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LETTER TO EDITOR

A Novel *STK4* Mutation Presenting with Juvenile Idiopathic Arthritis and Epidermodysplasia Verruciformis

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To the Editor

Serine/threonine kinase 4 (STK4, MST1, OMIM#614868) deficiency is an autosomal recessive (AR) combined immunodeficiency. Till now, only six different *STK4* mutations have been characterized in 13 patients of different ethnic origins [1–6]. Herein, we describe a 13-year-old patient presenting with a combination of chronic and recurrent respiratory infections, epidermodysplasia verruciformis (EV), and juvenile idiopathic arthritis (JIA). Immunologic studies showed CD4 lymphocytopenia and high concentration of IgM.

The whole exome sequencing exhibited a homozygous mutation in *SKT4* gene (NM_006282: Exon 7:c.821dupA). Sanger sequencing confirmed familial segregation of the mutation as an AR trait.

Case Presentation

The patient is the first child of consanguineous parents of Iranian origin. No evidence of rheumatic disorders and immunodeficiency states was traced in the family history.

She was a 13-year-old girl currently weighing 34 kg and being 141 cm tall. She was referred complaining about a painful swelling in her left ankle, generalized tinea versicolor–like rash (Fig. 1a), nail pitting, and periodic fevers. Three years ago, she was diagnosed with JIA and had been administrated prednisone, colchicine, and sulfasalazine treatments. Her medical history showed frequent and prolonged colds, periodic and spontaneous episodes of fever without accompanying symptoms, or clear causes. Additionally, she was admitted at the age of 7 and 10 because of pneumonia. She had experienced recurrent otitis and prolonged use of antibiotics and even ventilation tube insertion surgery following a severe hearing loss at the age of eight. Non-itchy tinea-versicolor rash was seen on her trunk, back, and forearm. Punch biopsy of skin lesions was compatible with EV caused by ß-human papillomaviruses (Beta-HPVs) also known as EV-HPVs (Fig. 1b).

Laboratory evaluation was remarkable for CD4 lymphocytopenia, impaired specific antibody responses to previous vaccinations, and very high IgM levels. Table 1 outlines the results of laboratory evaluation of the patient. Echocardiography and chest X-ray were normal.

Direct sequencing of *MEFV* gene to exclude familial Mediterranean fever showed no mutation. WES study showed a new homozygous mutation in *SKT4* gene (NM_006282: Exon 7:c.821dupA). Normally, the *STK4* gene generates a protein with 487 amino acids. The inherited mutation in our patient results in a frameshift and creation of the premature stop codon in coiled-coil domain and accordingly, production of truncated protein with 295 amino acids (Q274fs295X). The homozygous mutation was confirmed by Sanger sequencing

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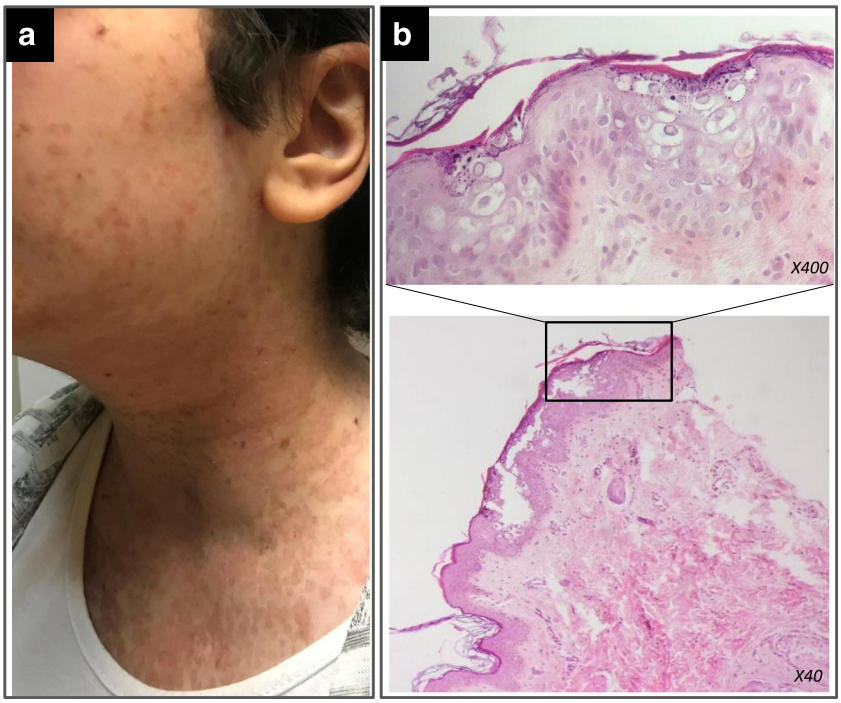

