

A Novel IL17RA Mutation In A Male Child With Chronic Mucocutaneous Candidiasis

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Research Article

Keywords: IL17RA deficiency, chronic mucocutaneous candidiasis, *Candida albicans*

Posted Date: June 3rd, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-186598/v1>

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Abstract

Purpose: Chronic mucocutaneous candidiasis (CMC) is characterized by persistent or recurrent fungal infections involving the nails, skin, oral and genital mucosa. Impaired IL17 mediated immunity is a cause for CMC.

Patient and Methods: After the next-generation sequencing analysis showed the IL17RA variant, confirmation by Sanger sequencing was done. Functional validation of the variant by flow cytometry was performed.

Results: We present a 6-year-old male patient who presented with recurrent oral and genital candida infections and eczema. He had staphylococcal skin lesions in addition to the fungal susceptibility and eczema. The patient was found to carry a previously unreported homozygous nonsense [(c.787C> T) (p.Arg263Ter)] mutation in the IL17RA gene. Sanger sequencing confirmed the variant and showed the segregation of the variant in the family. We used flow cytometry to detect IL17RA protein expression in patients' PBMCs and measured the Th17 cell percentages. Severely decreased IL17RA protein expression was observed in patient's PBMCs and decreased CD4+ IL17+ cell percentage as well as decreased IL17F expression in CD4+ cells compared with healthy control.

Conclusion: In patients with chronic recurrent fungal and bacterial and/or infections of the skin, mucosa, and nails, advanced immunological studies should be performed to document the genetic susceptibility even if basic immunological tests are normal.

Introduction

Chronic mucocutaneous candidiasis (CMC) is characterized with persistent and/or recurrent fungal infections involving the nails, skin, and oral and genital mucosa caused by candida species, mainly *Candida albicans* [1]. It is an infectious phenotype in patients with inherited or acquired T-cell deficiency [1- 3]. Studies to explain the etiology of CMC have shown that Th17 cells and IL17 are particularly important in mucocutaneous host defense against Candida species [4- 6].

The first sporadic cases of CMC were detected in 1967, while the first familial cases were reported in the 1970s [7, 8]. Subsequent studies have identified many inherited genetic defects that can cause isolated or syndromic CMC presentation [9,10]. 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 β 1 (IL12R β 1), IL12p40, caspase recruitment domain-containing protein 9 (CARD9) or retinoic acid-related orphan receptor γ T (ROR γ T) or AR autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED) deficiencies are referred to as syndromic CMC, since they show other infectious or autoimmune symptoms in addition to CMC [4- 6].

Isolated CMC or CMC disease (CMCD) is defined as a condition that is characterized by persistent or recurrent infections of the *nails, skin, and oral and genital mucosa, caused typically by C. albicans, and*

less often by Staphylococcus aureus, without other severe infectious or autoimmune findings [1].

The first genetic etiologies of the isolated CMC form were deciphered by identifying deficiencies in autosomal recessive (AR) IL17RA and autosomal dominant (AD) IL17F [9].

To date, four genetic etiologies have been identified in patients with CMCD: AD IL17F, AR IL17RA, AR IL17RC, and AR TRAF3IP2 (encoding ACT1) [9-11].

The IL17 family consists of six cytokines, including IL17A (IL17), IL17B, IL17C, IL17D, IL17E (IL-25) and IL17F. IL17A and IL17F are the members with the most similar molecular structures. IL17 cytokines function by forming homo- or heterodimers [12,13].

The IL17R family, includes five receptor subunits; IL17RA, IL17RB, IL17RC, IL17RD and IL17RE. These receptors form various heterodimers, through which different IL17 cytokines signal in an ACT1-dependent manner and IL17RA forms the most common subunit of all these receptor complexes. IL17A exerts its function through the heterodimeric structure created by IL17RA and IL17RC receptors [12].

This paper presents a case of a 6-year-old male patient with a clinical picture of CMCD who was found to carry a homozygous [(c.787C> T) (p.Arg263Ter)] mutation in IL17RA gene that has not been reported previously.

Methods

Genetic Analysis

Genomic DNA was isolated from the peripheral blood sample of the patient (EasyOne-Qiagen). A total of 266 PID-associated genes were sequenced so as to include exon-intron and splice-site regions using targeted next-generation sequencing on the ION Torrent platform [14]. The sequencing process detected 923 nucleotide changes in the patient, and these variants were analyzed using the Ionreporter 5.10 software (ThermoFischer). Filtering was carried out to identify the pathogenic gene mutation among the variations detected by the analysis. Alleles with an allele frequency of <1% were included in the analysis for filtering.

