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LETTER TO THE EDITOR

From agammaglobulinemia to neutropenia: 'The TCF-3 has different clinical presentations'

Autosomal-recessive agammaglobulinemia (ARA) is a form of primary immunodeficiency caused by genetic abnormalities that disrupt the development of B cells.[1] ARA presents with an earlier onset of immunodeficiency and more severe infections compared with X-linked agammaglobulinemia. Several genes, such as μ heavy chain, λ5, Igα, Igβ, BLNK, PIK3R1 and Transcription Factor 3 (TCF3), have been linked to autosomal-recessive agammaglobulinemia.[2] Transcription Factor 3 is a critical protein belonging to the TCF/LEF family of transcription factors, which plays a significant role in regulating gene expression and the development and functioning of B and T cells. TCF-3 is a downstream effector of the Wnt signalling pathway.[3] Upon activation of the Wnt pathway, β-catenin undergoes stabilization and accumulation within the cell, ultimately forming a complex with TCF-3. In particular, dysregulation of TCF-3 may cause changes in Wnt signalling, affecting the development and function of various immune cells, including T and B cells.[4] According to published literature, several cases have been reported wherein individuals have TCF-3 deficiency. We aimed to present our patients with TCF-3 mutations and four diverse clinical presentations. Informed consents were taken from patients.

Patient 1 involves an 8-year-old male patient with a history of bronchiolitis attacks, and hypogammaglobulinemia detected at the age of 4. During the follow-up of the patient diagnosed with asthma, IgG1 and IgG3 deficiency was detected. The mutation of Case 1 is classified as disease-causing in some databases and as a variant of uncertain significance (VUS) in others.

Patient 2, a 3-year-old male patient with a history of consanguineous marriage, was diagnosed with acute disseminated and viral encephalomyelitis. Enterovirus RNA was detected in the cerebrospinal fluid (CSF). TCF3 p.Ala161Val (c.482C>T) was heterozygous in genetic analysis. IVIG treatment was applied to the patient with agammaglobulinemia and severe B-cell lymphopenia. While the father exhibited the wild-type genotype for the given variant, the mother, who remained asymptomatic, was identified as heterozygous for the identical variant. This observation was attributed to incomplete penetrance, a characteristic feature of autosomal-dominant inheritance.

Patient 3, a 6-year-old boy with a history of parental consanguinity, examined for recurrent upper respiratory tract infections, and a peritonsillar abscess history. Neutropenia, hypogammaglobulinemia and B-cell lymphopenia CD19(4.7%) were detected. Neutropenia resolved at age 4 years with the help of IVIG treatment. According to the available literature, no documented cases of neutropenia in any patient have been documented.

Patient 4 is a male patient, currently 18 years old, with a history of consanguineous marriage and recurrent pneumonia. At the age of 12, IgG1 and IgG3 subgroup deficiency was detected, and IVIG treatment was commenced. Detailed clinical and laboratory characteristics of the patients are given in Table 1.

The schematic presentation of all variants is illustrated in Figure 1, and their effects on protein structure and pathogenicity scores are summarized in Table S1.

TCF3 deficiency is a primary immunodeficiency/immune dysregulation disease initially described as an autosomal-dominant condition.[4,5] Autosomal-recessive inheritance with biallelic LOF (loss of function) mutation and a novel haploinsufficiency trait has been identified.[5] Mutations of *TCF3* impair both T-cell-dependent and T-cell-independent pathways of B-cell activation and differentiation, leading to agammaglobulinemia and a decrease in B cells.[5,6] Among our cases presenting with different clinical and immunological phenotypes, the most severe one is the second patient diagnosed with enteroviral encephalitis, which is agammaglobulinemia associated with facial dysmorphism. In a recently published case report of TCF3 gene deficiency,[7] there was a similar picture of hypogammaglobulinemia and progressive multifocal leukoencephalopathy. Thus, our patient is the second case in the literature with central nervous system involvement.

The immunological phenotype of our two patients was IgG subgroup deficiency. Of these, Patient 1 had a less severe clinical course, and the p.Pro177Leu mutation was classified as the disease-causing variant. Although the c.1813 + 8C>T, TCF3 gene mutation in Patient 4 was listed

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TABLE 1 Clinical and immunologic parameters of the patients.

