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# Candidiasis associated with very early onset inflammatory bowel disease: First IL10RB deficient case from the National Iranian Registry and review of the literature

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ABSTRACT

Defects in interleukin-10 (IL10) and interleukin-10 receptors (IL10R) are closely related to very early onset (infantile) inflammatory bowel disease (VEO-IBD). In the present study, we report a novel homozygous null mutation within interleukin-10 receptor B (*IL10RB*) gene in a child presenting with severe VEO-IBD. In accordance with previous reports, our patient manifested with chronic diarrhea, failure to thrive, intermittent fever and multiple anal ulcers associated with Candidiasis. Homozygous null mutation within *IL10RB* gene (c.92C > T, p.S31P) affecting the extracellular domain of protein was discovered in this patient. In conclusion, the diagnosis of IL-10R gene mutations should always be considered as a possible cause of refractory diarrhea and failure to thrive. Mutation analysis could help detect the genetic defects associated with these clinical manifestations and to determine the most appropriate treatment option for patients affected by this disease.

## 1. Introduction

Interleukin-10 (IL-10) is an anti-inflammatory cytokine released by many cell types and has shown to have a various effects on B-, T- and myeloid cells. IL-10 is essential for preserving the gastrointestinal tract immune hemostasis [1] and plays an important role in preventing the release of pro-inflammatory cytokines such as tumor necrosis factor (TNF) and IL-12 [2,3]. The IL-10 receptor consists of two α subunits (IL-10RA) and two β subunits (IL-10RB). IL-10RA subunit of the receptor is specific for IL-10 while IL-10RB subunit acts as a receptor for a large number of cytokines. IL-10 binding to IL-10R activates downstream Janus kinase 1(JAK1)/ Tyrosine kinase 2 (TYK2)/ Signal transducer and activator of transcription 3 (STAT3) signaling which leads to prevention of inflammation [4].

Recent studies have revealed that loss of function mutations in IL-10RA and IL-10RB are related to inflammatory bowel disease (IBD). IBDs are a heterogeneous and relapsing family of chronic gastrointestinal inflammatory disorders, including Crohn's disease (CD) and ulcerative colitis (UC) [5]. Recent studies identified a number of genetic risk loci in adolescent and adult-onset IBD which are triggered by environmental factors. However, the effect of the host genome is involved in very early-onset pediatric IBD. IL-10 and IL-10R deficiencies are rare, with only a few cases published worldwide.

In this article, we described the first case of a novel mutation of *IL-10RB* from the national Iranian registry [6] and also reviewed previously reported patients with *IL10RA* and *IL10RB* mutations.

## 2. Case presentation

The patient is a 2.8-year-old Iranian boy with a birth weight of 3500 g. He is the first child of a consanguineous marriage from otherwise healthy parents. The case received all of his vaccinations according to the routine national vaccination program. At 2 months of age, he presented with chronic diarrhea and failure to thrive. These symptoms were attributed to food allergy. At 4 months of age, the patient was started on amino acid based formula as a result of his constant diarrhea

