the target sequence of RORC, which encodes RORY and RORYT, were identified in seven patients from three unrelated kindreds presenting with complex infectious phenotypes, with CMC and severe mycobacterial infections (OMIM ID: 616622).12 Six of seven patients developed mild mucocutaneous Candida infections, and mycobacterial infection was severe and observed in all patients. Four of the seven patients developed disseminated mycobacterial infection and one died because of BCG meningocerebralitis. The patients presented with mild T-cell lymphopenia, thymic hypoplasia, lack of palpable axillary and cervical lymph nodes, and absence of MAIT and iNKT cells that were consistent with the phenotype of Rorc−/− mice.12 Moreover, Rorc−/− mice were also susceptible to mycobacterial infection, suggesting that host susceptibility to mycobacteria was not a human-specific finding.12

All three homozygous mutations (S17L, Q308* and Q411*) in RORC identified in these patients were LOF and impaired DNA-binding ability of the target sequence of RORY and RORYT in the promoter region of IL-17A. CD3+ T cells from the patients displayed severe impairment in the production of IL-17A, IL-23+ T cells from the patients displayed severe impairment in the production of IL-17A, IL-23 and IL-22, and impaired IFN-γ production in response to mycobacterial challenge. These clinical and experimental observations demonstrate the essential role of RORY and RORYT not only for the development of IL-17-producing lymphocytes to protect the mucocutaneous barriers against Candida, but also for the activation of IFN-γ-producing T cells required for systemic protection against Mycobacterium.
misssense mutation, S95L (c.284C>T), in IL17F was identified in this family. The S95L mutation was found in four patients with CMC, as well as two asymptomatic family members (aged 9 months and 21 years), suggesting incomplete clinical penetrance. All four patients developed CMC from the first year of life. In addition to CMC, recurrent furunculosis and recurrent upper respiratory tract infections were observed in one patient. One sibling, who lacked genetic testing for IL17F, died at the age of 6 years from encephalopathy of unclear etiology associated with extensive oral candidiasis. The S95L IL17F mutant (IL17F−/−) was normally expressed and formed homo- and heterodimers with IL17F, IL17Fp95L, and IL17A. However, IL17Fp95L was severely hypomorph and exerted a dominant-negative effect by impairing the binding of its complexes to the receptor. Curiously, IL17F−/− mice do not show susceptibility to experimental infection with intravenously administered Candida. In contrast, IL17a−/− mice are susceptible only to cutaneous and systemic candidiasis. Possible explanations for this discrepancy could be a different function of IL17F between mice and humans, or the dominant-negative effect of IL17Fp95L on IL17A signaling. A subsequent study identified a second multiplex family with AD IL17F deficiency. The proband and his mother, carrying an undescribed heterozygous IL17F variation, developed CMC. Although no functional validation was performed, this might be the second family reported with AD IL17F deficiency.

**AR IL17RA deficiency**

The first patient reported with AR IL17RA deficiency (OMIM ID: 613953) was born to consanguineous Moroccan parents. A homozygous nonsense mutation, Q284*, in IL17RA that was inherited from asymptomatic consanguineous parents was identified. The patient developed recurrent CMC, and was resistant to local antifungal treatment from the first month of life. He was also susceptible to S aureus, presenting with skin abscess and folliculitis on the buttocks. Although the patient had several episodes of conjunctivitis, acute media otitis, lower respiratory tract infections and folliculitis, he never developed severe bacterial infection. Analysis of peripheral blood mononuclear cells and patient-derived fibroblasts showed no IL17RA protein expression on their surface. Moreover, no response to homo- and heterodimeric IL17A and IL17F was observed in fibroblasts and no response to IL17E (IL−25) was observed in peripheral blood mononuclear cells from the patient (Figure 2). A subsequent study identified a multiplex family with the combination of AR IL17RA and adenosine deaminase 2 deficiency. Two siblings with CMC identified in this study shared a homozygous large deletion including entire regions of IL17RA and CECR1 (encoding adenosine deaminase 2). The absence of IL17RA surface protein expression was confirmed with flow cytometry on patient neutrophils, monocytes and CD4+ T cells. Overall, the clinical observations in patients with AR IL17RA deficiency are comparable to those in IL17RA−/− mice that were inherited from asymptomatic parents, and absence of susceptibility to mucocutaneous pathogens, such as Candida and Staphylococcus. Together with the original case of AR IL17RA deficiency, complete clinical penetrance was observed in this disorder.