Fig. 1 Tinea versicolor–like lesions compatible with epidermodysplasia verruciformis caused by Beta-HPVs (**a**). Microscopic study of cutaneous lesions show focal acanthosis containing some large cells with blue gray cytoplasm and perinuclear halo, H&E staining (**b**)

Table 1 The clinical and laboratory results of the patient with STK4 deficiency

Variables	Results	Results	Normal ranges
Age	9 years	13 years	
Clinical manifestations	Painful swelling of left ankle, generalized erythematous rash, nail pitting, periodic fevers, epidermodysplasia verruciformis		
WBC (cells/μL)	6000	4960	4400–9500
Neutrophil (cells/μL)	3540	1984	
Lymphocyte (cells/μL)	1800	2480	1900–3700
Monocyte (cells/μL)	660	496	
RBC (*10^6/μL)	4.48	4.36	
Hemoglobin(g/dL)	10.9	9.9	
Platelet(/μL)	247,000	648,000	
CD3 (cells/μL)	–	2207	1200–2600
CD4 (cells/μL)	–	297	650–1500
CD8 (cells/μL)	–	1463	370–1100
CD19 (cells/μL)	–	272	270–860
CD56 (cells/μL)	–	49	10–48
HLA-DR (%)	–	12	
IgG (mg/dL)	627	678	764–2134
IgM (mg/dL)	2755	> 2000	69–387
IgA (mg/dL)	233	323	70–303
IgE (IU/mL)	75	22	
Anti-tetanus Ab (mg/dL)	< 0.1	–	> 0.1
Anti-diphtheria (mg/dL)	< 0.1	–	> 0.1
ESR (mm/h)	66	116	< 20
CRP (mg/L)	55	12	< 5
C3 (mg/dL)	104	–	88–201
C4 (mg/dL)	13	–	15–45
CH50	102	–	41–90
ANA	Negative	–	
RF	Negative	–	
HLA-B27	–	Negative	
EBV viral load		Negative	
CMV viral load		Negative	

of affected exon. Parents and her healthy brother were heterozygous for the same mutation (Fig. 2a and b).

At present, her JIA is under control with Prednisone 5 mg/every other day and Methotrexate 2.5 mg three times per week. Isotretinoin is effective against EV; however, lesions recur after cessation of therapy.

Discussion

Seine-threonine kinase 4 (STK4) is necessary for the activity of forkhead box protein O1 (FOXO1) and FOXO3, key transcription factors for T cell homeostasis, and efficient cytotoxic T cell responses to chronic viral infections [1, 7].

Characterization of 13 patients from six unrelated families who had homozygous nonsense mutations in *STK4* (Fig. 2c), the gene encoding STK4, outlined its role as a critical regulator of T cell homing and function [1–6]. Clinically, patients shared recurrent pulmonary infections and superficial bacterial/viral infections. Intermittent neutropenia and lymphopenia also dominated in some of them.

Here, we described a new case of STK4 deficiency with JIA and EV lesions caused by a novel mutation located in the coiled-coil domain.

Chronic and recalcitrant EV lesions in sun-exposed areas were a dominant feature in our patient that has been documented in previous reported patients as well [1, 2]. EV results from an abnormal, genetically determined susceptibility to Beta-HPVs [2]; however, we did not verify the specific HPV types in skin lesions of the patient. Interestingly, persistent non-EV-type common warts have been reported as well in one of the original Iranian patients with STK4 deficiency [1]. Epstein-Barr virus (EBV) is another indicator virus that could be traced in about one third of patients in the form of chronic viremia or lymphoproliferative disease [1, 3, 6]. So, STK4 deficiency could be considered as genetic etiology of susceptibility to EV-HPV and EBV-induced lymphoproliferation, at least in some individuals [1, 2, 6, 7]. Another interesting presentation of our patient was oligoarticular JIA, without any serologic markers of autoimmunity. Review of the published patients documented autoimmune cytopenias in three patients, autoimmune hemolytic anemia in two, and immune thrombocytopenic purpura in one patient [3, 4]. Furthermore, different autoantibodies were detected in STK4-deficient

