A Novel TTC37 Mutation Causing Remarkable Trichohepatoenteric Syndrome Clinical Findings Such as Pyoderma Gangrenosum and Immunodeficiency without Severe Diarrhea

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Targeted next generation sequencing (TNGS) applications are used to identify specific cohort of mutations by sequencing a panel of diseases and reverse phenotyping sometimes plays a crucial role in correct diagnosis.

TTC37 deficiency is included in "predominantly antibody deficiency" group in "IUIS-2017"phenotypic classification of primary immunodeficiency disorders (PID)[1,2].Herein, a patient with recurrent infections and pyoderma gangrenosum-like lesions is presented. Diagnosis of trichohepatoenteric syndrome (THES) without severe diarrhea due to a novel homozygous mutation in *TTC37* gene was confirmed by reversed phenotyping.

A 22-month-old boy,third-child of consanguineous-parents, was admitted for recurrent skin abscesses and oral lesions.He was born at term with a weight of 3400gr(25-50%percentile). Developmental milestones were normal.Physical examination revealed oral aphthous lesions and ulcerous lesions on hands. His weight was 11kg(3-10%percentile) and height was 82cm(3-10%percentile).Laboratory investigations showed leukocytosis, thrombocytosis,high IgG/IgM and low IgA levels(*Supplementary Material,Table-1*) with adequate antibody responses to childhood-vaccines. Lymphocyte subgroups, CD11a-CD18 expression on neutrophils,quantitative oxidative-burst activity and IgE levels were normal, excluding severe combined immunodeficiency, chronic granulomatous disease, leukocyte adhesion defects

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and hyper-IgE syndromes. Clinical and laboratory findings improved with antibiotic therapy.He was discharged with the diagnosis of selective IgA deficiency.

He was noted to have coarse hair and sterile erythematous-to-violaceous pyoderma gangrenosum-like plaques on neck and 1/6 systolic murmur on apex 3-months later(Figure-1).Skin biopsy showed hyperkeratosis, acanthosis in epidermis, and inflammatory infiltration. Purified-protein-derivative skin test was negative.There were no mutations in *MEFV,PSTPIP2*, and *IL1RN* genes. Autoantibodies (anti-nuclear antibody, anti-neutrophil-cytoplasmic antibody, rheumatic factor) were negative.Echocardiography showed minimal tricuspid valve regurgitation.Dermatitis herpetiformis was ruled-out by normal small bowel histopathology, negative anti-gliadin and anti-endomysial antibodies.He was treated with intravenous antibiotics and discharged with trimethoprim/sulfamethoxazole prophylaxis.

IgA levels were noted to increase,IgG levels decreased by time(IgG:598 mg/dl)(*Supplementary Material,Table-1*).Lymphocyte proliferation tests and class-switched-memory-B cells were normal.Coarse face appearance (large ears,broad flat nose and prominent forehead) and diffuse xerosis became evident (*Supplementary Material,Figure-1*). He began to receive intravenous-immunoglobulin(IVIG) therapy to control recurrent skin and oral lesions following upper respiratory tract infections at age-4. He benefited from regular IVIG, although he had severe oral mucositis requiring hospitalization twice-a-year.It had been observed he had peg-teeth anomaly.Also primary teeth had been getting-out easily and the newly erupting teeth rapidly developing caries with short-root abnormalities(*Supplementary Material,Figure-1*).

At 6-years,a homozygous mutation in *TTC37* gene(c.2210T>C,p.Val737Ala) was detected by TNGS of a comprehensive Ion AmpliSeq™PID Panel designed for sequencing 264 PID

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genes(*Supplementary Material,Figure-2*).*TTC37* mutations cause trichohepatoenteric syndrome characterized by early-onset diarrhea.After the genetic diagnosis,the patient reevaluated for THES;liver was normal and trichorrhexis nodosa was detected in hair shaft(Figure-1).He had slight,intermittent diarrhea lasting two-to-three days following infections.Colonoscopy was normal.The parents were heterozygous for the same mutation.