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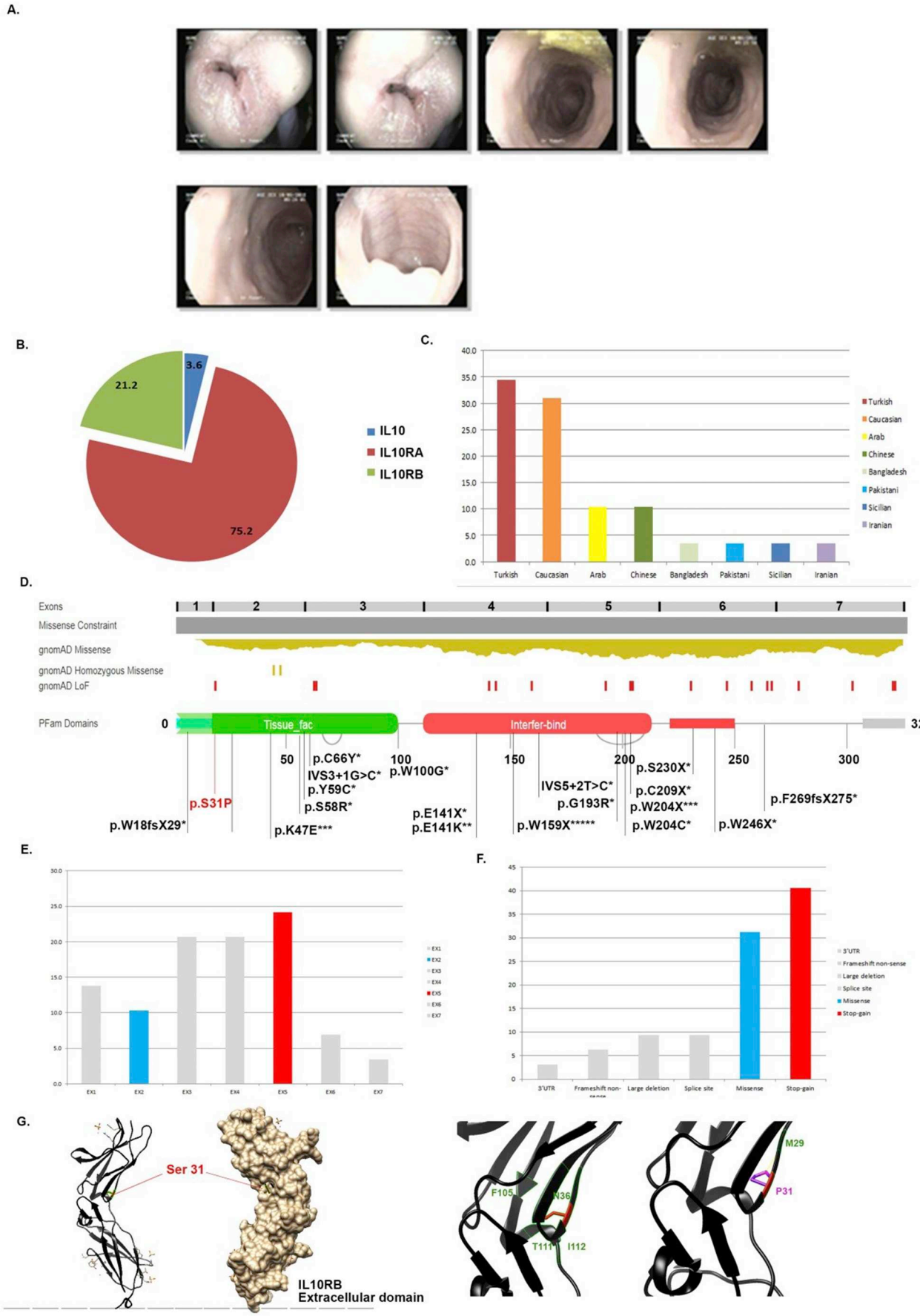


*(caption on next page)*

**Fig. 1.** A. Colonoscopy showed fragile mucosa and multiple aphthous lesion. B. Proportion of affected genes in IL10 axis in patients with VEO-IBD. Summary of Data from 29 patients with mutations reported in *IL10RB* gene regarding ethnicity (C), mutation location (D), proportional distribution (E), type of mutation (F). Effect of novel p.S31P mutation in the current patient on the extracellular domain of IL10RB protein.

and poor gain weight showed a poor response to this regimen. He was referred to children's medical center at the age of 6 months for chronic diarrhea, failure to thrive, intermittent fever and multiple anal ulcers.