	Patient 1	Patient 2	Patient 3	Patient 4
Age/gender	8/M	3/M	5/M	18/M
Clinical findings	Recurrent bronchiolitis, failure to thrive	Enterovirus encephalitis, facial dysmorphism	Recurrent upper respiratory tract infections, peritonsillar abscess	Recurrent otitis media and pneumonia, hearing loss
Current immunological phenotypes	Ig subgroup deficiency	Agammaglobulinemia	Hypogammaglobulinemia	Ig subgroup deficiency
Genetics	TCF-3 p.Pro177Leu (c.530C>T) heterozygous	TCF-3 p.Ala161Val (c.482C>T) heterozygous	TCF-3 C.1939C>A p.(pro647Thr) heterozygous	TCF-3 c.1813+8C>T (rs993094051) heterozygous
Immunologic parameters				
ANS $\times 10^9$ cells/L	3240	5660	**62** (1500–3000) ⬇	3290
ALS $\times 10^9$ cells/L	3780	2010	2850	2730
IgG (mg/dL)	**304** (764–2134) ⬇	**145**< (604–1401) ⬇	**528** (745–1804) ⬇	910
IgA (mg/dL)	81	**6.7**< (13–72) ⬇	**33** (57–282) ⬇	110
IgM (mg/dL)	105	**18**< (52–297) ⬇	113	113
Ig subgroups (mg/dL)	**IgG1:238** (532–923) ⇓ IgG2:255 **IgG3:16.7** (42–92) ⇓	**N/A**	**N/A**	IgG1 483 **IgG2 166** (186–487) ⬇ **IgG3 36.7** (57–113) ⬇
CD3 $\times 10^9$ cells/L	2683	1440	1995	1701
CD4 $\times 10^9$ cells/L	1738	**274** (1130–1732) ⇓	769	1107
CD8 $\times 10^9$ cells/L	793	1080	1254	**459** (1288–3417) ⬇
CD19 $\times 10^9$ cells/L	756	**44** (1025–3198) ⬇	**133** (870–2921) ⬇	351
$CD3^-CD16CD56^+$ cells $\times 10^9$ cells/L	185	880	684	459
Switched memory B cells CD19-IGgM-IgD+CD27 $\times 10^9$ cells/L	**18.9** (33–74) ⬇	**0**	**28** (52–121) ⇓	**21.6** (33–96) ⇓
Antibody responses to tetanus toxoid	Positive	Positive	Positive	Positive
Familial case	No	Yes	No	No

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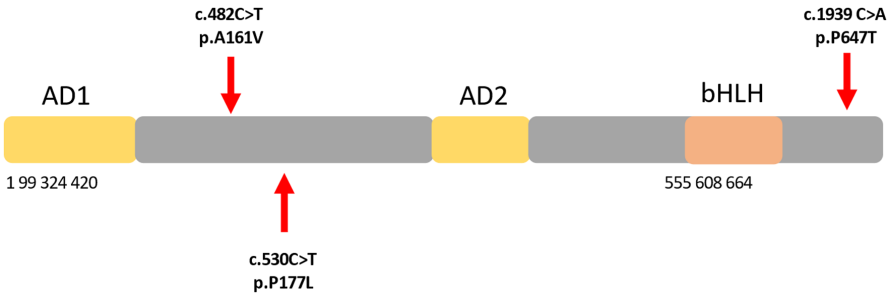


FIGURE 1 Schematic diagram of the Transcription Factor 3 (TCF3) protein and its domains, accompanied by the anticipated impact of each mutation on the amino acid sequence and its respective location.

as a variant of undetermined significance (VUS) in the databases, this case was evaluated as TCF3 deficiency due to IgG subgroup deficiency and recurrent infections.

Patient 3 had neutropenia, partial IgA deficiency and B-cell lymphopenia. The β-catenin-TCF/LEF transcription complex plays a critical role in the development and proliferation of T cells. One study[8] has shown that this pathway is essential in differentiating myeloid progenitors into granulocytes during steady-state and emergent granulopoiesis. If the interaction between β-catenin and TCF/LEF is disrupted, it may lead to the accumulation of immature cells and decreased granulocytic differentiation.[8]

