Immunol Genet J, Vol. 4, No. 3, Sep 2021, pp.166-170 **DOI: https://doi.org/10.18502/igj.v4i3.12117**

Original Article

The Novel ZBTB24 Mutation Identified in an Iranian Patient with Type 2 ICF Syndrome

Saba Arshi[1], Mohammad Nabavi[1], Mohammad Hasan Bemanian[1], Morteza Fallahpour[1], Samaneh Delavari[2,3], Nima Rezaei[2,3,4], Sima Shokri[1*]

[1] Department of Allergy and Clinical Immunology, Rasool e Akram Hospital, Iran University of Medical Sciences, Tehran, Iran.
[2] Research Center for Primary Immunodeficiencies, Pediatrics Center of Excellence, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran.
[3] Primary Immunodeficiency Diseases Network (PIDNet), Universal Scientific Education and Research Network (USERN), Tehran, Iran.
[4] Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.

Received: 15 May 2021; Accepted: 07 July 2021

Abstract

Autosomal-recessive immunodeficiency, centromeric instability, and facial anomalies (ICF) syndrome is mainly determined by recurrent tract respiratory and gastrointestinal infections in early childhood due to agammaglobulinemia. Most patients with ICF syndrome die of infection at a young age, usually in the first or second decade of life. The leading cause of ICF disorders is mutations in genes whose products play a role in DNA methylation. ICF syndrome is classified into two groups: type 1 (ICF1) patients have mutations in the DNMT3B gene, and about half of type 2 (ICF2) patients have mutations in the ZBTB24 gene. In this study, we report the case of a 34-year-old female of Iranian consanguineous parents, who was diagnosed at one year of age with ICF-2 syndrome with recurrent infections, mental retardation, and a homozygous novel mutation in the ZBTB24 gene.

Keywords: Chromosomal Instability; Immunodeficiency-Centromeric Instability-Facial Anomalies Syndrome; Mental Retardation

***Corresponding Author:** Sima Shokri, MD
Department of Allergy and Clinical Immunology, Rasool e Akram Hospital, Iran University of Medical Sciences, Tehran, Iran
E-mail: dr.shokri.83@gmail.com

How to cite this article

Arshi S, Nabavi M, Bemanian M, Fallahpour M, Delavari S, Rezaei N, Shokri S. The Novel ZBTB24 Mutation Identified in an Iranian Patient with Type 2 ICF Syndrome. Immunology and Genetics Journal, 2021; 4(3): 166-170. DOI: https://doi.org/10.18502/igj.v4i3.12117

Introduction

Immunodeficiency, centromeric instability, and facial anomalies (ICF [MIM 242860]) is a scarce autosomal recessive genetic disease described in the 1970s. Although the frequency of both B and T lymphocytes is predominantly normal in this rare disease, hypogammaglobulinemia or even agammaglobulinemia is observed in most cases which finally bring about various respiratory and gastrointestinal (GI) infections. These mentioned infections might be lethal in some patients, especially before adulthood (1-3). The distinctive facial anomalies, including hypertelorism, flat nasal bridge, low-set ears, macroglossia, and epicanthal folds, are also among the typical characteristics of this syndrome (4, 5). Furthermore, centromeric instability is the most notable hallmark of this disease. The juxtacentromeric heterochromatin of three chromosomes, including 1, 9, and 16, are substantially under condensed and multi-radial chromosome configurations involving these regions. These instabilities result in DNA hypomethylation of classical satellite-2 and satellite-3 repeats at the pericentromeric heterochromatin regions (1, 6).

In nearly half of patients diagnosed with ICF, which is categorized as type-1 ICF (ICF-1), mutations in the highly conserved domain of DNA methyltransferase 3B gene (DNMT3B [MIM 602900]) were detected. Besides, mutations in this gene are only restricted to DNA hypomethylation of satellite-2 and -3. DNMT3B, which is located at 22q11.2, is a critical gene in de novo DNA methylation (7-9).

The remainder of ICF cases that have identical clinical manifestations but without any specific mutations in DNMT3B are classified as type-2 ICF (ICF-2). Patients diagnosed with ICF-2 have mutations in the ZBTB24 gene located at 6q21 (ZBTB24 [MIM 614069]). In these patients, in addition to the DNA hypomethylation of satellite-2 and -3 repeats, hypomethylation of α-satellite repeats is also observed. ZBTB24 gene encodes a protein that belongs to a large family of transcription factors that has a major role in both malignancy and hematopoietic development (10, 11).

Here, we describe a novel homozygous frameshift insertion variant in the ZBTB24 gene (ICF-2) in an Iranian female.

Case Presentation

We describe a 34-year-old female of the second child of consanguineous parents (first cousins) who have no family history of primary immunodeficiency. Her brother died due to severe diarrhea at the age of 2 months. Her mother has a history of abortion, and her aunt (mother-side) died of uterus cancer. The patient has no family history of autoimmunity. At eight months of age, she presented with diarrhea, pneumonia, high fever, and severe cough. At the age of 1 year, she was hospitalized due to severe diarrhea for the first time. At this time, she was evaluated for immunologic investigations. Her immunological workup revealed a decreased level of IgG, IgA, and IgM. Then, she was treated with prophylactic treatment and intravenous immunoglobulin (IVIG) replacement.