Furthermore, He had a history of recurrent oral candidiasis (*Candida albicans* but not refractory to treatment, without cutaneous or esophageal involvement), eczematous lesions on the face, irritability due to painful defecations, as well as two hospitalizations for pneumonia and multiple hospitalizations for anemia and thrombocytopenia. On initial exam, he was found to have a growth index of < 3 percentile his age group, as well as face eczema and oral candidiasis. Multiple (2.2 cm) anal ulcers were evident at 4, 7 and 12 o'clock sites. There was no erythema, ulcer or secretion at the site of Bacillus Calmette–Guérin incubation and no evidence of lymphadenopathy or organomegaly. Laboratory results did not show any abnormalities in the number of B- and T- lymphocytes, leukocyte adhesion markers, serum immunoglobulin concentrations (IgG:650 mg/dl, IgM: 44 mg/dl, IgA: 35 mg/dl), antibody response to vaccine antigens, 50% complement hemolytic activity (CH50) and nitroblue tetrazolium (NBT) assays.

Stool culture failed to show any pathogens but was significant for an inflammatory pattern in his stool exam (WBC: many, RBC: 3, 4 in high power field). There were > 1000 μg/g faeces calprotectin in the stool test. Perinuclear antineutrophil cytoplasmic (p-ANCA) and anti-saccharomyces cerevisiae antibodies (ASCA) were in the normal ranges in addition to normal liver function tests. Colonoscopy with biopsies revealed fragile mucosa and multiple aphthous lesions (Figure). Pathology report of the colon biopsy revealed an acute reactive pattern of infectious colitis but negative for mycobacterium or cytomegalovirus. Based on the clinical features, laboratory and endoscopic findings, an IL-10 signaling defect was suspected. Targeted gene panel sequencing revealed a novel homozygous null mutation within *IL10RB* gene (c.92C > T, p.S31P) affecting the highly conserved region of extracellular domain of the protein (combined annotation dependent depletion [CADD] score: 33.0, the mutation significance cutoff: 23.8, frequency in gnomAD: 0). Based on the genetic diagnosis, the patient was referred for bone marrow transplantation.

## 3. Discussion

In the present study, we reported a novel homozygous mutation of *IL10RB* (c.92C > T, p.S31P) which would be the 29th patient with a defect in this gene. Among 137 patients reported with defective IL10 axis, IL10RB deficiency accounts for 21.2% of VEO-IBD patients (103

**Table 1**
Laboratory and immunologic data of patients with the *IL10RB* mutation.

| Laboratory results | values | Reference values |
|---|---|---|
| Complete blood count | | |
| White blood cells/$mm^3$ | 14.2 | 3.5–10 |
| Neutrophils (%) | 8.5 | 1.5–8.4 |
| Lymphocytes (%) | 5.4 | 2.0–8.0 |
| Erythrocytes ($10^6$/UL) | 4.68 | 3.6–6.1 |
| Platelets ($10^3$/UL) | 489 | 165–415 |
| Hemoglobin (gr/dl) | 11.1 | 11.5–18.5 |
| Erythrocyte sedimentation rate 1 h (mm) | 51 | Up to 12 |
| C-reactive protein (mg/l) | 2+ | – |
| Lymphocytes | | |
| $CD_3^+$ T cells (% of lymphocyte) | 58.9 | 60–85% |
| $CD_4^+$ helper T cells (% of lymphocyte) | 34.0 | 40–75% |
| $CD_8^+$ cytotoxic T cells (% of lymphocyte) | 27.6 | 25–30% |
| $CD_{16}^+$ natural killer cells (% of lymphocyte) | 7.8 | 5–30% |
| $CD_{19}^+$ B cells (% of lymphocyte) | 17.9 | 5–25% |
| $CD_{20}^+$ B cells (% of lymphocyte) | 17.2 | 5–25% |
| $CD_{56}$ natural killer cells (% of lymphocyte) | 4.0 | 5–30% |
| Vaccine antibodies | | |
| Anti-tetanus (IU/mL) | 28.4 | < 0.1 basic immunization |
| Anti-diphtheria (IU/mL) | 1.3 | < 0.1 basic immunization |
| Thyroid markers | | |
| Thyroid stimulating hormone (mIu/L) | 1.64 | 0.3–5.0 |
| T3, ECL (ng/ml) | 2.42 | 0.8–2 |
| T4, ECL (microg/dl) | 12.2 | 4.5–12.5 |
| Microbiology | | |
| Stool culture | Normal flora isolated | – |
| Urine culture | No growth after 24 h | – |
| Calprotectin stool antigen | > 1000 | – |
| PCR | | |
| Cytomegalovirus RT | Negative | – |
| Tuberculosis RT | Negative | – |
| Immunology | | |
| perinuclear anti-neutrophil cytoplasmic antibodies (U/mg) | 1.1 | – |
| 50% complement hemolytic activity, CH50 (U) | 110 | – |