Flow Cytometry

The analysis of peripheral blood lymphocyte populations was performed by one laser three-color flow cytometry (BD Biosciences FACSCalibur, USA), using 100 µl of whole blood stained with 20 µl of the following monoclonal antibodies against lymphocyte subsets with fluorescein isothiocyanate (FITC), phycoerythrin (PE) (obtained from Beckton Dickinson, BD, USA) ((CD3 (FITC), CD4 (FITC), CD8 (PE), CD16+56 (PE), and CD19 (PE)), and incubated in the dark for 15 min at room temperature.

For the detection of IL17RA expression, peripheral blood mononuclear cells (PBMCs) were separated by density gradient method. Then, cells were washed and stained with anti-IL17RA antibody (Biolegend,

USA). For the determination of CD4+ IL17A+ and CD4+ IL17F Th17 cells, PBMCs were stained with anti-CD4, anti-IL17A and anti-IL17F antibodies (BD, USA). Stained cells were analysed using FACS CANTO II flow cytometer (BD, USA).

To determine lymphocyte proliferation, following separation of PBMCs, cells were washed with PBS (Phosphate -Buffer- Saline) and stained with CFSE for 5 min. After washing steps cells were seeded with RPMI including L-Glutamine (1 %) and penicillin/streptomycin (1%) and incubated in 37 C° incubator including 5% CO₂ for 96 hours. Analysis was performed by using FACS CANTO II flow cytometer (BD, USA).

Results

Patient Report: A 3.5-year-old male patient with consanguineous (Figure 1A) parents presented to the Pediatric Immunology Clinic of Hacettepe University School of Medicine with eczema, and recurrent oral and genital candida infections.

His symptoms started at the age of 8 months as watery, itchy and eczematous lesions on the neck, back ear and inner side of the arms and legs, oral candida plaques and candida infection in the genital area. Skin lesions were alleviated by local corticosteroid and oral antifungal therapy, but no improvement in oral candida plaques or genital fungal infection was observed.

Upon physical examination, oral and genital candida infections and dry skin were observed, and there was no failure to thrive in the patient.

Scalp and nails were not affected by candida infection. In addition, there was no history of bacterial respiratory tract infections such as pneumonia, sinusitis or otitis at the time of diagnosis, and the patient did not have bacterial skin infections such as skin abscess, psoriasis or folliculitis.

The whole blood count, immunoglobulin and lymphocyte subgroup levels were normal. T and B cell subgroups and lymphocyte proliferation values were also normal (Table 1).

Prophylaxis with fluconazole was initiated. Oral and genital candida infections resolved after fluconazole treatment.

The patient was followed up for 2.5 years with fluconazole prophylaxis without symptoms. However, in the last 6 months, purulent bullous lesions developed especially on the fingertips, and sometimes around the mouth (Figure 2). These lesions recurred 5-6 times within 6 months. *Staphylococcus aureus* grew in the microbial sample taken from the lesion.

Mutation in IL17RA

We detected a homozygous mutation [(c.787C> T (p.Arg263Ter)] in the exon 8 of the IL17RA gene, being identified as a mutation occurring in the extracellular domain of the protein, and resulting a premature

stop codon using NGS panel (Figure 1B). Then we confirm the mutation by Sanger sequencing (Figure 1C). This variant was not identified in 400 individuals examined for an NGS PID panel study in the Pediatric Immunology Laboratory of Hacettepe University and 1000 healthy Turkish individuals.

Detection of IL17RA expression and Th17 cell percentage

IL17RA expression was observed to be severely reduced in patients' PBMCs. Furthermore we detected decreased CD4+ IL17A+ Th17 cell percentage as well as reduced IL17F expression in patients' CD4+ T lymphocytes. T lymphocyte proliferation was evaluated as normal compared to healthy control samples (Figure 3).

Discussion

Chronic mucocutaneous candidiasis (CMC) is characterized by recurrent or persistent infection of the nails, skin, and oral and genital mucosa by *Candida* species, mainly *Candida albicans* [1].

