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Chronic Candidiasis in Children

Laura Green[1] · **William K. Dolen**[1]

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Abstract
Purpose of Review Healthy children may develop candidal infections as the result of exposure to antibiotics or corticosteroids, but chronic candidiasis in children after the newborn period is unusual. Chronic mucocutaneous candidiasis (CMC) refers to a group of conditions characterized by recurrent or persistent infections with *Candida* species, particularly *Candida albicans*. CMC is a phenotype observed in a spectrum of immunologic disorders, some with endocrinologic and autoimmune features.
Recent Findings CMC can arise secondary to inherited or acquired T cell deficiencies, but in children is largely due to inborn errors impairing the dectin pathway and IL-17 immunity. We review the current understanding of the pathogenesis of chronic mucocutaneous candidiasis and discuss the immunologic pathways by which the immune system handles *Candida*. We highlight the historical and recent knowledge of CMC in children, emphasizing recent insights into basic science aspects of the dectin pathway, IL-17 signaling, consequences of AIRE gene defects, and clinical aspects of inheritance, and features that distinguish the different syndromes.
Summary The clinical phenotype of CMC has many underlying genetic causes. Genetic testing is required for definitive diagnosis.

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✉ William K. Dolen
bdolen@augusta.edu

Laura Green
laugreen@augusta.edu

[1] From the Department of Pediatrics, Allergy-Immunology and Pediatric Rheumatology Division, Medical College of Georgia at Augusta University, 1120 15th Street, Augusta, GA 30912, USA

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Introduction

Candida albicans is a dimorphic (with both yeast and filamentous forms) fungus that is part of the normal microbiome of the mouth, gastrointestinal and genitourinary tracts, and skin in humans. The normal host defense against infection involves the innate and adaptive immune systems. In children, candidal infections can occur for various reasons (Table 1). Thrush, diaper rash, and genital candidiasis may present in otherwise healthy individuals, but candidiasis after the newborn period in a person not receiving antibiotics, corticosteroids, or immunosuppressive therapy is unusual, warranting evaluation for comorbidities, including primary immunodeficiency. In immunocompromised patients, *Candida* can cause chronic or invasive infections. Neonatal candidiasis can be observed in infants in intensive care settings, especially in those patients with history of extremely low birth weight (<1000 g), exposure to empiric antibiotics, or prolonged administration of parenteral nutrition [1]. Patients with severe combined immunodeficiency (SCID) lack autologous T cells and are extremely vulnerable to bacterial, viral, and fungal infections, including *C. albicans*; other primary immunodeficiency disorders are associated with candidal and other infections [2–4]. HIV1 disease and neoplasia can also cause chronic candidiasis. The hyperglycemia of diabetes mellitus favors candidal growth.

Chronic candidiasis in childhood also raises concern for a group of rare primary immunodeficiency disorders loosely termed chronic mucocutaneous candidiasis or chronic mucocutaneous candidiasis (CMC) (Table 2). These patients

Table 1 Underlying problems causing chronic candidiasis in children

Infancy
Long-term antibiotic use
Long-term inhaled steroid use
Immunosuppressive therapy
Diabetes mellitus
Neoplasia, including lymphoreticular malignancy
HIV1 infection; AIDS
SCIDs, other combined immunodeficiency

present with the common phenotypic feature of chronic or recurrent candidal infections of the nails, skin, oral, and genital mucosae, particularly by *C. albicans* [6••]. The dectin pathway of the innate immune system, which involves Th17 cells and their cytokines IL-17 and IL-22 is essential for human antifungal immunity [7], and various reported inborn errors confer a predisposition to infection with *C. albicans*. Clinical presentation, including the presence of other infections, help distinguish the primary cause of CMC, although molecular diagnosis is necessary for confirmation. Here, we will review the genetic etiologies responsible for, and clinical phenotypes associated with, CMC.