**Table 2**
Clinical characteristics and mutation analysis of 28 previously reported patients with *IL10RB* mutations.

| | Origin | Age (Dead) | Sex | AOO | Consanguinity | Ab level | Lymph subsets | Zygosity | Exon | Mutation type | DNA change | Protein change | Perianal lesion | Major clinical findings | Ref. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Turkish | 6.5y | F | 3 mo | + | | | homozygous | 4 | Stop-gain | c.G477A, | p.Trp159X | Fistula | Abdominal Pain Diarrhea Bloody stool, gonarthritis, Folliculitis, renal abscesses | [19,28] |
| 2 | Turkish | 12y | M | 1 mo | + | | | homozygous | 4 | Stop-gain | c.G477A, | p.Trp159X | proctitis and abscesses in the perianal | Skin rash, Folliculitis, gonarthritis | [19,28] |
| 3 | Arab | 25y | F | 1 mo | + | High IgG and IgA | NL | homozygous | 3 | Splice site | IVS3 + 1G > C, | p.Tyr59fsX72 | | Severe colitis, therapy resistant Frequent bronchitis in childhood Oral ulcers Gingivitis | [32] |
| 4 | Pakistani | 12y | F | 1 mo | Suspected | High IgA | NL | homozygous | 2 | Frameshift non-sense | c.53delT | p.Trp18fsX29 | Anal stenosis | Severe colitis, therapy resistant Recurrent infections of the ear | [32] |
| 5 | Turkish | 1 m (D) | M | 10 d | + | | Not determined | homozygous | 5 | Missense | c. G577C | p.Gly193Arg | | Severe colitis Life-threatening bacterial infections | [32] |
| 6 | Caucasian | – | M | – | – | | | homozygous | 1 | Missense | c. G139A | p.Lys47Glu | crypt abscesses | UC, bloody diarrhea, asthenia, fever, severe anemia | [24] |
| 7 | Chinese | – | M | 4 mo | | | | homozygous<br>heterozygote | 1<br>4 | Missense<br>Missense | c. G139A<br>c.G421A | p.Lys47Glu<br>p.Glu141 Lys | Fistula, abscess | abdominal pain<br>Sepsis, oral candidiasis, fungemia, *Clostridium difficile* infection Diarrhea Bloody stool | [38] |
| 8 | Chinese | – | M | 9 mo | | | | homozygous | 1 | Missense | c. G139A | p.Lys47Glu | | Diarrhea Bloody stool | [38] |
| 9 | Turkish | 8 y | M | 3 mo | + | | | homozygous | 3 | Stop-gain | c.G421 T | p.Glu141X | Fistula | Pancolitis | [17] |
| 10 | Turkish | 11.9 | M | 1 mo | + | | | homozygous | 4 | Stop-gain | c.G477A | p.Trp159X | anocutaneous fistulas | skin folliculitis | [4] |
| 11 | USA | 15y | F | 2 weeks | | | | Compound heterozygote | 2<br>5 | Missense<br>Stop-gain | c. 172 A > G<br>c. 611 G > A | p.Ser58Arg<br>p. Trp 204× | anal fissures | failure to thrive bloody diarrhea anemia rectovaginal fistula hepatosplenomegaly B cell lymphoma | [33] |
| 12 | Kurdish | 6y | M | 3 mo | + | | NL | homozygous | 4 | Stop-gain | c.G477A | p.Trp159X | | Autoimmune hepatitis, folliculitis | [19] |
| 13 | Bangladesh | 7 mo | F | 3 mo | + | | NL | homozygous | 3 | Missense | G197A | p.Cys66Tyr | | Folliculitis | [19] |
| 14 | Arab | 0.5 | M | 3 mo | + | | NL | homozygous | 3 | 3'UTR | c.C52T | – | perianal abscesses | Arthritis (large joints), folliculitis | [19] |
| 15 | Caucasian | 1.5y | F | 3 mo | – | | NL | Compound heterozygote | 5<br>6 | Stop-gain<br>Stop-gain | c.G611A<br>c.C689A | p.Trp204X<br>p.Ser230X | | Dermatitis, folliculitis | [19] |
| 16 | Caucasian | 5.5 y | F | 3 mo | Unknown | | NL | homozygous | 5 | Stop-gain | c.G611A | p.Trp204X | | Folliculitis | [19] |