**AR IL17RC deficiency**

So far, three unrelated CMCD patients, one from Argentina and the others from Turkey, have been reported with AR IL17RC deficiency (OMIM ID: 616445). Three different nonsense homozygous mutations, Q138*, R376* and R378*, in IL17RC that were inherited from asymptomatic parents, were identified in the patients. All patients with biallelic mutations in IL17RC developed CMC, suggesting complete clinical penetrance for this disorder. Unlike AR IL17RA and ACT1 deficiencies, patients with AR IL17RC deficiency did not have recurrent staphylococcal infections. Moreover, none of the patients suffered from severe or recurrent bacterial infections. All mutations were shown to be loss-of-expression, with a lack of IL17RC cell surface expression in HEK293T-transfected cells and normal IL17RA expression on SV-40-immortalized fibroblasts obtained from the patients. The specific IL17RC defect in these patients was demonstrated by a lack of cellular responses to homo- and heterodimers of IL17A and IL17F, but normal responses to IL17RC-independent signaling via IL-25 (Figure 2). Staphylococcal disease is frequently observed in patients with AR IL17RA and ACT1 deficiency (described below), whereas it is not obvious in patients with AD IL17F or AR IL17RC deficiency. The infectious phenotype of patients with AR IL17RC deficiency resembled that of observed in patients with AD IL17F deficiency, and was consistent with that of IL17rc−/− mice. This clinical observation supports the contribution of an additional defect in the signaling pathway, downstream of IL-17E, in patients with AR IL17RA and ACT1 deficiency.

**AR ACT1 deficiency**

AR ACT1 deficiency was first reported in 2013 in two siblings born to consanguineous Algerian parents. A homozygous mutation, T536I, in the SEF/IL17 receptor (SEFIR) domain of TRAF3IP2 (encodes ACT1) that was inherited from asymptomatic parents was identified. Both patients developed CMC, suggesting complete clinical penetrance for this disorder. One patient also had recurrent episodes of folliculitis decalvans and bilateral blepharitis caused by S aureus. ACT1 is an adaptor molecule that interacts with multiple partners, including members of the IL-17R family. Upon stimulation, ACT1 is recruited to IL17RA, IL17RB and/or IL17RC (and probably IL17RE) by homotypic dimerization of two SEFIR domains, and activates the Nfkb, mitogen-activated protein kinase and CCAAT enhancer-binding protein pathways (Figure 2). ACT1 also has an inhibitory role in B-cell survival by negatively regulating CD40 and B-cell-activating factor receptor interaction through interaction with TRAF3. The T536I ACT1 mutation does not disturb its protein expression. However, this mutation specifically impairs the homotypic interaction of ACT1 with IL17RA, IL17RB and IL17RC, abolishing responses to IL17A and IL17F in fibroblasts and to IL17E and IL17F in leucocytes. The T536I ACT1 mutation does not affect SEFIR domain-independent interactions. This mutant normally interacts with CD40 and other SEFIR-independent interaction partners such as heat-shock proteins 70 and 90. The selective defect in the IL-17 signaling due to T536I-specific ACT1 mutation in the SEFIR domain may explain the phenotypic discrepancy between identified human AR ACT1 deficiency and Act1−/− mice. Unlike human AR ACT1 deficiency, Act1−/− mice display enhanced B-cell responses to CD40L and BAFF, resulting in hypergammaglobulinemia. In conclusion, the specific TRAF3IP2 mutation that selectively impairs the function of ACT1 SEFIR domain is responsible for CMCD.