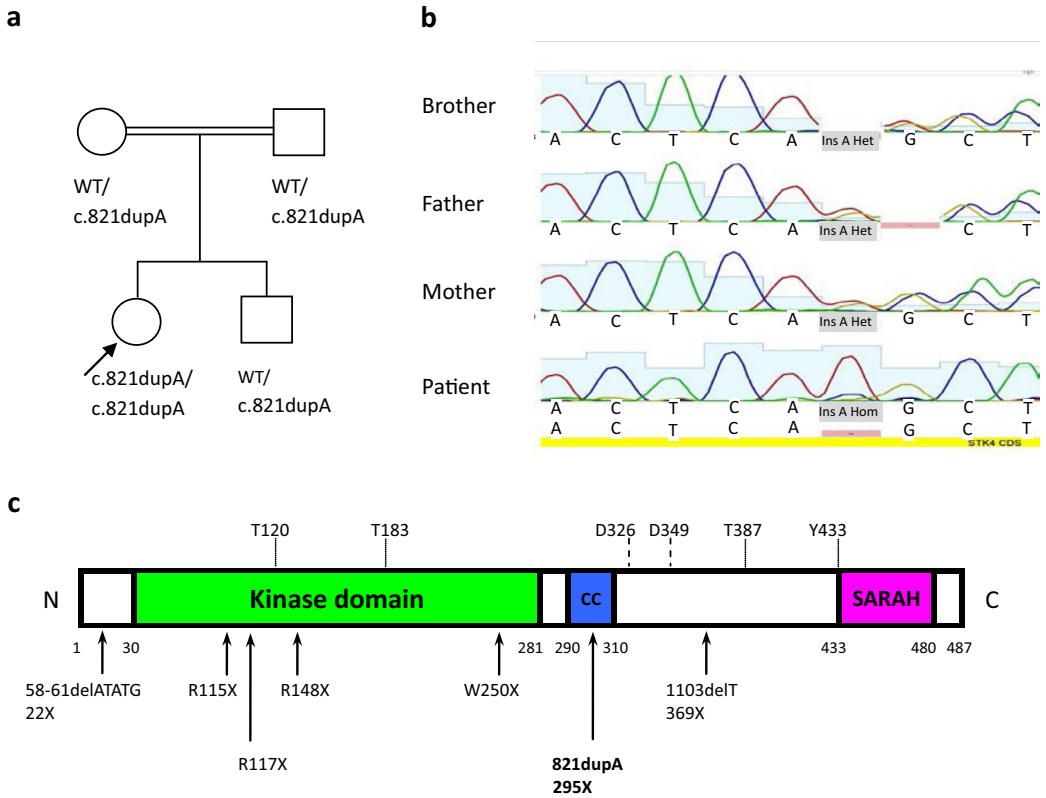

Fig. 2 Pedigree of the family (**a**). The familial segregation of the mutation is shown. Homozygous *STK4* mutation c.821dupA (Q274fs295X) (**b**). Schematic representation of the structure of the STK4 protein (https://www.uniprot.org/uniprot/Q13043) (**c**). STK4 is regulated by phosphorylation at T120, T183, T387, and Y433 and caspase cleavage at D326 and D349. Reported published mutations and c.821dupA are indicated by black arrows

patients, although these patients did not develop symptoms of autoimmune diseases [1, 2].

Monogenic defects of immunity could present primarily with autoimmunity [8]. Rheumatologic autoimmune diseases especially are noted in humoral, combined, and complement deficiencies. The mechanisms of autoimmunity predisposition are diverse and include different pathophysiologic pathways [9]. Impaired development and function of regulatory T cells and uncontrolled B cell activation may underlie autoimmunity predisposition in STK4 deficiency [10, 11].

Increased IgA and IgG and normal/decreased IgM concentrations are suggested as characteristics of STK4 deficiency [1, 3, 4]. But our patient presented with very high IgM levels for currently unknown cause. Through phosphorylation of histone H2B, STK4 may have a role in somatic hypermutation and class switching [12, 13]. The exact result of a mutation located at coiled-coil domain over class switching should be studied further.

STK4 deficiency is an interesting CID that shares clinical and immunologic feature with other genetic defects of T lymphocytes. RHOH deficiency, DOCK8 deficiency, and GATA2 gain of function mutation are among most important differential diagnoses. Utilization of novel diagnostic studies such as targeted resequencing and WES study could help to make a definitive diagnosis.

Our case report broaden previous findings regarding clinical and laboratory features of STK4 deficiency that deserves further studies to make genotype and phenotype correlation possible.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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