Inherited deficiencies of IL17-associated immunity are known to cause CMC [1]. To date, four genetic etiologies have been identified in patients with isolated CMC: AD IL17F, AR IL17RA, AR IL17RC, and AR TRAF3IP2 (encoding ACT1) mutations. A direct IL17 signaling pathway disorder is present in diseases included in the etiology of isolated CMC [9-11]. However, isolated CMC resulting from inborn errors of IL17 cytokines or receptors is relatively rare, and patients with 5 (IL17F) [9], 23 (IL17RA) [9, 15, 16], 3 (IL17RC) [10] and 7 (TRAF3IP2) [11, 17, 18] mutations have been reported to date.

The first genetic cause of isolated CMC was reported in 2011. Puel et al. identified IL17RA and ILF deficiency, two genetic etiological causes of isolated CMC [9].

IL17F deficiency was first described in 2011 by Puel et al in several members of an Argentine family suffering from mucocutaneous candidiasis [9]. The index patient, a five-year-old boy, was the second of a family of three children. His family was unrelated and of Spanish descent living in Argentina. His oldest sister, mother, grandmother and uncle also suffered from CMC from the first year of her life, her grandmother had cutaneous and recurrent vaginal candidiasis and her uncle showed interdigital intertrigo. His older sister died at the age of six of sudden encephalopathy of uncertain etiology associated with diffuse oral candidiasis. The index patient does not have growth disorders and developmental abnormalities with normal hair, nails, teeth and sweating. He had persistent oral candidiasis with thrush of the soft palate, cheek, and tongue from the first year of his life.

IL17RC was described by Ling et al in 2015 in 3 patients, one of Argentina and two of them Turkish origin [10]. The 37-year-old female patient of Argentine origin suffered from chronic intertrigo and pustules on her face since the age of 4 year, but with a normal scalp, nails and teeth. She developed recurrent oral and esophageal thrush. However, she had never suffered from any severe bacterial, viral or other fungal infection. Other patient was a 12-year-old boy born to Turkish parents, with no known parental consanguinity. He has suffered from CMC since the age of 2 mo, with chronic intertrigo, aphthous

stomatitis, oral thrush, and onychomycosis, but no reported serious bacterial, viral or other fungal infections. The third patient was an 8-year-old boy from a third-degree relative Turkish family. He displayed persistent oral candidiasis, with white plaques all over the buccal mucosa and dorsal surface of the tongue since early infancy and pustules on the skin and scalp. He had no history of any other significant bacterial, viral or other fungal infectious disease or significant developmental defects, with normal hair, nails, teeth.

Deficiency of activator 1 of nuclear factor kappa-beta (ACT1) has been described in 7 patients to date. ACT1 deficiency was first reported in 2013 in two siblings born to consanguineous Algerian parents [11]. One of the patients was a 29-year-old male and the other a 26-year-old female. Both had seborrheic dermatitis severe enough to require hospitalization in infancy. At the age of eight, the brother developed macrocheilitis with frequent *Candida albicans* infections of the tongue and mouth. He had never had cutaneous disease due to *Candida* or any other fungus. He had no cutaneous staphylococcal disease. Bilateral staphylococcal blepharitis occurred at the age of seven years, with many recurrences. She developed folliculitis decalvans at the age of 17 years. She had cicatricial alopecia due to *Staphylococcus aureus* and several episodes of *Candida albicans* infection in the buccal and genital areas. There was also nails infection due to several episodes of *Candida parapsilosis*. The third case described in 2019 was an 18-year-old Indian boy born to consanguineous parents. Genetic testing showed a novel homozygous mutation in the TRAF3IP2 gene, which was not previously reported. This patient had recurrent attacks of thrush and pneumonia since the first year of his life. There were dental abnormalities, esophageal stricture possibly due to previous esophageal candidiasis, and hypergammaglobulinaemia due to recurrent infections [16].

In 2020, a novel missense mutation in the TRAF3IP2 gene was detected in 4 siblings (two sisters and two brothers) from Lebanon whose parents are related [17]. There were similar clinical findings in all siblings. They suffer from pustular lesions on the scalp especially in the second year of life. These lesions were progressive and resulted in alopecia that scarred over the following months and years. Later pustular lesions appeared over the entire body and resulted in scarring hair loss at certain areas of the body, particularly the lower extremities. These histological findings were suggestive of discoid lupus erythematosus. Swab cultures taken from pustules grew *Staphylococcus aureus*.