(*continued on next page*)

**Table 2** (*continued*)

| | Origin | Age (Dead) | Sex | AOO | Consanguinity | Ab level | Lymph subsets | Zygosity | Exon | Mutation type | DNA change | Protein change | Perianal lesion | Major clinical findings | Ref. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 17 | Turkish | 2y (D) | M | 3 mo | + | | NL | homozygous | 7-Mar | Large deletion | c.331_907_574del | – | | Folliculitis | [19] |
| 18 | Chinese | 5.5y | M | 11 d | + | | | homozygous | 6 | Stop-gain | c. G737A | p.Trp246X | Abscess, skin tag, fistula | Bloody diarrhea, oral ulcer, Arthritis | [34] |
| 19 | France | 2y | – | 2 week | – | | | homozygous | 2 | Large deletion | Deletion exon2 | – | Deep fissures | Bloody diarrhea | [23] |
| 20 | France | 10.5y (D) | – | 2 week | + | | | homozygous | 2 | Missense | c.A177G | p.Tyr59Cys | Abscesses | Bloody diarrhea B-cell lymphoma | [23] |
| 21 | Sicilian | 10.5y (D) | M | 2 week | – | | | Compound heterozygote | 5<br>7 | Missense<br>Frameshift non-sense | – | p.Trp204Cys<br>p.Phe269fsX275 | Abscesses | Bloody diarrhea B-cell lymphoma | [23] |
| 22 | Turkish | 18y | M | 2 week | + | | | homozygous | 5 | Large deletion | g.11930–17,413 del | – | Abscess and fissures | Bloody diarrhea B-cell lymphoma | [23] |
| 23 | France | 2.5y | M | 12 week | Very likely | | | homozygous | 3 | Missense | c. T229G | p.Trp100Gly | Complex fistula | Bloody diarrhea inflammatory arthritis | [23] |
| 24 | France | 10y (D) | – | 2 week | | NL | | homozygous | 3 | Stop-gain | c.G421A | p.Glu141 Lys | Abscess | EBV induced lymphoma, Folliculitis | [22] |
| 25 | Caucasian | 15y | – | 3mo | | | | homozygous | 1 | Splice site | c.50-2A > T | – | perianal abscesses | Colitis, bronchiectasis | [41] |
| 26 | Turkish | 2y | F | 10 d | + | | | homozygous | 4 | Stop-gain | c.G477A, | p.Trp159X | gluteal abscess | Skin rash, sepsis, diarrhea, respiratory distress, fever, and urinary tract infection with *Klebsiella pneumoniae* | [42] |
| 27 | Arab | 3y | F | 1 m | + | | | homozygous | 5 | Stop-gain | c.T627A | p.Cys209X | | Skin rash, oral ulcer, arthritis, Chronic diarrhea | [43] |
| 28 | Caucasian | 5y (D) | F | 7d | + | | | homozygous | 6 | Splice site | IVS5 + 2 T > C | – | | Chronic diarrhea | [43] |