Dectin Pathway Deficiency

Protection against candidal infections relies upon the ability of phagocytic cells to recognize, digest, and kill the organism. This mechanism is mediated by the recognition of the β-glucan component in fungal cell walls by C-type lectin receptors like dectin-1 (C-type lectin domain family 7, member A; CLEC7A) [2, 8]. A dectin-1 receptor defect causes the type of familial candidiasis that is designated CANDF4. These antifungal pattern recognition receptors activate caspase recruitment domain-containing protein 9 (CARD9), an adaptor molecule in myeloid cells [9]. A CARD9 gene defect causes the type of familial candidiasis termed CANDF2. Activated CARD9 couples with BCL10 and MALT-1 to induce activation of nuclear factor-κB (NF-κB), initiating a cascade of pro-inflammatory cytokines (IL-6, IL-23, TNF-alpha, IL-1β). IL-6 induces transcription factor signal transducer and activator of transcription 3 (STAT3), which binds the IL-17 promoter, inducing T lymphocytes to differentiate into IL-17 producing-T cells. STAT3 mutations cause one form of hyper-IgE syndrome that is associated with CMC. IL-17, along with IL-22 stimulates production of chemokines, defensins, and inflammatory cells. Defects in IL-17 signaling have a substantial role in the body's immunity against *Candida* species; a defect in the *IL17RA* gene causes CANDF5 (also termed immunodeficiency 51); gene mutations in *IL17F* cause CANDF6. Defects in the dectin pathway are not associated with endocrinopathy.

In 2009, homozygosity mapping was performed on 36 members of a large, consanguineous family, in an effort to evaluate the cause of CMC and invasive fungal disease in several of the family members; a homozygous mutation in CARD9 was identified [2]. Patients with CARD9 deficiency (CANDF2) display low IL-17A producing T cells, which predisposes these individuals to CMC, as well as invasive candidiasis. Subsequent reports have revealed CARD9-deficient patients are at risk for subcutaneous phaeophyphomycosis,

Table 2 Primary immunodeficiency disorders causing primarily chronic mucocutaneous candidiasis, with or without endocrinopathy

Disorder	Gene	Inheritance	MIM entry (gene)	MIM entry (disease)
Dectin-1 deficiency CANDF4	CLEC7A	AR	*606264	#613108
CANDF2	CARD9	AR	*607212	#212050
Immunodeficiency 31C (CANDF7)	STAT1 gain of function	AD	*600555	#614162
Immunodeficiency 42 (RORγ and RORγt)	RORC	AR	*602943	#616622
Immunodeficiency 51 (formerly termed CANDF5)	IL17RA	AR	*605461	#613953
CANDF6	IL17F	? (one family)	*606496	#613956
CANDF9	IL17RC	AR	*610925	#616445
CANDF8	TRAF3IP2	AR	*607043	#615527
CANDF3 (ICAM1 deficiency)	Unknown	AD	n/a	%607,644
CANDF1	Unknown	AD	n/a	%114,580
AD hyper IgE syndrome (STAT3)	STAT3	AD	*102582	#147060
AR hyper IgE syndrome (DOCK 8)	DOCK8	AR	*611432	#243700
APS1/APECED	AIRE	AR (AD reported)	*607358	#240300

MIM numbers are from Online Mendelian Inheritance in Man (OMIM) [5]

deep dermatophytosis, meningoencephalitis, and colitis [10•, 11, 12]. Furthermore, patients may develop other chronic invasive fungal infections, including *Aspergillus* spp., *Pneumocystis jirovecii*, and *Cryptococcus neoformans* [10•, 13•, 14].

STAT1 Gain of Function Mutations

In 2011, whole exome sequencing (WES) identified gain of function mutations in the signal transducer and activator of transcription 1 (*STAT1*) gene as a cause of autosomal dominant CMC, termed "Immunodeficiency 31C" or CANDF7. Since that time, *STAT1* gain of function mutations has been found to underlie the majority of cases of syndromic CMC. These mutant alleles increase STAT1-dependent responses to cytokines, more specifically to IL-6 and IL-21 that activate STAT3 and induce the IL-17 pathway. Enhanced STAT1 activation by these cytokines, as well as stronger responses to STAT1-dependent IL-17 inhibitors IFN-α/β, IFN-γ, and IL-27 obstruct the development of IL-17A, IL-17F, and IL-22 [15].