**MANAGEMENT AND TREATMENT OF PATIENTS WITH CMCD AND AD STAT1-GOF**

Most patients with CMCD are treated with topical and/or systemic antifungal agents. Fluconazole is the main first-line oral therapy, followed by itraconazole, posaconazole and/or voriconazole. As for topical treatment, nystatin is a good alternative to triazoles. CMC in approximately one-third of patients with GOF-STAT1 mutations is successfully treated with azoles, whereas a partial response is observed in the others. In general, long-lasting treatments and/or prophylaxis are required to treat persistent and prevent
recurrence of CMC. Patients with AR IL-17RA and ACT1 deficiency develop staphylococcal infections in addition to CMC. Antibiotic prophylaxis with sulfamethoxazole–trimethoprim seems to be effective to treat these patients. Patients with GOF-STAT1 mutations present various clinical manifestations in addition to CMC. Many patients suffer from bacterial infections, such as lower respiratory infections (in 47% patients), ear-nose-and-throat infections (44%) and skin infections (28%), associate with infections of S. aureus (36%), Streptococcus sp. (20%), Pseudomonas aeruginosa (13%) and Haemophilus influenzae (9%). Thus, some patients are also considered for antibiotic prophylaxis, such as sulfamethoxazole–trimethoprim, to prevent bacterial infections. Moreover, patients with GOF-STAT1 mutations occasionally develop severe autoimmune disorders that require immunosuppressive treatment. The Janus kinase inhibitor, ruxolitinib, has been trialed in two patients with GOF-STAT1 mutations, leading to improvement of CMC and autoimmune syndrome, without significant adverse effects. Hematopoietic stem cell transplantation might be considered as a treatment option for patients with GOF-STAT1 mutations, especially for those with severe clinical presentations, such as recurrent severe viral and/or bacterial infections, IPEX-like syndrome or hemophagocytic syndrome. Indeed, invasive infections, cerebral aneurysms and cancers are considered to be strong predictors of poor outcome. Hematopoietic stem cell transplantation seems to be an effective cure for these patients. Patients with no ANR-10-IAHU-01), US National Institutes of Health (NIH; Grant no. SU01AI09697-02), the Rockefeller University and the St Giles Foundation.