The lymphocyte subgroup analysis was conducted during routine examinations, and a decrease in the number of crucial memory B cells was observed in all our patients and B-cell deficiency in two patients. Upon T-cell-dependent activation, B cells deficient in TCF3 can initiate germinal centres, but the number of centres formed is significantly reduced.[9] TCF-3 has been shown to play a crucial role in initiating activation-induced cytidine deaminase (AICDA) expression, which is required for class-switch recombination. TCF-3 also takes place in plasma cell differentiation and antibody production.[10] These mechanisms explain the lack of key-memory B cells. The underlying reasons for the observed clinical variability among patients have not been fully elucidated, primarily due to the limited availability of functional studies. It is posited that a confluence of intrinsic and extrinsic factors related to the affected gene, as well as the specific localization of gene variations, collectively contribute to this phenomenon. Intrinsic factors, such as functional thresholds, alongside extrinsic factors, for example epigenetic methylation during the terminal differentiation of human B cells into plasma cells, are hypothesized to exert influence over the clinical manifestations of the condition.

We aim to highlight the clinical heterogeneity of TCF-3 mutations because it is important to note that these mutations can lead to various clinical findings.

AUTHOR CONTRIBUTIONS

Research area and study design: Prof. Dr. Sara Sebnem Kilic. Sample and data acquisition: Hulya Kose and Akcahan Akalin. Data analysis: Hulya Kose. Writing and editing: Prof. Dr. Sara Sebnem Kilic, Hulya Kose and Akcahan Akalin. All listed authors reviewed and revised the manuscript.

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CONFLICT OF INTEREST STATEMENT

We declared that we have no commercial, financial and other relationships in any way related to the subject of this article all that might create any potential conflict of interest. Informed consents were taken from patients.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CONSENT FOR PUBLICATION

All authors give consent for publication.

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REFERENCES

1. Aadam Z, Kechout N, Barakat A, et al. X-linked Agammagobulinemia in a large series of north African patients: frequency, clinical features and novel BTK mutations. *J Clin Immunol*. 2016;36(3):187-194. doi:10.1007/s10875-016-0251-z
2. Conley ME, Dobbs AK, Farmer DM, et al. Primary B cell immunodeficiencies: comparisons and contrasts. *Annu Rev Immunol*. 2009;27:199-227. doi:10.1146/annurev.immunol.021908.132649
3. Ben-Ali M, Yang J, Chan KW, et al. Homozygous transcription factor 3 gene (TCF3) mutation is associated with severe hypogammaglobulinemia and B-cell acute lymphoblastic leukemia. *J Allergy Clin Immunol*. 2017;140(4):1191-1194.e4. doi:10.1016/j.jaci.2017.04.037
4. Boisson B, Wang YD, Bosompem A, et al. A recurrent dominant negative E47 mutation causes agammaglobulinemia and BCR(−) B cells. *J Clin Invest*. 2013;123(11):4781-4785. doi:10.1172/JCI71927
5. Boast B, Goel S, González-Granado LI, et al. TCF3 haploinsufficiency defined by immune, clinical, gene-dosage, and murine studies. *J Allergy Clin Immunol*. 2023;152(3):736-747.
6. Al Sheikh E, Arkwright PD, Herwadkar A, Hussell T, Briggs TA. TCF3 dominant negative variant causes an early block in B-Lymphopoiesis and Agammaglobulinemia. *J Clin Immunol*. 2021;41(6):1391-1394. doi:10.1007/s10875-021-01049-9
7. Li Q, Tang C, Zhu J, Zhang L. A case of progressive multifocal leukoencephalopathy with hypogammaglobulinemia and a TCF3 mutation. *J Neurovirol*. 2022;28(4–6):616-618. doi:10.1007/s13365-022-01092-1
8. Danek P, Kardosova M, Janeckova L, et al. β-Catenin-TCF/LEF signaling promotes steady-state and emergency granulopoiesis via G-CSF receptor upregulation. *Blood*. 2020;136(22):2574-2587. doi:10.1182/blood.2019004664
9. Boudousquié C, Danilo M, Pousse L, et al. Differences in the transduction of canonical Wnt signals demarcate effector and memory CD8 T cells with distinct recall proliferation capacity. *J Immunol*. 2014;193(6):2784-2791. doi:10.4049/jimmunol.1400465
10. Gloury R, Zotos D, Zuidscherwoude M, et al. Dynamic changes in Id3 and E-protein activity orchestrate germinal center and plasma cell development. *J Exp Med*. 2016;213(6):1095-1111. doi:10.1084/jem.20152003

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