CMC is the most common infectious manifestation in patients carrying *STAT1* gain of function mutations. In a recently described cohort of 274 patients from 167 kindreds originating from 40 different countries, CMC was documented in 98% of patients, with a mean age of onset at 1 year [16••]. Similarly, Dhalla et al. describe a kindred of seven patients who all developed candidiasis in infancy or early childhood. Symptoms in this group primarily presented as episodes of mild disease affecting the nails and oral mucosa, but progressed to more severe and persistent oropharyngeal, esophageal, and genital involvement as they reached adulthood [17]. Patients also have increased susceptibility to dermatophytic infections of the scalp, skin, or nails by *Trichophyton* or *Microsporon* spp., and more rarely can develop invasive candidiasis [16••], disseminated coccidiodomycosis, histoplasmosis [18], or disseminated mucormycosis [19].

In addition to fungal infections, these patients are at risk for recurrent bacterial pneumonias, chronic sinusitis, and otitis media. *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, and *Haemophilus influenzae* are frequently documented pathogens. Recurrent viral infections are also described, including herpes simplex virus, varicella-zoster virus, molluscum contagiosum virus, cytomegalovirus, and Epstein-Barr virus [6••, 16••].

Many patients with *STAT1* gain of function mutations display autoimmune manifestations, including thyroid disease, type I diabetes mellitus, vitiligo, psoriasis, autoimmune hepatitis, and autoimmune cytopenias. More concerning though is the increased likelihood for these patients to develop aneurysms and malignancy. Cerebral aneurysms have been observed at a higher rate in patients with *STAT1* gain of function mutations than in the normal population, with a much earlier median age of diagnosis of 23 years [16••].

RORC Deficiency

In 2015, WES and genome wide linkage (GWL) analysis revealed biallelic loss-of-function mutations in the *RORC* gene, which encodes retinoid-related orphan receptor gamma (RORγ) and RORγt, in seven patients with candidiasis and severe mycobacteriosis. In addition to CMC that presented in early childhood, these patients exhibited mild T cell lymphopenia, thymic hypoplasia, and absence of palpable lymphadenopathy. Distinguishing this cohort from those with other forms of CMC, however, was the presence of disseminated *Mycobacterim bovis*-BCG and *Mycobacterium tuberculosis* [20]. RORγT is expressed by Th17 cells and serves as a key transcription factor for Th17 cytokine production [21]. In these patients, the *RORC* mutations and the subsequent deficiency of RORγ and RORγt resulted in impaired production of IL-17A, IL-17F, and IL-22, accounting for the predisposition to CMC. Moreover, T cells from these patients displayed significant impairment in IFN-γ production in response to *Mycobacterium* [20]. This demonstrates the critical role of RORγt in protection against both *Candidiasis* and mycobacterial infections.

IL-17RA Deficiency (immunodeficiency 51; CANDF5)

Autosomal recessive deficiency in the cytokine receptor, interleukin-17 receptor A (IL-17RA), was first reported as a genetic etiology of CMC in 2011. Originally termed CANDF5, the condition is now known as immunodeficiency 51. This first report described a single patient who presented with *C. albicans* dermatitis during the neonatal period, and subsequently displayed *S. aureus* dermatitis by 5 months of age. Genetic sequencing identified a homozygous nonsense mutation in the *IL17RA* gene [4]. In 2016, a cohort of 21 patients with AR IL-17A deficiency was described. All of these patients displayed CMC before 6 months of age, and two thirds had also developed recurrent staphylococcal skin infections by that time. Patients with AR IL-17A deficiency appear to be more susceptible to respiratory infections. No autoimmune endocrinopathy, aneurysms, or mucosal carcinomas were reported in these patients [22••].