CONCLUSION

The recent identification of genetic etiologies of Syndromic CMC and CMCD has revealed the nonredundant role of IL-17 in mucocutaneous immunity to Candida in humans. These discoveries have improved our understanding of CMC, by revealing inheritance, clinical course and prognosis. Furthermore, clarification of the molecular pathogenesis potentially gives us the opportunity to find target molecules, such as Janus kinase inhibitors, which target signaling, to improve the clinical symptoms. It might also inform the potential risk of increased susceptibility to Candida in patients treated with anti-IL-17-targeted immunotherapies. The discovery of GOF-STAT1 mutation as a molecular pathogenesis of Syndromic CMC was a breakthrough in this field. From the first identification, more than 300 of patients with GOF-STAT1 have been identified. However, there are still many patients with CMC who lack a genetic etiology. Further studies are required to validate the wider application of this treatment for all individuals with CMC.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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1 Kirkpatrick CH. Chronic mucocutaneous candidiasis. Pediatr Infect Dis J 2001; 20: 197–206.
2 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: 616–621.
3 Lanternier F, Cypowyj S, Picard C, Bastamante J, Lorholtay O, Casanova JL et al. Primary immunodeficiencies underlying fungal infections. Curr Opin Pediatrics 2013; 25: 736–747.
4 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.
5 Conti HR, Shen F, Nayyar N, Stocum E, Sun JN, Lindemann MJ et al. Th17 cells and IL-17 receptor signaling are essential for mucosal host defense against oral candidiasis. J Exp Med 2009; 206: 299–311.
6 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.
7 Glocke ED, Hennigs A, Nabavi M, Schaffer AA, Wielin C, Salzer U et al. A homozygous CARD9 mutation in a family with susceptibility to fungal infections. N Engl J Med 2009; 361: 1727–1735.
8 Drewinko A, Gazendam RP, Tool AT, van Houdt M, Jansen MH, van Hamme JL et al. Invasive fungal infection and impaired neutrophil killing in human CARD9 deficiency. Blood 2013; 121: 2385–2392.
9 Kisand K, Bofe WW, Podkrajsek KT, Tserel L, Link M, Kisand KV et al. Chronic mucocutaneous candidiasis in APECED or thymoma patients correlates with autoreactivity to T(H)17-associated cytokines. J Exp Med 2010; 207: 299–308.
10 Prando C, Samarina A, Bastamante J, Boisson-Dupuis S, Cobat A, Picard C et al. Inherited IL-12p40 deficiency: genetic, immunologic, and clinical features of 49 patients from 30 kindreds. Medicine (Baltimore) 2013; 92: 109–122.
11 de Beaucoudrey L, Samarina A, Bastamante J, Cobat A, Boisson-Dupuis S, Feinberg J et al. Revisiting human IL-12Rbeta1 deficiency: a survey of 141 patients from 30 countries. Medicine (Baltimore) 2010; 89: 381–402.
12 Okada S, Markle JG, Deenick EK, Mele F, Averbuch D, Lagos M et al. Immunodeficiencies underlying fungal infections in humans with bi-allelic RORC mutations. Science 2015; 349: 606–613.
13 Puel A, Doffinger R, Natalvich A, Chrabieh M, Barcenas-Morales G, Picard C 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.
14 Freeman AF, Holland SM. The hyper-ILgE syndromes. Immunol Allergy Clin North Am 2008; 28: 277–291.
15 Minegishi Y, Saito M, Nagasawa M, Takada H, Hara T, Tsujiyua S et al. Molecular explanation for the contradiction between systemic Th17 defect and localized bacterial infection in hyper-ILgE syndrome. J Exp Med 2009; 206: 1299–1301.
16 Ouederni M, Sanal O, Ikinciogullari A, Tezcan I, Dogu F, Sologuren I et al. Clinical features of Candidiasis in patients with inherited interleukin 12 receptor beta2 deficiency. Clin Infect Dis 2014; 58: 204–213.
17 de Beaucoudrey L, Puel A, Filipe-Santos O, Cobat A, Ghandil P, Chrabieh M et al. Mutations in STAT3 and IL12RB1 impair the development of human IL-17-producing T cells. J Exp Med 2008; 205: 1543–1550.
18 Lanternier F, Mahdaviia SA, Barbati E, Chaussade H, Koumar Y, Levy R et al. Inherited CARD9 deficiency in otherwise healthy children and adults with Candida species-induced meningocerebritis, colitis, or both. J Allergy Clin Immunol 2015; 135: 1588–1598.e1592.
19 Renner ED, Rylaarsdam S, Anover-Sombee S, Rack AL, Reichenbach J, Carey JC 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-ILgE syndrome. J Allergy Clin Immunol 2008; 122: 181–187.
