A Novel *TTC37* Mutation Causing Clinical Symptoms of Trichohepatoenteric Syndrome Such as Pyoderma Gangrenosum and Immunodeficiency Without Severe Diarrhea

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Targeted next-generation sequencing (TNGS) is used to identify specific cohorts of mutations by sequencing a panel of diseases. Reverse phenotyping can play a crucial role in diagnosis.

TTC37 deficiency is included in the "predominantly antibody deficiency" group of the IUIS-2017 phenotypic classification of primary immunodeficiency disorders [1,2]. We report the case of a patient with recurrent infections and pyoderma gangrenosum–like lesions. Reverse phenotyping was used to confirm diagnosis of trichohepatoenteric syndrome (THES) without severe diarrhea due to a novel homozygous mutation in the *TTC37* gene.

The patient was a 22-month-old boy and the third child of consanguineous-parents. He was born at term (3400 g, percentile 25-50), and his developmental milestones were normal. He was admitted for recurrent skin abscesses and oral lesions. Physical examination revealed oral aphthous lesions and ulcerous lesions on his hands. His weight was 11 kg (percentile 3-10) and his height was 82 cm (percentile 3-10). Laboratory investigations showed leukocytosis, thrombocytosis, and high IgG/IgM and low IgA levels (Supplementary Material), with adequate antibody responses to childhood vaccines. Normal results were recorded for lymphocyte subgroups, CD11a-CD18 expression on neutrophils, quantitative oxidative-burst activity, and IgE levels, thus excluding severe combined immunodeficiency, chronic granulomatous disease, leukocyte adhesion defects, and hyper-IgE syndromes. Clinical and laboratory findings improved with antibiotic therapy. The patient was discharged with a diagnosis of selective IgA deficiency.

The patient also had coarse hair and sterile erythematous-violaceous pyoderma gangrenosum–like plaques on his neck and developed a 1/6 systolic murmur at the apex 3 months later (Figure). Skin biopsy showed hyperkeratosis, acanthosis, and inflammatory infiltration. The result of a purified protein

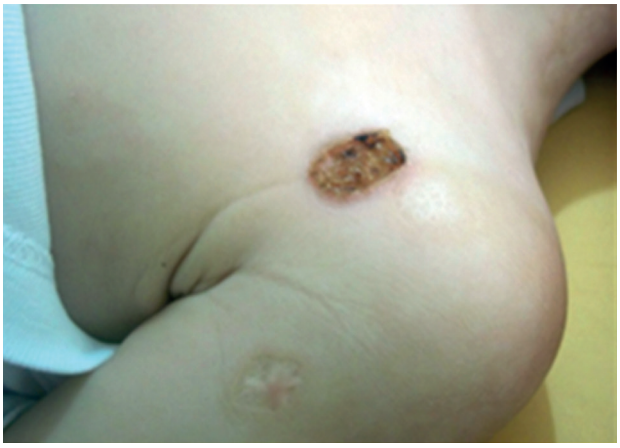

Figure. Pyoderma gangrenosum–like skin lesions.

derivative skin test was negative. There were no mutations in the *MEFV, PSTPIP2*, or *IL1RN* genes. Autoantibody titers (antinuclear antibody, antineutrophil cytoplasmic antibody, rheumatoid factor) were negative. Echocardiography showed minimal tricuspid valve regurgitation. Dermatitis herpetiformis was ruled out by normal small bowel histopathology and negative antigliadin and antiendomysial antibody titers. The patient was treated with intravenous antibiotics and discharged with trimethoprim/sulfamethoxazole prophylaxis.

IgA levels increased and IgG levels decreased over time (IgG, 598 mg/dL) (Supplementary Material, Table 1). Findings for lymphocyte proliferation were normal, as were those for class-switched memory B cells. The patient's coarse facial appearance (large ears, broad flat nose, and prominent forehead) and diffuse xerosis became increasingly evident (Supplementary Material, Figure 1). At age 4 years, he began to receive intravenous immunoglobulin therapy to control recurrent skin and oral lesions following upper respiratory tract infections. He benefited from regular intravenous immunoglobulin, although he had severe episodes of oral mucositis requiring hospitalization twice per year. He also had peg teeth; his primary teeth had emerged quickly, with rapid development of caries and short root anomaly (Supplementary Material, Figure 1).

At age 6 years, a homozygous mutation in the *TTC37* gene (c.2210T>C,p.Val737Ala) was detected by TNGS with a comprehensive Ion AmpliSeq PID Panel designed for sequencing 264 PID genes (Supplementary Material, Figure 2). *TTC37* mutations cause THES, which is characterized by early-onset diarrhea. After the genetic diagnosis, the patient was reevaluated for THES; liver values were normal, and trichorrhexis nodosa was detected in the hair shafts (Figure). He had mild intermittent diarrhea lasting 2-3 days following infections. Colonoscopy findings were normal. The parents were heterozygous for the same mutation.

THES is caused by loss-of-function mutations in the tetratricopeptide repeat domain–containing protein 37 gene (*TTC37*) and superkiller viralicidic activity 2 gene (*SKIV2L*) [3,4]. The condition is characterized by intractable diarrhea, facial dysmorphism, hair abnormality, intrauterine growth retardation, immunodeficiency, skin abnormalities, liver disease, and platelet abnormalities (Supplementary Material, Table 2) [3-6].

The present case clearly shows that THES can cause immunodeficiency and pyoderma gangrenosum–like skin lesions without significant diarrhea. This patient had typical facial features of THES, wooly and coarse hair, trichorrhexis nodosa, and hypogammaglobulinemia. He did not have chronic/intractable diarrhea or liver disease. His height and weight percentiles were 50%, with normal intelligence at 7 years of age (Supplementary Material, Figure 3). He also had peg teeth and short root anomaly. Peg teeth were reported in a patient with an *SKIV2L* mutation, although they had not previously been reported in patients with a *TTC37* mutation [6]. Pyoderma gangrenosum is usually associated with systemic diseases such as inflammatory bowel disease, rheumatologic disorder, immunodeficiency, or autoinflammation [7,8]. The presentation we report on here involved recurrent oral aphthous lesions and pyoderma gangrenosum–like skin eruptions. Deficiency of IL-1R-antagonist (DIRA) and IL-36R (DITRA) and PAPA (pyogenic arthritis, pyoderma gangrenosum, acne) are autoinflammatory disorders with cutaneous pustular lesions [7,8]. No mutations were found in the *MEFV, PSTPIP2*, or *IL1RN* genes. Half of all children with THES have cutaneous abnormalities such as cafe-au-lait spots, xerosis, and rubbery skin. To our knowledge, there are no previously described cases of THES presenting with pyoderma gangrenosum.

Approximately 90% of THES cases have immunodeficiency, which takes the form of hypogammaglobulinemia, defective specific antibody production, reduced memory B cell counts, and abnormal T lymphocyte proliferation [6,9,10]. In the present case, the patient had selective IgA deficiency at admission, although he had decreasing IgG levels. IgA levels returned to normal over time.

The spectrum of THES is widened by pyoderma-like scarring skin lesions and dental abnormalities, in addition to classic findings such as immunodeficiency and trichorrhexis nodosa. To date, mutations have been described in more than 300 different genes causing primary immunodeficiency disorders. Diagnosis can be costly and time-consuming because of the genetic and phenotypic heterogeneity of these disorders. TNGS enables rapid genetic testing across a large number of diseases in clinical practice and facilitates the diagnosis of atypical PID presentations. The power of reverse phenotyping needs to be emphasized in cases involving uncertain features or when findings become obvious with age.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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