IL17F Gene Deficiency

Autosomal dominant deficiency of the cytokine IL-17F, termed CANDF6, was first identified in 2011 in a multiplex

family from Argentina. A heterozygous missense mutation in the *IL17F* gene was identified in four family members who had all developed CMC within the first year of life, as well as in two asymptomatic family members [4]. Whereas IL-17RA deficiency is complete, with abolished cellular responses to IL-17A and IL-17F homo and heterdimers, IL-17F deficiency is partial, resulting in impaired but not completely absent activity in the mutant alleles. These patients also present primarily with CMC but appear to have a milder phenotype. They do not appear to suffer from staphylococcal disease, as is observed in patients with IL-17RA and ACT1 deficiency [22••].

IL-17RC Deficiency

In 2015, three unrelated patients were reported with autosomal recessive IL-17RC deficiency, termed CANDF9, stemming from three different nonsense homozygous mutations in the *IL17RC* gene inherited from asymptomatic parents. All three patients developed CMC in early childhood, but none had a history of significant bacterial or viral infections. No endocrine, metabolic, or autoimmune abnormalities were reported [23•].

TRAF3IP2 Deficiency

Autosomal recessive TRAF3-interacting protein 2 (TRAF3IP2) deficiency, termed CANDF8, was first reported in 2013 in two siblings born to consanguineous parents. Both siblings developed oral thrush due to *C. albicans* in early childhood and suffered also from recurrent blepharitis due to *S. aureus*. Genome-wide linkage mapping was combined with whole exome sequencing, and results revealed a biallelic missense mutation in the TRAF3IP2 gene [24]. TRAF3IP2 (also called ACT1) is an adaptor molecule that interacts with members of the IL-17R family to activate NF-κB, MAPK, and C/EBP pathways, leading to induction of genes in keratinocytes, fibroblasts, and epithelial cells [25]. This specific mutation abolished responses to IL-17A and IL17F in fibroblasts and to IL-17E in leukocytes, thus, causing impaired fungal immunity in these patients [24].

CANDF3, CANDF1

This type of familial candidiasis typically involves only the nails of the fingers and toes. It is associated with a quantitative deficiency of intracellular adhesion molecule-1 (ICAM-1). The causative gene has not been identified. Likewise, the causative gene for CANDF1 has not been identified.

The Hyper-IgE Syndromes

The hyper-IgE syndromes (HIES) are primary immunodeficiency disorders characterized by elevated serum IgE levels, rash, and recurrent bacterial and/or fungal infections involving the skin and respiratory tract.

Autosomal dominant HIES (AD HIES) was first described as Job's Syndrome in 1966 due to the presence of recurrent staphylococcal abscesses [26]. The disease was further defined as having high serum concentrations of IgE and eosinophilia in 1972 [27]. AD HIES is primarily caused by loss-of-function mutations in STAT3, a major protein and component of the dectin pathway, involved in wound healing, angiogenesis, and immunity, and important in the signal transduction of IL-6, IL-10, IL-17, IL-22, IL-23, and IL-27 [28]. Because of this impaired STAT3-mediated response, patients with AD HIES have low levels of IL-17A and IL-22-producing T cells, and thus an increased susceptibility to fungal infections. CMC is seen in up to 83% of patients with AD HIES due to a STAT3 defect, commonly presenting as oral, genital, or cutaneous candidiasis, or onychomycosis. Systemic *Candida* infections are rare [28]. Eczematous or pustular rashes in infancy are often the earliest manifestations of AD HIES, frequently appearing within the first month of life. Over time, boils or abscesses are characteristic of the disease, and despite originally being described as "cold" abscesses, culture results are often positive for *S. aureus*. Another hallmark of AD HIES is pyogenic pneumonias starting in early childhood, with *S. aureus*, *S. pneumoniae*, and *H. influenzae* isolated most frequently in cultures. In addition to classic triad of elevated serum IgE, eczema, and recurrent infections, patients with AD HIES due to STAT3 mutations present with characteristic coarse facies, retained primary teeth, scoliosis, osteoporosis, and hyperextensibility of joints.