IL17RA deficiency, which is the genetic etiologic cause of CMCD, was first identified by Puel et al. in 2011 in a French child of Morocco origin, whose parents were consanguineous [9]. The index patient, a seven-year-old boy, was the youngest of a family of five siblings. Neither his siblings nor his father had any particular medical history, except for his eldest brother who died at birth. His mother suffered from severe atopic dermatitis and chronic allergic rhinitis. The index patient had no failure to thrive and no developmental abnormalities. He had normal hair, nails, teeth, and sweating. Beginning in the first month of life, the patient suffered from recurrent mucocutaneous candidiasis (buttocks and thrush) resistant to local antifungal therapy. He had also developed a chronic candidal interdigital intertrigo at the age of six. At the age of 5 months, the patient also developed *S. aureus* skin abscess and folliculitis on the hip. He was also treated for several attacks of conjunctivitis, acute media otitis, bronchitis and folliculitis in the

first four years of his life. He had developed severe atopic dermatitis from the age of 1.5 years and was diagnosed with chronic allergic rhinitis at the age of 5. A gradual spontaneous improvement in eczematous dermatitis had been observed over the years, and at the age of seven only retroauricular fissures were persistent.

Then, in 2015, Fellmann et al. in two siblings from Sri Lanka who presented with recurrent mucocutaneous candidiasis, chronic skin infections, respiratory tract infections, and vasculitis since childhood, detected a large chromosomal deletion, including entire regions of the genes IL17RA, CECR1 (encoding adenosine deaminase 2) and XKR3 (X Kell blood group 3) [16]. The first of the siblings presented with growth retardation, recurrent orovaginal candida infection and skin lesions. At the age of 6 years, splenomegaly, scaly ichthyosiform skin lesions on the extremities, neck and chest, and psoriasiform skin lesions on the scalp developed. *Candida albicans* and *Staphylococcus aureus* were grown in the cultures taken from the lesioned skin areas. When she was 10 years old, progressive central neutropenia, recurrent lung infections and lung abscess developed. She died from septic shock when she was 16 years old. The second of the siblings had no failure to thrive and no developmental abnormalities. She had orovaginal candidiasis and staphylococcal skin infections that could not be controlled with antifungal and antibiotic treatments from the age of 2 years. She also developed splenomegaly, nonscathrical alopecia, progressive psoriasiform scalp lesions, scaly ichthyosiform skin lesions appearing on the extremity, neck, and chest. At the age of 18, signs of retinal vasculitis, venous occlusion and bleeding occurred. It has been reported that chronic mucocutaneous infections seen in these patients are due to IL17RA deficiency and vasculitis and chronic inflammation due to ADA2 deficiency.

Later in 2016, Levy et al. [15] reported the largest case series with an autosomal recessive mutation in the IL17RA gene in 21 patients from 12 families, 11 of whom were relatives, including the initial case. In all of these patients, the first episode of CMC occurred in the first 6 months of life, and 14 patients had various staphylococcal skin infections (skin abscesses, folliculitis, furuncles, crusted pustular lesions on the face and scalp) at the same age. CMC affected skin (intertrigo), scalp, mucosal areas (oral thrush, anogenital candidiasis) or nails. In addition to these skin infections, 8 patients had recurrent respiratory tract infections (sinusitis, otitis, lobar pneumonia, bronchitis). One patient was treated with a diagnosis of suspected pulmonary tuberculosis and one with a diagnosis of tuberculous meningitis. Three patients had only oral mucosal candidiasis. Eczema was detected in 4 patients.

IL17RA gene consists of extracellular (EC), transmembrane (TM), intracellular (IC) and SEFIR (SEFIR (similar expression to fibroblast growth factor genes) and IL17R) domains [12]. Mutation in the EC domain was found in our patient. Including the first case identified, 8 different mutations in the EC domain were detected in 15 of the 21 cases described by Levy et al. Three of these mutations were detected in patients of Turkish origin. Of these 15 cases, 14 had oral mucosal candidiasis, 5 had genital candidiasis, 10 had skin, 4 had nail, and 6 had scalp candidiasis. Eight patients had various staphylococcal skin infections (skin abscesses, folliculitis, furunculosis). 2 patients had eczema. A total of 6 patients were treated for upper and lower respiratory tract infections (sinusitis, otitis, bronchitis, lobar pneumonia) including 1 patient suspected pulmonary tuberculosis.