20 Ma CS, Chew GY, Simpson N, Priaydarsi A, Wong M, Grimbach B et al. Deficiency of TH17 cells in hyper IgE syndrome due to mutations in STAT3. J Exp Med 2008; 205: 1591–1597.
21 Minegishi Y, Saito M, Morio T, Watanabe K, Agematsu K, Tsujiyua S et al. Human tyrosine kinase 2 deficiency reveals its requisite roles in multiple cytokine signals involved in innate and acquired immunity. Immunity 2006; 25: 745–755.
22 Kreins AJ, Ciancianelli MJ, Okuda S, Kong XF, Ramirez-Reja N, Klic SS et al. Human TYK2 deficiency. Mycobacterial and viral infections without hyper-ILgE syndrome. J Exp Med 2015; 212: 1641–1662.
23 Finnish-German AC. An autoimmune disease, APECED, caused by mutations in a novel gene encoding two PHD-type zinc-finger domains. Nat Genet 1997; 17: 399–403.
24 Nagamine K, Peterson P, Scott HS, Kudoh J, Minoshima S, Heino M et al. Positional cloning of the APECED gene. Nat Genet 1997; 17: 393–398.
25 Kisand K, Lilic D, Casanova JL, Peterson P, Meager A, Willcox N. Mucocutaneous candidiasis and autoimmune against cytokines in APECED and thymoma patients: clinical and pathogenetic implications. Eur J Immunol 2001; 41: 1517–1527.
26 Lanternier F, Pathan S, Vincent QB, Liu L, Cypowyj S, Prando C et al. Deep dermatophytosis and inherited CARD9 deficiency. N Engl J Med 2013; 369: 1704–1714.
27 Altare F, Durandy A, Lammas D, Emile JF, Lamhamdi S, Le Deit F et al. Impairment of mycobacterial immunity in human interleukin-12 receptor deficiency. Science 1998; 280: 1432–1435.
28 de Jong R, Altare F, Haagen IA, Efferink DG, Boer T, van Breda Vriesman PJ et al. Severe mycobacterial and Salmonella infections in interleukin-12-receptor-deficient patients. Science 1998; 280: 1435–1438.
29 Altare F, Lammas D, Reyw P, Jouanguy E, Dof
30 Liu L, Okada S, Kong XF, Kreins AY, Cypowyj S, Abhyankar A et al. IL-17 and Th17 cells.
31 Mizoguchi Y, Tsumura M, Okada S, Hirata O, Minegishi S, Imai K et al. Simple diagnosis of STAT1 gain-of-function alleles in patients with chronic mucocutaneous candidiasis. J Exp Med 2011; 208: 1635–1641.
32 Depner M, Fuchs S, Raabe J, Frede N, Glocker C, Dof
33 Hori T, Ohnishi H, Teramoto T, Tsubouchi K, Naiki T, Hirose Y et al. Heterozygous STAT1 gain-of-function mutations underlie an unexpectedly broad clinical spectrum in a French national survey. Medicine 2012; 91: e1–e9.
34 Lanternier F, Barbati E, Meinzer U, Liu L, Pedergnana V, Migaud M et al. IL-17RC deficiency associated with heterozygous mutation in STAT1. J Allergy Clin Immunol 2014; 133: 807–817.
35 Liu H, Rohowsky-Kochan C. Interleukin-27-mediated suppression of human Th17 cells is associated with activation of STAT1 and suppressor of cytokine signaling protein 1. J Interferon Cytokine Res 2011; 31: 459–469.
36 Li C, Spaun E, Lannert CM, Hille J, Guo Y, Li Z et al. Chronic mucocutaneous candidiasis, psoriasis vulgaris and dermatophytosis. J Allergy Clin Immunol 2016; 137: 1275–1284.
37 Wang X, Wang W, Lin Z, Wang X, Li T, Yu J et al. CARD9 mutations linked to subcutaneous phaeohyphomycosis and TH17 cell deficiencies. J Allergy Clin Immunol 2014; 133: 905–908:e903.
38 Gavino C, Colter A, Lichterstein D, Lefeltyen D, Fortin C, Legault C et al. CARD9 deficiency is a central nervous system candidate for complete clinical remission with GM-CSF therapy. Clin Disord Influen 2014; 59: 81–84.
39 Gazendam RP, van Hamme JL, Tool AT, van Houdt M, Verkuilen PJ, Herbst M et al. Two independent killing mechanisms of Candida albicans by human neutrophils: residual fungicidal activity and phagocytosis. J Leukoc Biol 2016; 99: 690–695.
40 Boissieux B, Wang C, Pedergnana V, Wu L, Cypowyj S, Rybojad M et al. An ACTN1 mutation selectively abolishes interleukin-17 responses in humans with chronic mucocutaneous candidiasis. Immunity 2013; 39: 676–686.
41 Depner M, Fuchs S, Raabe J, Frede N, Glocker C, Dof
42 Lee Y, Spaun E, Lannert CM, Hille J, Guo Y, Li Z et al. Chronic mucocutaneous candidiasis in patients with recurrent interlukin-17 deficiency. Science 2011; 332: 1317–1316.
43 Boissieux B, Wang C, Pedergnana V, Wu L, Cypowyj S, Rybojad M et al. An ACTN1 mutation selectively abolishes interleukin-17 responses in humans with chronic mucocutaneous candidiasis. Immunity 2013; 39: 676–686.
44 Li X, Wang X, Lin Z, Wang X, Li T, Yu J et al. CARD9 mutations linked to subcutaneous phaeohyphomycosis and TH17 cell deficiencies. J Allergy Clin Immunol 2014; 133: 905–908:e903.