Autosomal recessive HIES (AR HIES) was first linked to mutations in the dedicator of cytokinesis 8 (DOCK8) gene in 2009 through genomic hybridization arrays and targeted genetic sequencing [29]. Like the dominant form of hyper-IgE syndrome, DOCK8 defects also present with elevated serum IgE, eosinophilia, atopic dermatitis, *S. aureus* skin abscesses, and upper and lower respiratory tract infections. However, the clinical features distinguishing DOCK8 defects from other syndromes include asthma, severe food hypersensitivities possibly including anaphylaxis, and cutaneous viral infections. The most common viruses involved are herpes simplex virus (HSV), human papillomavirus (HPV), molluscum contagiosum virus (MCV), and varicella-zoster virus (VZV) [30]. CMC can also occur in AR HIES, although involvement is less than with the autosomal dominant form. A recent report describing the clinical characteristics of 64 patients with

DOCK8 defects found 64% were affected by mucocutaneous infections with *Candida* species [31]. Other types of hyper IgE syndrome do not appear to be associated with chronic candidiasis.

APS1/APECED

Autoimmune polyendocrinopathy syndrome type 1 (APS1), also called autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), is a rare syndrome resulting from various loss-of-function mutations in the autoimmune regulator (AIRE) gene [32]. Inheritance is usually autosomal recessive, but autosomal dominant inheritance has been reported. The classic triad of APECED consists of CMC, hypoparathyroidism (HP), and Addison disease (AD), with approximately two-thirds of patients developing all three conditions [33]. Other endocrinopathies such as hypergonadotropic hypogonadism, alopecia, type 1 diabetes mellitus, autoimmune thyroiditis, chronic hepatitis, pernicious anemia, and pituitary failure are observed less frequently [34•]. CMC is the presenting feature of APECED in the majority of cases, usually appearing in infancy or early childhood [35]. It may be several more years before the development of endocrinopathies, but this varies from patient to patient [33]. Ectodermal disturbances associated with APECED include vitiligo, alopecia, keratoconjunctivitis, dental enamel hypoplasia, pitted nail dystrophy, and tympanic membrane calcification [33–35].

The AIRE defect in patients with APS1/APECED affects T cell tolerance to self-antigens [36••]. B cell tolerance is affected during affinity maturation, a process that requires T cell collaboration. As a result, these patients produce high-affinity autoantibodies to various cytokines, including type I interferons, IL-17A, IL-17F, and IL-22, to other interleukins and to various enzymes involved in endocrine function. The pattern of autoantibody formation determines the clinical presentation. Patients who form autoantibodies against the type I interferons appear to have protection from developing type 1 diabetes mellitus, whereas the autoantibodies to the IL-17 family cause chronic candidiasis, and other autoantibodies affect endocrine function [36••, 37••].

Conclusions

Candidiasis in children may arise secondary to antibiotic or long-term steroid use, or may be the consequence of low birth weight or prolonged management in an intensive care setting. However, in the absence of underlying SCID or HIV, chronic candidiasis after the newborn period is unusual. This review highlights the critical role of the dectin pathway and IL-17 in immunity to *Candida* and illuminates key differences between the various CMC-causing syndromes with regard to inheritance and clinical presentation. These features, considered in light of a meticulous differential diagnosis, will signal the alert physician to obtain selective genetic testing for an accurate diagnosis.

As demonstrated throughout this review, whole exome sequencing and genome-wide linkage mapping have been paramount in the discovery of many genetic abnormalities, making CMC very much a "provocative experiment of nature" [38] that has led to a greater understanding of mechanisms of innate immunity and autoimmunity. The many patients with CMC in whom no etiology has yet been defined provide opportunities for further discoveries and understanding.

Compliance with Ethical Standards

Conflict of Interest Drs. Green and Dolen declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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