Our patient had eczema, thrush and genital candididisis that started at the age of 8 months. Scalp and nails were not affected by fungal infection. There was no recurrent upper and lower respiratory tract infection. There was no history of any skin disease other than eczema at the time of diagnosis. However, in the last 6 months, purulent bullous lesions due to staphylococcus developed especially on the fingertips. The clinical features of the 24 cases identified so far, including our patient, are shown in table 2.

We found a novel homozygous mutation that cause premature stop codon. Detecting severely decreased IL17RA protein expression in patients' PBMCs in parallel with decreased CD4+ IL17A+ cells and reduced expression of IL17F supported the pathogenicity of the mutation. IL17A and IL17F produced by Th17 cells bind to IL17RA and activate cellular signaling to start inflammatory response. In the absence and reduced expression of IL17RA, decreased Th17 cell numbers were seen in the reported patients with IL17RA defects as in our study.

Staphylococcal infections have been reported so far only in IL17RA and ACT1 deficiencies among isolated causes of CMC, but has not been reported in patients with IL17F and IL17RC deficiencies [9-11]. Although the mechanism is not clear, it is thought that staphylococcal infections may result from the inability of IL17E [15]. In the studies unlike patients with IL17RC and IL17F deficiency, PBMCs of patients with IL17RA and ACT1 deficiency did not respond to IL17E [9-11]. IL17E exerts its function through the heterodimeric structure created by IL17RA and IL17RB receptors [12]. ACT1 is an essential adapter protein in the signaling of all IL17 cytokines [11]. This mechanism may also explain the staphylococcal skin abscess that developed in our patient.

In conclusion, immunologic studies should be carried out for IL17- associated mechanisms, including AR IL17RA mutations, in patients with chronic moniliasis, genital candidiasis, recurrent bacterial and/or fungal infections of the skin and nails, psoriatic and eczematous skin lesions and recurrent bacterial respiratory tract infections in the absence of other systemic and laboratory findings.

Declarations

Acknowledgment

This study received grants number TSA- 2018- 17339 and 315S125 from Hacettepe University and TUBITAK, respectively. We thank Ekim Taşkıran for his help in the genetic analysis. The authors would like to thank participants for being a part of this study.

Funding: This study received grants number TSA-2018-17339 and 315S125 from Hacettepe University and TUBITAK, respectively.

Conflicts of interest/Competing interests: The authors declare that there are no conflicts of interest.

Ethics approval: This study was approved by the Ethics Committee of Hacettepe University with the number TSA-2016-9087.

Consent to participate: Written informed consent was obtained from the parents.

Consent for publication: Parents signed informed consent to publish their data and photos.

Availability of data and material: The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Code availability: Not applicable.

Authors' contributions: Each author contributed equally to this article

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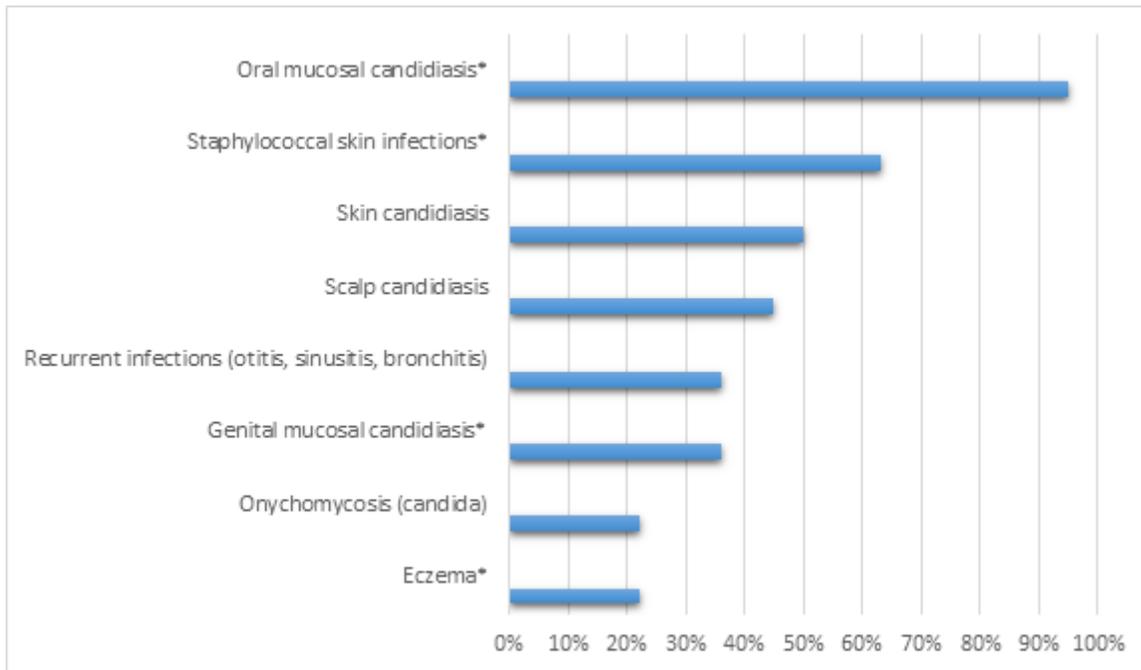
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Tables

