



## Letter to the Editor

## Autosomal Recessive Agammaglobulinemia - first case with a novel TCF3 mutation from Pakistan



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## ABSTRACT

Autosomal Recessive Agammaglobulinemia (ARA) is an uncommon type of primary immunodeficiency characterized by mutations in genes responsible for early B cell differentiation and function. One such gene is the TCF3 gene, which encodes a transcription factor important for immunoglobulin gene expression. We present the case of a 9 year old girl with history of diarrhea and recurrent pneumonias. Laboratory investigation showed significantly reduced levels of immunoglobulins along with a significant fall in the number of CD19+ cells. Genetic analysis identified a TCF3 gene base deletion covering exons 5–11.

## To the editor:

Agammaglobulinemia in the absence of B cells is a type of primary immunodeficiency resulting from defects in genes important for B cell development. Approximately 85% of patients with this disease have mutations in the gene encoding Bruton tyrosine kinase (Btk), resulting in X-linked agammaglobulinemia (XLA). [1] The disease can also be inherited as an autosomal recessive trait, classified as Autosomal Recessive Agammaglobulinemia (ARA). The autosomal recessive form of the disease is associated with an earlier onset of immunodeficiency and a more severe form of complications including otitis, sinusitis and pneumonia compared to the X-linked variant of the disease [2]. TCF3 encodes the two alternatively spliced transcription factors E12 and E47, both of which regulate *Igh* germline transcription and expression of activation-induced cytidine deaminase for B cell development and function [3]. Hypogammaglobulinemia and low numbers of B cells have been shown to result from either a dominant negative TCF3 mutation [4] or a homozygous loss of function mutation in TCF3 [5]. We present here a large deletion in TCF3 associated with chronic diarrhea, recurrent pneumonias, hypogammaglobulinemia, and very low B cell numbers.

A 9 years old daughter of consanguineous parents presented with a history of chronic diarrhea and recurrent pneumonias since one year of age. She had received both inactivated and live vaccines without sequelae. No other family members had a history suggestive of a primary immunodeficiency. Her physical examination was notable for signs of anemia. Her height and weight were found to be below the fiftieth percentile. Lymph nodes and tonsils were normal in size. Her laboratory evaluation confirmed the presence of anemia, absent CD19+ B cells, and pan-hypogammaglobulinemia. (Table 1). The patient improved on antibiotics and intravenous immunoglobulin replacement.

Targeted next-generation sequencing revealed a large deletion spanning exons 5 through 11 in TCF3. These exons encompass 238 of the protein's 652 amino acids, and encode the region between the two

activation domains, as well as part of the second activation domain. A deletion of exons 5 through 11 is predicted to be out of frame. E12 and E47, the transcription factors encoded by TCF3, are class I helix-loop-helix (HLH) proteins that bind DNA and dimerize through a basic HLH

Table 1

Immunological profiles of the proband at 9 year of age.

Hemogram (unit)	Value	Normal range
Hemoglobin (g/dl)	7.8	(11.5–15.5)
Total leucocyte counts( $10^9/L$ )	13.1	(5.0–13.0)
Neutrophils (%)	59	(45–50)
Lymphocytes (%)	32	(40–45)
Basophils (%)	1	(0–1)
Eosinophil (%)	2	(1–6)
Monocytes (%)	5	(4–8)
<b>Lymphocyte Subsets</b>		
CD3, cells/ $mm^3$	3472	(1300–2200)
CD4, cells/ $mm^3$	1513	(600–1100)
CD8, cells/ $mm^3$	1787	(500–1000)
CD19, cells/ $mm^3$	49	(300–500)
NK, cells/ $mm^3$	176	(300–500)
<b>Immunoglobulins</b>		
Ig G, G/L	1.11	(7.3–15.1)
Ig A, G/L	< 0.15	(0.7–3.25)
Ig M, G/L	0.14	(0.55–2.1)
Ig E, G/L	< 0.1	(0.5–393)
<b>Genetic Sequencing</b>		
Gene:	TCF3	
Zygoty:	Homozygous	
Loss of coverage:	Total loss of coverage of exons 5–11, which suggests a large deletion in this area	
<b>Miscellaneous</b>		
Sweat chloride:	Normal	
delta-F508 Mutation =	Not done	
Tissue Transglutaminases: IgA:	3.44 IU	
IgG:	10.22 IU	

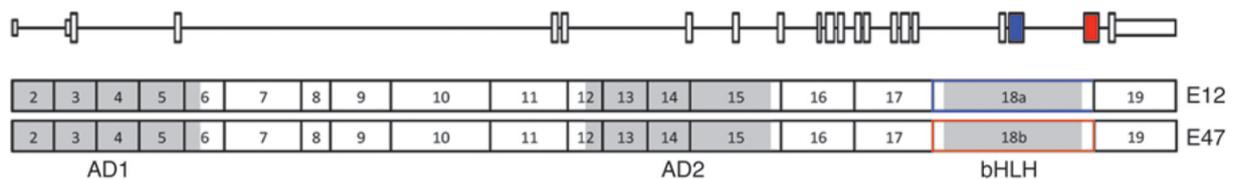
**Abbreviations:** TCF3, Transcription factor 3; ARA, Autosomal Recessive Agammaglobulinemia; Btk, Bruton tyrosine kinase; XLA, X-linked agammaglobulinemia.

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**Fig. 1.** Characterization of TCF3 gene showing total loss of coverage of exons 5–11, which suggests a large deletion in this area. **AD1:** activation domain 1, **AD2:** activation domain 2, **NLS:** nuclear localization signal, **bHLH:** basic helix-loop-helix.

domain [6]. (Fig. 1) Mouse models of TCF3 deficiency result in impaired postnatal growth, absence of circulating B cells, and susceptibility to systemic infections [7, 8]. A dominant negative mutation in TCF3 (E555K) was reported in four unrelated patients with a block in B cell development at the common lymphoid precursor to pro-B cell transition [4]. Most recently, a homozygous nonsense mutation in TCF3 was found in a patient with hypogammaglobulinemia and B cell acute lymphoblastic leukemia [5]. The patient we present had no history of malignant disease. Classically, patients with agammaglobulinemia and absent B cells have absent tonsils. The patient we present had normal tonsil size, indicating the variability in this clinical finding.

To our knowledge, this is the second case report of a homozygous mutation in TCF3. Immunoglobulin replacement therapy and antimicrobials are the mainstay of treatment for agammaglobulinemia with absent B cells. Typically, a dose ranging from 400 to 600 mg/kg is recommended every three weeks. However, these modalities are not curative and there is an ongoing struggle to come up with new treatment modalities to cure this primary immunodeficiency.

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