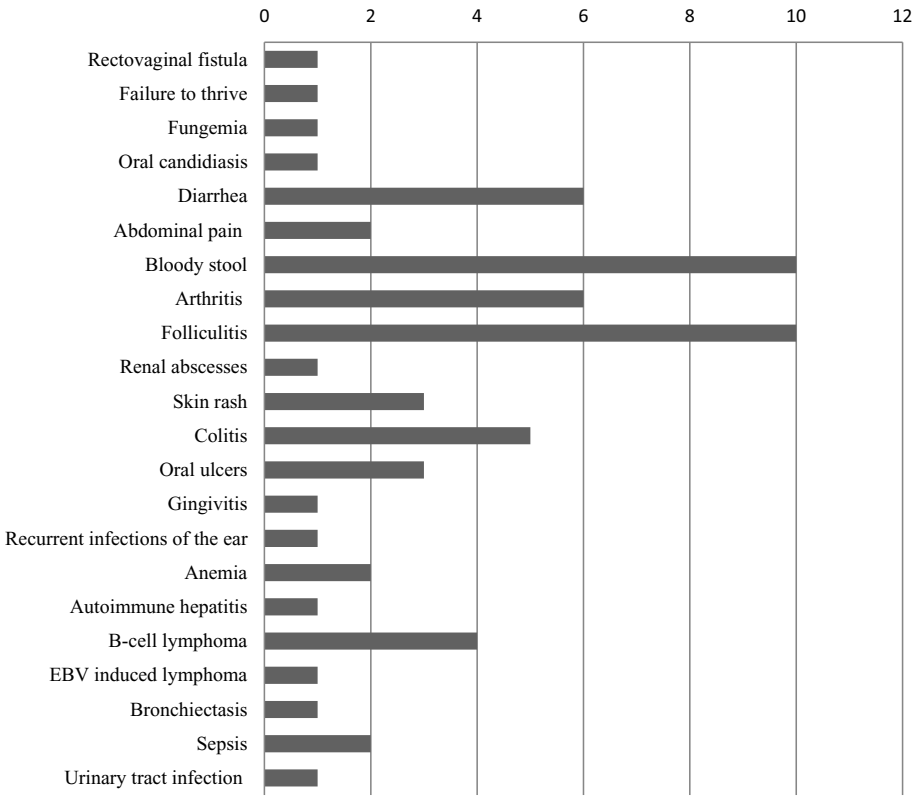


**Fig. 2.** Clinical features among reported patients with IL-10RB deficiency.

unique patients with IL10RA deficiency mainly from East Asia and 5 patients with IL10 deficiency (Fig. 1) [7]. Our patient manifested with recurrent diarrhea, failure to thrive, and intermittent fever and with otherwise unremarkable laboratory findings. Genetic testing confirmed a diagnosis of IL10RB deficiency according to American College of Medical Genetics and Genomics (ACMG) criteria. To the best of our knowledge, this mutation has not been previously described in the literature.

Previous studies have shown monogenic disorders responsible for VEO-IBD with mutations identified in IL10 [4], X-linked inhibitor of apoptosis protein (*XIAP*) [8], neutrophil cytosolic factor 2 (*NCF2*) [9], Mediterranean fever (*MEFV*) [10], and lipopolysaccharide-responsive and beige-like anchor protein (*LRBA*) [11] genes, resulting in alteration of intestinal immune homeostasis. Defects in immune inhibitory mechanisms such as IL-10 signaling lead to hyper-activation of the immune response, which in turn can cause extensive tissue damage by excessive inflammatory reactions. IL-10 is considered an important anti-inflammatory cytokine which is secreted following immune activation by a wide range of cell types [2,12–15]. IL-10 plays a critical role in the maintenance of immune homeostasis in gastrointestinal tract through suppression excessive productions of pro-inflammatory cytokines including TNF [16] (Table 1).