Table 1: Clinical and laboratory features of the patient

Age (month)	42	72
Complete blood count		
Hemoglobin (gr/dl)	12.9	13.9
Leukocyte (/mm³)	8900	5800
Platelet count (/mm³)	283.000	248.000
Absolute neutrophil count (/mm³)	3900	2400
Absolute lymphocyte count (/mm³)	4300	3100
Serum immunoglobulin levels		
IgG (mg/dl)	538 (451-2599)	612 (591-2768)
IgM (mg/dl)	85.4 (33-459)	85 (44-644)
IgA (mg/dl)	63.2 (28-376)	105 (49-437)
IgE (U/ml)	36.2 (15-150)	16 (15-150)
Lymphocyte subgroup (%/count) (/μl)		
CD3	72 (55-83) 3096 (1656-3841)	68 (56-75) 3944 (991-2997)
CD4	44 (28-47) 1360 (871-2379)	43 (25-48) 1695 (635-1620)
CD8	28 (16-32) 866 (518- 1433)	20 (16-43) 788 (293-1221)
CD19	15 (13-31) 464 (421-1397)	16 (11-28) 631 (249-865)
CD16+56	9 (3-19) 278 (123-785)	14 (5-21) 552 (128-474)

Table 2: Clinical presentation of 24 patients with IL17RA deficiency (* indicates our patient's clinical presentation) [9, 15, 16]



