Research Paper

Pathological Variants of Aminoacyl-tRNA-synthetase-Interacting Multifunctional Protein 1 Gene in an Iranian Consanguineous Family With Autosomal Recessive Intellectual Disability

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ABSTRACT

Background Intellectual disability (ID) is one of the most common neurodevelopment disorders that caused by both environment and genetic factors. Genetic diseases account for 50% of ID incidents and have important role in its development. One of the most important risk factors of ID in most countries is consanguineous marriage. In consanguineous families, the risk of developing autosomal recessive ID is 3.6-fold higher. There is high prevalence of consanguineous marriage in Iran (about 40 %).

Objective In this study, we aimed to investigate the pathological variants of aminoacyl-trna-synthetase-interacting multifunctional protein 1 (*AIMP1*) in an Iranian consanguineous family with multiple-ID affected members.

Methods this analytical epidemiological study, whole exome sequencing method was used to examine the molecular etiology in two female ID patients of a consanguineous family living in Qazvin, Iran. Sanger sequencing was carried out for validating potential causative variants in patients, and co-segregation analysis for other family members.

Findings A stop-gain variant (p. Arg158*) in the AIMP1 gene was identified as pathological variant in the study family according to American College of Medical Genetics and Genomics guidelines.

Conclusion The found variant in the AIMP1 gene caused truncated protein and clinical manifestations such as developmental delay, ID, spastic paraplegia, thin corpus callosum, and speech impairment in the two patients.

Extended Abstract

1. Introduction

Intellectual disability (ID) is a common neurodevelopmental disorder that is characterized by an intelligence quotient (IQ) score of 70 or below, and also by deficits in at least two adaptive skills. The age of onset of ID is 18 years [1]. ID can occurs during prenatal, fetal and postnatal brain development [4]. It is mostly caused by genetic defects. About 50% of human genes are expressed in the brain and 86% of these genes are involved in brain differentiation and development; hence, genetics play an essential role in brain dysfunction [5, 6]. The important risk factor in most countries is consanguineous marriage that can lead to the high incidence of recessive disorders [7, 8]. Consanguineous marriage increases the prevalence of ID by 3.6% [9]. In this

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study, we performed a molecular investigation in a family with consanguineous marriage having multiple ID-affected children by whole exome sequencing (WES) method.

2. Materials and Methods

The study was performed in a family with consanguineous marriage having two ID-affected girls living in Qazvin, Iran. The study was approved by the Genetic Research Center at the University of Social Welfare and Rehabilitation Sciences, and Qazvin University of Medical Sciences. Prior to study, informed consent was obtained from the parents of the patients. The first female proband had an occipitofrontal circumference (OFC) of 33 cm (-1.22 SD) at birth. At the time of examination, she was 19 years old with an OFC of 54 cm (-0.28 SD), height of 159 cm (-0.65 SD), and weight of 40 kg (-2.60 SD). The second female proband was younger with an OFC of 33.5 cm (-0.88 SD) at birth. During the examination, she was 13 years old, with an OFC of 51 cm (-2.04 SD), height of 136 cm (-3.01 SD), and weight of 25 kg (-3.12 SD). The both patients had developmental delay, moderate ID, speech delay, thin corpus callosum, foot deformity, spastic paraplegia, hyperactivity, aggregation and self-biting.

To determine the molecular etiology in this family, WES was performed. The patients first were clinically examined and then fragile-X (FrX) syndrome test was performed as the first diagnostic screening test. Peripheral blood samples were collected from the all family members and their genomic DNA was extracted using the salting out method [10]. The Agilent SureSelect kit was used for DNA library preparation and capturing. WES was carried out by an Illumina NextSeq 500 system using paired-end reads with average coverage depth per sample. The sequencing quality was measured by FastQC software [11]. The row reads alignment with reference genome was performed by Burrows-Wheeler Aligner software, and variant calling and annotation were then implemented by GATK and ANNOVAR tools, respectively. Variants first were filtered out based on Minor Allele Frequency (MAF)>1% in different population databases. All non-coding regions and synonymous variants were then excluded. Finally, the pathogenicity of remaining variants was assessed by In Silico prediction algorithms, In Silico nucleotide conservation, and based on american college of medical genetics and genomics (ACMG) guidelines. Potential causative variants were validated in patients by Sanger sequencing. Afterwards, co-segregation analysis was performed for the family members.