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

Our patient is presented to emphasize that THES may 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 and liver disease. His height and weight percentiles were 50%, with normal intelligence at 7-years of age (*Supplementary Material,Figure-3*).He had short teeth roots and peg-teeth anomaly. Peg-teeth anomaly was described in a patient with *SKIV2L* mutation, but not reported in patients with *TTC37* mutation up to now[6]. Pyoderma gangrenosum(PG) is usually associated with a systemic disease, such as inflammatory bowel disease, rheumatologic disorder, immunodeficiency or autoinflammation[7,8].Our patient's presentation was recurrent oral aphthous lesions and PG-like skin eruptions. Deficieny of IL-1R-antagonist (DIRA), deficiency of IL-36R (DITRA) and PAPA (pyogenic arthritis, PG, acne) are among the autoinflammatory disorders with cutaneous pustular lesions[7,8]. No mutation was found in *MEFV, PSTPIP2*,

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and *IL1RN* genes. Half of the THES children reported as having skin abnormalities such as *cafe-au-lait* spots, xerosis and rubbery skin. To our knowledge, there are no previously described THES cases presenting with PG.

Approximately 90%of THES cases have immunodeficiency in terms of hypogammaglobulinemia, defective specific antibody production, reduced memory-B cells and abnormal T lymphocyte proliferation[6,9,10].Our patient was noted to have selective-IgA deficiency at admission, but he had decreasing IgG levels with normalization in IgA by time.

The spectrum of THES is widened by pyoderma-like scarring skin lesions and dental anomalies in addition to classic findings such as immunodeficiency and trichorrhexis nodosa by this case. Thus far, mutations in more than 300 different genes causing PIDs have been described. Diagnosis can be costly and time-consuming because of genetic and phenotypic heterogeneity of these disorders. TNGS allows rapidly genetic testing across a large number of diseases in clinical practice, enables the diagnosis of atypical PID presentations, and the power of reverse phenotyping needs to be emphasized in clinical settings with uncertain features or findings becoming obvious with age.

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Conflicts of Interest

The authors have no conflicts of interest.

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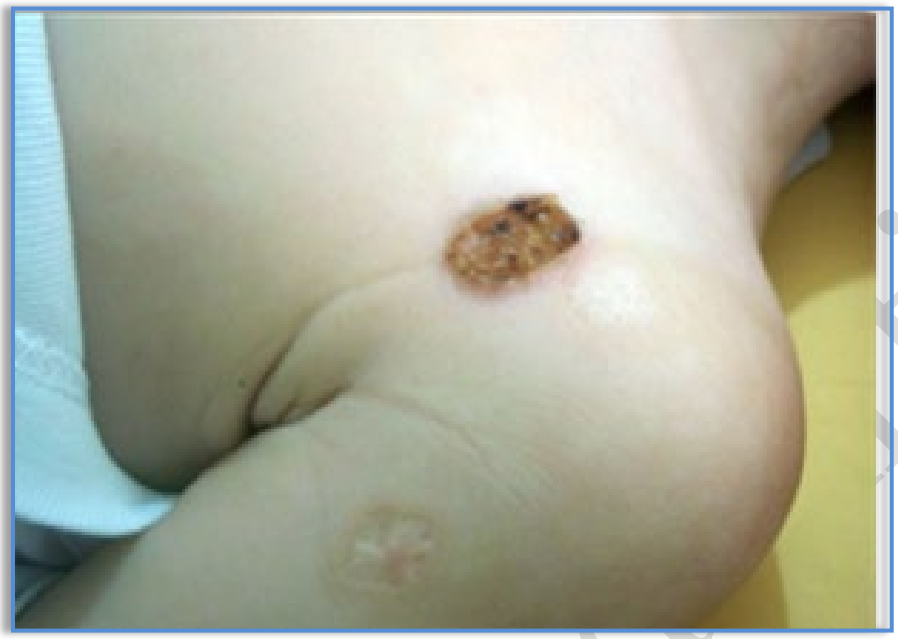
FIGURE

Figure 1. Pyoderma gangrenosum like skin lesions.



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