45 Gavino C, Colter A, Lichterstein D, Lefeltyen D, Fortin C, Legault C et al. CARD9 deficiency is a central nervous system candidate for complete clinical remission with GM-CSF therapy. Clin Disord Influen 2014; 59: 81–84.
46 Gazendam RP, van Hamme JL, Tool AT, van Houdt M, Verkuilen PJ, Herbst M et al. Two independent killing mechanisms of Candida albicans by human neutrophils: residual fungicidal activity and phagocytosis. J Leukoc Biol 2016; 99: 690–695.
47 Boissieux B, Wang C, Pedergnana V, Wu L, Cypowyj S, Rybojad M et al. An ACTN1 mutation selectively abolishes interleukin-17 responses in humans with chronic mucocutaneous candidiasis. Immunity 2013; 39: 676–686.
48 Li X, Wang X, Lin Z, Wang X, Li T, Yu J et al. CARD9 mutations linked to subcutaneous phaeohyphomycosis and TH17 cell deficiencies. J Allergy Clin Immunol 2014; 133: 905–908:e903.
49 Gavino C, Colter A, Lichterstein D, Lefeltyen D, Fortin C, Legault C et al. CARD9 deficiency is a central nervous system candidate for complete clinical remission with GM-CSF therapy. Clin Disord Influen 2014; 59: 81–84.
50 Gazendam RP, van Hamme JL, Tool AT, van Houdt M, Verkuilen PJ, Herbst M et al. Two independent killing mechanisms of Candida albicans by human neutrophils: residual fungicidal activity and phagocytosis. J Leukoc Biol 2016; 99: 690–695.
51 Boissieux B, Wang C, Pedergnana V, Wu L, Cypowyj S, Rybojad M et al. An ACTN1 mutation selectively abolishes interleukin-17 responses in humans with chronic mucocutaneous candidiasis. Immunity 2013; 39: 676–686.
52 Li X, Wang X, Lin Z, Wang X, Li T, Yu J et al. CARD9 mutations linked to subcutaneous phaeohyphomycosis and TH17 cell deficiencies. J Allergy Clin Immunol 2014; 133: 905–908:e903.
53 Gavino C, Colter A, Lichterstein D, Lefeltyen D, Fortin C, Legault C et al. CARD9 deficiency is a central nervous system candidate for complete clinical remission with GM-CSF therapy. Clin Disord Influen 2014; 59: 81–84.
54 Gazendam RP, van Hamme JL, Tool AT, van Houdt M, Verkuilen PJ, Herbst M et al. Two independent killing mechanisms of Candida albicans by human neutrophils: residual fungicidal activity and phagocytosis. J Leukoc Biol 2016; 99: 690–695.
55 Boissieux B, Wang C, Pedergnana V, Wu L, Cypowyj S, Rybojad M et al. An ACTN1 mutation selectively abolishes interleukin-17 responses in humans with chronic mucocutaneous candidiasis. Immunity 2013; 39: 676–686.
56 Li X, Wang X, Lin Z, Wang X, Li T, Yu J et al. CARD9 mutations linked to subcutaneous phaeohyphomycosis and TH17 cell deficiencies. J Allergy Clin Immunol 2014; 133: 905–908:e903.
57 Gavino C, Colter A, Lichterstein D, Lefeltyen D, Fortin C, Legault C et al. CARD9 deficiency is a central nervous system candidate for complete clinical remission with GM-CSF therapy. Clin Disord Influen 2014; 59: 81–84.
58 Gazendam RP, van Hamme JL, Tool AT, van Houdt M, Verkuilen PJ, Herbst M et al. Two independent killing mechanisms of Candida albicans by human neutrophils: residual fungicidal activity and phagocytosis. J Leukoc Biol 2016; 99: 690–695.
59 Boissieux B, Wang C, Pedergnana V, Wu L, Cypowyj S, Rybojad M et al. An ACTN1 mutation selectively abolishes interleukin-17 responses in humans with chronic mucocutaneous candidiasis. Immunity 2013; 39: 676–686.
60 Li X, Wang X, Lin Z, Wang X, Li T, Yu J et al. CARD9 mutations linked to subcutaneous phaeohyphomycosis and TH17 cell deficiencies. J Allergy Clin Immunol 2014; 133: 905–908:e903.
61 Gavino C, Colter A, Lichterstein D, Lefeltyen D, Fortin C, Legault C et al. CARD9 deficiency is a central nervous system candidate for complete clinical remission with GM-CSF therapy. Clin Disord Influen 2014; 59: 81–84.
62 Gazendam RP, van Hamme JL, Tool AT, van Houdt M, Verkuilen PJ, Herbst M et al. Two independent killing mechanisms of Candida albicans by human neutrophils: residual fungicidal activity and phagocytosis. J Leukoc Biol 2016; 99: 690–695.
63 Boissieux B, Wang C, Pedergnana V, Wu L, Cypowyj S, Rybojad M et al. An ACTN1 mutation selectively abolishes interleukin-17 responses in humans with chronic mucocutaneous candidiasis. Immunity 2013; 39: 676–686.
64 Li X, Wang X, Lin Z, Wang X, Li T, Yu J et al. CARD9 mutations linked to subcutaneous phaeohyphomycosis and TH17 cell deficiencies. J Allergy Clin Immunol 2014; 133: 905–908:e903.
65 Gavino C, Colter A, Lichterstein D, Lefeltyen D, Fortin C, Legault C et al. CARD9 deficiency is a central nervous system candidate for complete clinical remission with GM-CSF therapy. Clin Disord Influen 2014; 59: 81–84.