3. Results

We identified a homozygous stop-gain variant (NM_001142415: c.C472T: p.Arg158*) in aminoacyl-trna-synthetase-interacting multifunctional protein 1 (AIMP1) gene. The variant caused a truncated protein. Sanger sequencing confirmed the homozygous pathogenic allele in the affected members, and heterozygous status of the variant region was detected in the parents. According to ACMG guidelines, the variant is considered to be a pathogen. The observed variant has not been reported in Clinvar and IRANOME database (www.iranome.com).

4. Discussion

AIMP1 gene encodes a cytokine protein with 312 amino acids and is involved in controlling inflammation and angiogenesis. AIMP1 act as a noncatalytic component of a tRNA multi-synthetase complex (MSC). The MSC contains three noncatalytic proteins (AIMP1, AIMP2, AIMP3), joined to nine catalytic aminoacyl-tRNA synthetases (ARS) [21, 22]. Studies have shown that AIMP1 expression is observed in hippocampus and spinal horn [23]. The catalytic reaction of arginyl-tRNA synthetase is facilitated by AIMP1 binding. AIMP1 is also involved in diverse physiological processes such as extracellular cytokine activities including endothelial cells, monocytes and fibroblasts and glucagon-like hormonal activity. AIMP1 is an inactive precursor of endothelial monocyte activating polypeptide II (EMAP II) [24]. The AIMP1 interacts with neurofilament light subunit helping to optimally modulate neurofilament light phosphorylation. The neurofilaments play crucial role in the neuron development and function [22, 24]. Homozygous mutation in the AIMP1 gene cause hypomyelinating leukodystrophy-3 (HLD3) which is characterized by global developmental delay, speech impairment, and peripheral spasticity associated with decreased myelination in the central nervous system [25]. In this study, homozygous stopgain mutation was identified in tRNA-binding domain (151-252 residues). The homozygous form of variant has not been observed in population databases until now.

In Iqbal et.al.'s study, two novel missense variants (a homozygous frameshift and a stop codon change) were reported in AIMP1 that were associated with moderate-to-severe ID in two Pakistani and Iranian families. In one of the families, the mutation was observed in tRNA-binding domain and caused truncated AIMP1 production, and in other family, the defective protein was targeted by nonsense-mediated mRNA decay. In both families, clinical manifestations such as global developmental delay, lack of leukodystrophy, speech impairment and paraplegia were observed.

[22]. Armstrong et al. reported severe clinical manifestations in a Filipino girl that lead to her premature death [26]. BoAli et. al. found a new homozygous variant in AIMP1 gene in six members of a large consanguineous family who had progressive microcephaly and epilepsy, in addition to the above mentioned clinical manifestations [27].

The decrease in the signal of N-acetylaspartic acid (NAA) in the brain was observed in two twins with AIMP1 mutation. The NAA is synthesized in the mitochondria through acetylation of aspartate by the membrane-bound enzyme of L-aspartate N-acetyltransferase and transported out by dicarboxylic acid. The NAA is required for myelination by an aspartate donor. Pathogenic variants in AIMP1 can cause dysfunction in neuromuscular junction which can lead to hypotonia in patients with AIMP1 deficiency [21]. In a functional study, muscular atrophy and motor dysfunction have also been reported in AIMP1-deficient mice [28]. Our findings showed the clinical spectrum of mutations in AIMP1 and can be used for medical purposes, genetic counseling and prevention strategies in individuals and families that are at risk.

Ethical Considerations

Compliance with ethical guidelines

The present study was approved by the Research Ethics Committee of Qazvin University of Medical Sciences (Code: QUMS.REC.1396.264).

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Authors' contributions

Writing and data analysis: Sara Cheraghi; Editing and project administration: Reza Najafipour and Sahar Moghbelinejad; Resources and review: Reza Najafipour.

Conflicts of interest

The authors declared no conflict of interest.

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