Examination of the patient's liver and spleen was normal. Furthermore, she had a normal vaccination history without any unexpected reaction. During this period, the patient suffered from Lower respiratory tract infections. One of the main complaints of the patient was paroxysmal nocturnal dyspnea (PND) and sputum cough. Until the age of 15 years, she was hospitalized six times due to pneumonia and sinusitis. At this time, she underwent sinus surgery. When she was 24 years old, she was referred due to recurrent pneumonia. At the age of 28 years, PCR test for Cytomegalovirus, Enterovirus, Rotavirus, and Norovirus in stool sample were performed and the results were negative. By the age of 29 years, she had developed significant bronchiectasis. Until this moment, she has been receiving regular intravenous immunoglobulin (IVIG) replacement. Of note, she has a bird-like face, flat nasal bridge, and strabismus. She also has mental retardation. Genetic testing by whole-exome sequencing (WES) was performed to investigate the underlying genetic defect, and a homozygous frameshift insertion variant exon 2:c.795_796insA of the ZBTB24 gene was identified as compatible with the clinical and immunologic phenotype of the proband. The laboratory and immunological findings of the patient are presented in **Table 1**.

Discussion

In this study, we introduced a female who was diagnosed with ICF-2 recently. She is the second child of a consanguineous family, and her disease was confirmed at the molecular and cytogenetic level; the patient has a novel homozygous mutation in the ZBTB24 gene. ZBTB24, also known as PATZ2 and ZNF450, is a member of the large family of transcriptional factors, which consists of the BTB (bric-a-bric, tramtrack, broad complex) domain, a DNA-binding A-T hook domain, and eight C2H2 zinc finger domain. Previous studies reported that ZBTB24 is highly expressed in naïve B cells. However, DNMT3B is considered as the co-regulator of ZBTB24 during the B cell differentiation stage. Therefore, any mutations in these genes may have a consequence on immunoglobulin production. These findings align with the hypogammaglobulinemia phenomenon, which is reported in most patients diagnosed with different ICF types, including our patient (10). Bone morphogenic protein 2 (BMP-2), a member of the transforming growth factor-beta (TGF-β) superfamily and the most investigated research topic in skeletal biology, induces cartilage and bone formation. Regarding that, ZBTB24 is an essential factor in the BMP-2 signaling pathway; hence, any defects in this gene results in skeletal disorders and developmental delay (12, 13).

The ZBTB24 gene is highly expressed in the critical part of the brain's memory and learning system. These findings may explain the high rate of intellectual disability in patients with ICF2, including walking, speaking, memory, and learning problems. Consistent with our patient neurological manifestation, she has a degree of mental retardation, including defects in learning and speaking (14).

As mentioned earlier, most ICF patients experience recurrent and prolonged infection, especially in their GI and respiratory tract, which causes failure to thrive (FTT) and bronchiectasis in some cases. These complications are the results of hypogammaglobulinemia (15). As described, our patient experienced both pneumonia and severe diarrhea due to her low levels of immunoglobulins, resulting in several hospitalizations. The decreased level of IgG, IgG subclasses, IgM, and IgA, or a combination of them, are reported in patients diagnosed with ICF (3). However, all immunoglobulins' levels in our patient were diminished, which might be the primary reason for the disease's severity. Furthermore, in some cases, the number of lymphocytes, neutrophils, and platelets decrease in the second decade of their life (16). In contrast, our patient's neutrophil, lymphocyte, and platelets numbers did not show a decrease. So, it might be concluded that ICF disease has a broad spectrum of clinical manifestations and laboratory data. Altogether, it is suggested that genetic tests should be employed for an exact diagnosis. Besides, ICF patients without any specific mutation in two previous genes might have mutations in another gene(s) that its functions overlap with them. It is also possible that these patients have mutations in genes regulated by DNMT3B or ZBTB24 (17). Due to several immune system defects in ICF patients, most of them usually die at a young age. Our patient, like the case reported in Sathasivam et al., known as the oldest survivor of the ICF, is now well and under IVIG treatment (18).

Table 1. Laboratory and immunologic data of ICF case

Parameter	Result
WBC (10^3/μL)	5100
Neutrophils (%)	44%
Lymphocyte (%)	49%
Platelets (10^3/μL)	185
HGB (g/dL)	13.6
ESR 1 h (mm/hr)	1
Creatinine (mg/dL)	0.8
(SGPT) ALT	32
(SGOT)AST	25
IgG (mg/dL)	120
IgG3 (mg/dL)	171
IgA (mg/dL)	12
IgM (mg/dL)	<5
IgE (IU/mL)	<5
CD3+ (%)	80%
CD4+ (%)	39%
CD8+ (%)	46%
CD20+ (%)	8.8%
CD16+ (%)	7.3%
NBT	98%
C3	128
C4	33
CH50	96
T3	177
T4	196

WBC, white blood cells; RBC, red blood cell; HGB, hemoglobin; ESR, erythrocyte sedimentation rate; BUN, Blood urea nitrogen

For patients diagnosed with ICF, intravenous immunoglobulin (IVIG) replacement therapy and antibiotics are prescribed commonly for lowering the severity of the infections since they are the leading cause of mortality among these populations (3, 5). In our patient, IVIG therapy started at the early diagnosis and properly controlled the respiratory and GI complications. Although some patients undergo bone marrow transplantation (BMT), it was unnecessary in our patient, based on her physicians' recommendations (3).

Conflict of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

We appreciate the Tehran university of medical sciences (TUMS) for their support.

Funding Sources

The present study was supported by the Tehran university of medical sciences under Grant No. 56640.

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