Figures

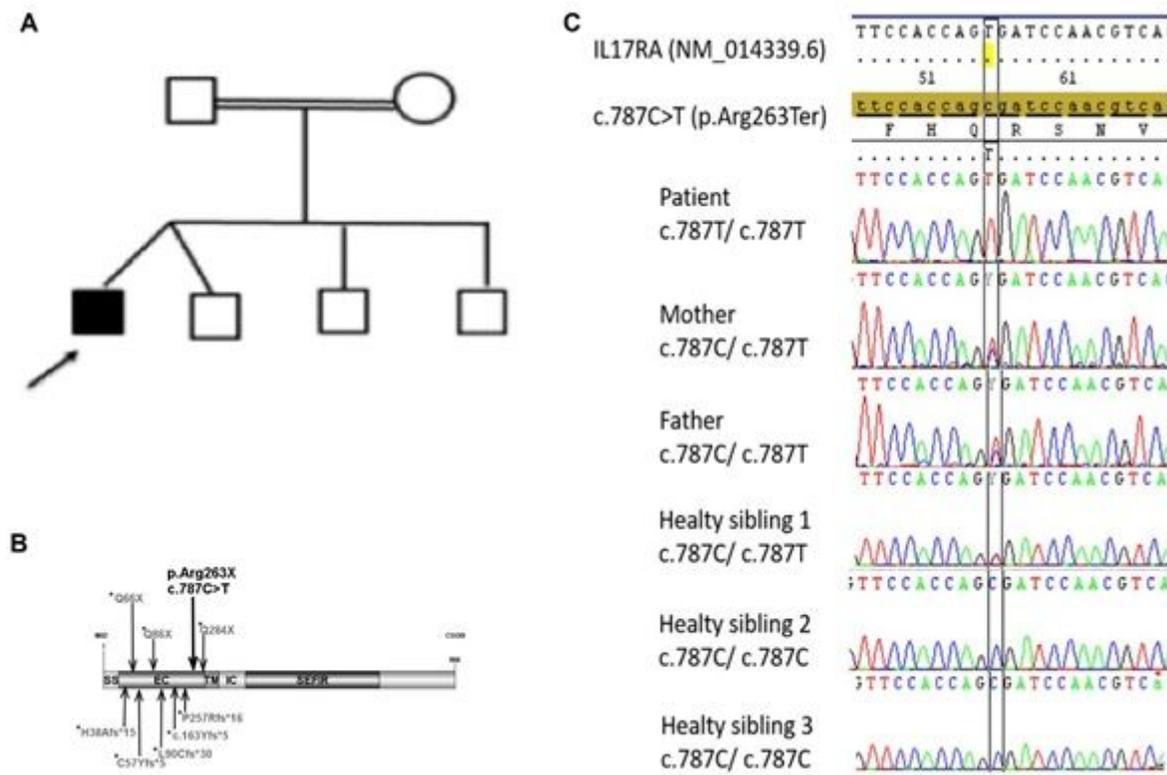


Figure 1

A) Pedigree (Fraternal twins) B) Schematic diagram of the IL-17RA protein, with its extracellular (EC), transmembrane (TM), intracellular (IC), and SEFIR [SEF (similar expression to fibroblast growth factor genes) and IL-17R] domains and the region affected by the mutation. C) Sanger sequence analysis of IL-

17RA mutation in patient and family members. While the patient was homozygous for the IL-17RA mutation ((c.787C> T) (p.Arg263Ter)) his parents and one sibling (Healthy sibling 1) were heterozygous for the same mutation. No mutation was found in the patient's twin sibling (Healthy sibling 3)



Figure 2

A) Purulent lesion at the edge of the mouth B-C) Purulent lesions on the fingertips D) Folliculitis in the axillary area

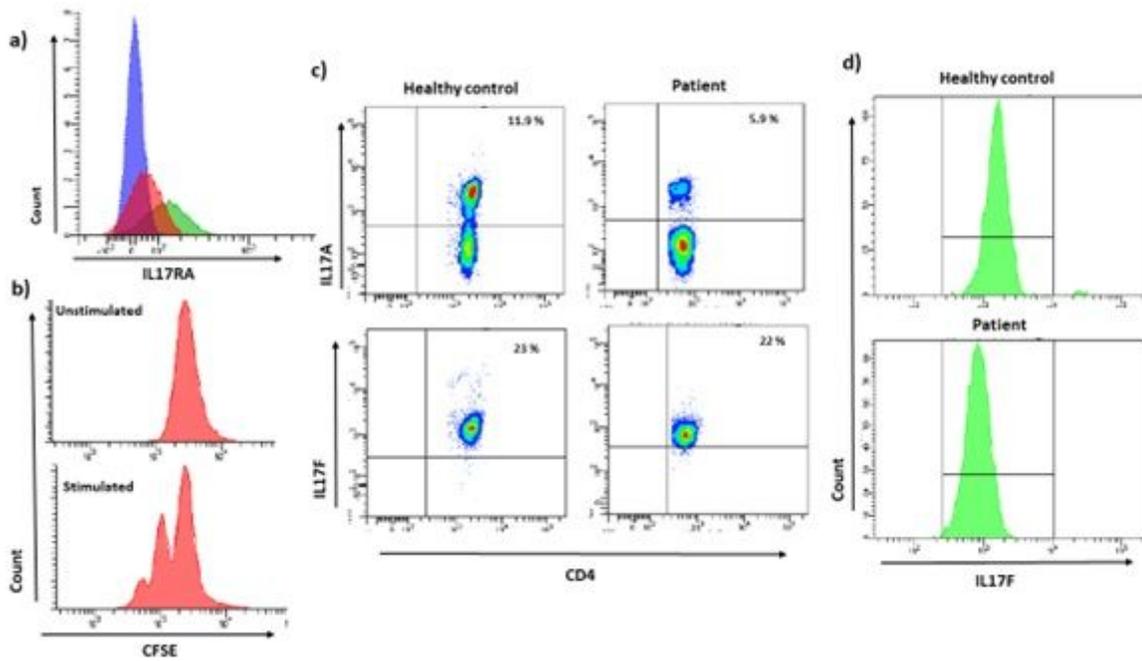


Figure 3

a) Flow cytometric analysis of IL17RA expression in the patient (Isotype control (blue), healthy control (green), patient (red)) b) Proliferation analysis of the patients' unstimulated (up) and stimulated T cells (below) c) Analysis of Th17 cells. d) IL17F expression in CD4⁺ cells in the healthy control and the patient