Since the first report of gene mutations in components IL-10 signaling sub types by Glocker et al. [4], several studies have reported mutations in IL10 (2 unique variants), IL10RA (40 unique variants) and IL10RB (updated to 22 unique variants) [7] and its link to VEO-IBD with the disease onset in a neonatal period characterized by a phenotype of severe perianal disease and colitis [17–37]. To date, ninety-one cases of IL10RA and thirty cases of IL10RB deficiency during the infancy period have been reported and only 3 patients with IL10 deficiency has been discovered. The frequency of IL10RA mutations has shown to be more predominant among Asian countries, while the numbers of mutated cases of both IL10RA and IL10RB in European countries are equal [7]. Consanguineous marriages have been seen in the majority of cases with the onset of symptoms occurring in early childhood. Aligned with this notion only mutations identified in 3 patients with IL10RB deficiency were compound heterozygous (Table 2) and the oldest reported age of onset among patients with IL10RB mutations (Homozygous missense p.Lys47Glu) has been reported in patient manifesting the symptoms at 9 months of age [38]. Although the majority of previous patients had defect in exon 5 (24.1%), the present case indicated a novel homozygous mutation of IL10RB (p.S31P) located in exon 2. The hot spot for mutation is p.W159X with 5 reported patients located in exon 4. The patient also carry a missense mutation which is the second most common variants after stop-gain mutations in reported patients with IL10RB deficiency (40.6% of mutations).

*Considering the broaden function of IL-10RB (in signaling of IL-22, IL-26 and interferon γ) and extended expression in non- hemtopoetic organs (epithlial cells and keratinocytes), it has been proposed that the clinical phenotype associated with mutation in* IL10RB might be more severe than IL10RA. *This notion is further supported by results from a large scale cohort of 137 patients with confirmed mutations in components of IL-10 axis where rate of B-cell lymphoma, and surgery rate were significantly higher in IL-10R deficient patients[7]. Although discrepancy was observed in the age of onset and may indicate that patients with the IL10RB deficiency have a more severe disease course and therefore manifest earlier, this difference was not statistically significant. Regarding extra-intestinal manifestation also skin rash and folliculitis (presented in at least 51% of patients) and oral ulcers (presented in at least 33% of patients) were the most common complications but there was no difference between IL10RB and IL10RA deficiencies (Fig. 2). Although the Candidiasis in our patient is not the first record in the cohort, it has not been addressed by other groups with dominancy in IL10RB deficiency (6.8% of patients vs. 0.9% in IL10RA deficiency). The exact underlying etiology of candidiasis in our patient was not clear however it could be associated with the overexpression of IL10 in IL10RB deficient patients. Previous studies indicated the expression of IL-10 significantly exacerbate in murine model of systemic candidiasis[39]. Moreover* Candida albicans *induces immunosuppression through TLR2-derived signals that*

*mediate increased IL-10 production and survival of regulatory Tcells which may only depend on IL10RA[40].* Most of the reported IL10RB cases had normal immunologic profile (Table 2). Similarly, no abnormal laboratory values were observed in our patient suggesting the important role of genetic testing to diagnose this rare disease which manifests as both VEO-IBD and Candidiasis.

The management of patients with IL-10 or IL-10R deficiencies is challenging due to the aggressive course of the disease and the resistance to a variety of immunosuppressive therapies such as azathioprine, methotrexate, corticosteroid, and infliximab. The use of allogeneic hematopoietic stem cell transplantation (HSCT) has been suggested as a potentially curative approach in VEO-IBD patients with IL-10 or IL-10R mutations. However, little is known about the use and efficacy of HSCT as a therapeutic option, due to use in a few numbers of patients and relatively short follow up durations (Table S1). Therefore, future prospective studies with large sample sizes are warranted in order to elucidate its long-term safety and efficacy in VEO-IBD patients due to IL-10 or IL-10R mutations.

In conclusion patients with bloody diarrhea, growth retardation and perianal lesions with neonatal presentation should be considered for IL-10 signaling pathway defects, even in the absence of laboratory abnormalities. Given the fact that an increasing number of patients are now being diagnosed with IL-10 and/or IL-10R gene mutations, the diagnosis of IL-10 receptor gene mutations should be considered as a possible cause of refractory diarrhea and failure to thrive patients with or without Candidiasis. Mutation analysis could help determine the genetic defects underlying these mutations and can help determine the most appropriate treatment options for these patients.

## Declaration of conflict of interest

The authors declare no conflict of interest.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clim.2019.05.007.

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