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ORIGINAL ARTICLE

A deleterious frameshift insertion mutation in the *ZNF142* gene leads to intellectual developmental disorder with impaired speech in three affected siblings: Clinical features and literature review

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Abstract

Background: *ZNF142* gene is a protein-coding gene encoding Zinc Finger Protein 142. ZNF proteins are a vast group of cellular effectors with a wide range of functions such as signal transduction, transcriptional regulation, meiotic recombination, DNA repair, development, and cell migration. Mutations in the *ZNF142* gene are related to neurodevelopmental disorder with impaired speech and hyperkinetic movements (NEDISHM). This study on a family with three affected siblings identified a pathogenic frameshift insertion variant. In addition, we conducted a review of the literature on previously reported *ZNF142* gene variants and their clinical manifestations.

Materials and Methods: Three affected siblings with severe intellectual developmental disabilities and speech impairments, their parents, and other sibs in the family were included. The patients were studied by the whole exome sequencing. Sanger sequencing, co-segregation analysis, and in silico analysis were carried out to verify candidate variant. The identified variant was interpreted based on the ACMG guideline.

Results: We identified a frameshift insertion variant in the *ZNF142* gene, NM_001379659.1: c.3755dup (NP_001366588.1:p.Arg1253ThrfsTer15), that was related to the clinical features of three patients. The identified variant was found to be pathogenic.

Conclusion: The current study findings expand the existing knowledge of the variant on the *ZNF142* gene implicated in the neurodevelopmental disorder, intellectual disability, and impaired speech and it presents a detailed clinical feature associated with related conditions. The data have implications for genetic diagnosis and counseling in families with the same disorders.

KEYWORDS

developmental delay, exome sequencing, intellectual disability, Iran, speech disorder, ZNF142

1 | INTRODUCTION

The *ZNF142* gene (OMIM: 604083; HGNC ID:12927) is a protein-coding gene that encodes Zinc Finger Protein 142. The encoding protein belongs to the zinc-finger protein (ZNF) superfamily. The ZNF superfamily is one of the largest groups of mammalian transcription factors. ZNF proteins contain the Cys2His2 (C2H2) motif coordinating a Zn^{2+} ion and are known as zinc fingers. They include a large number of cellular effectors with a variety of functions. Several biological functions, including signal transduction, transcriptional control, meiotic recombination, DNA repair, development, and cell migration, are mediated by proteins having zinc-finger domains (Schwarz et al., 2019). Therefore, the ZNF proteins are one of the major transcription factor families in humans, and pathogenic variants in these proteins were reported to be associated with neurodevelopmental disorders (Al-Naama et al., 2020; Tommerup & Vissing, 1995).

ZNF142 is a member of the ZNF family encoded by the *ZNF142* gene. The gene is located on 2q35. It consists of 11 exons and encodes 1887 amino acids (Stelzer et al., 2016). The ZNF142 protein includes 31 C2H2-type zinc fingers domains which belong to the Kruppel C2H2-type zinc-finger protein family. The possible role that could be suggested for ZNF142 is the transcriptional regulation (O'Leary et al., 2016). Pathogenic variants in the *ZNF142* gene are reported to be related to 10 phenotypes including global developmental delay, ataxia, dystonia, tremor, dolichocephaly, torticollis, delayed speech, and language development, bilateral tonic–clonic seizure, chorea, and hyperkinetic movements (Köhler et al., 2021).

At first, Khan et al. (2019) reported that the *ZNF142* gene defects lead to a neurological condition named Neurodevelopmental Disorder with Impaired Speech and Hyperkinetic Movements (NEDISHM; MIM: 618425) (Khan et al., 2019). To our knowledge, our work is the fifth study on the *ZNF142* gene related to intellectual disability, and neurodevelopmental disorder with impaired Speech. However, few studies are reported on the clinical spectrum and pathogenic variants of this gene.

In this study, we focused on a family with three affected siblings with severe intellectual developmental disabilities and speech impairments who were found to have a pathogenic frameshift insertion variant. We also thoroughly reviewed the literature on previously reported *ZNF142* gene variants and their clinical manifestations.

2 | METHODS AND SUBJECTS

2.1 | Family recruitment and DNA extraction

The Ethics Committee of the Isfahan University of Medical Sciences, Isfahan, Iran, authorized this research (Ethics code: IR.MUI.MED.REC.1400.042). Three individuals with severe intellectual disability (ID) belonging to a consanguineous family were identified in the Iranian province of Sistan and Balouchestan. Medical history was obtained via genetic counseling, and the pedigree was drawn by the "Progeny" software (Progeny Software, LLC). The peripheral blood was taken after getting informed written consent from the legal guardian. DNA extraction was done using the DNSol Miniprep Kit provided by ROJETECHNOLOGIES company, Tehran, Iran.

2.2 | Whole-exome sequencing and variant prioritization

Exome capturing was performed using xGen Exome Research Panel v2 kit (Integrated DNA Technologies, Coralville, Iowa, USA), and whole exome sequencing (WES) was performed using NovaSeq 6000 (Illumina, San Diego, CA, USA) in 3Billion Inc. (Seoul, South Korea). The quality of FASTQ Illumina Novaseq 6000 output files was assessed using FASTQC (http://www.bioinformatics.babraham.ac.uk/projects/fastqc/). Subsequently, the base and sequence adapters with low base quality were removed using Trimmomatic (Bolger et al., 2014). Pre-processed FASTQ files were aligned to the reference sequence by BWA-MEM (v.0.7.17) (Li & Durbin, 2009). Aligned BAM files were sorted and extracted using the statistical metric by samtools (v.1.9) (Li et al., 2009). Duplication was marked by Picard (v.2.20.8) (http://broadinstitute.github.io/picard/). Single nucleotide variants and indel variants were called by HaplotypeCaller of GATK (v.3.8) (McKenna et al., 2010). In total, 9,745,010,591 bases of the sequence were generated and uniquely aligned to the Genome Reference Consortium Human Build 37 (GRCh37) and Revised Cambridge Reference Sequence (rCRS) of the mitochondrial genome, generating 139.03 mean depth-of-coverage within the 34,366,188 bases of the captured region, which is approximately 99.3% of the RefSeq protein coding region. Approximately 98.80% of the targeted bases were covered to a depth of ≥20× (Gene or exon level depth-of-coverage information is available upon request). In total, 67,572 single nucleotide variants (SNV) and 10,888 small insertions and deletions (indel) were identified (The entire variant list

without annotation or clinical interpretation is available upon request). The EVIDENCE software (Seo et al., 2020), a software tool developed in-house, has been used to prioritize variants and interpreted based on the guideline recommended by the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology (AMP) (Richards et al., 2015) in the context of the patient phenotypes. Through genetic counseling, pertinent family history and past clinical test findings were supplied. At the time of variant interpretation, only clinically important variations related to the patient's principal clinical indications were examined.

2.3 | Sanger sequencing and co-segregation analysis

The candidate variant was confirmed using Sanger sequencing, and co-segregation analysis was performed on affected and unaffected members of family. Specific primers for the variant were designed using the Primer3 online tool (Primer3web, version 4.1.0) and validated by online tools such as Primer-BLAST (Ye et al., 2012), MFEprimer3.1 (Wang et al., 2019) and SNPCheck (gene tools, SNPCheck V3). The used primer sequences are listed in Table 1.

2.4 | *In silico* analysis

We used the Genome Aggregation Database (gnomAD v2.1.1) and Iranome (http://www.iranome.ir/) for population allele frequency analysis. The potential pathogenicity of the variants was assessed using the NMDEscPredictor server (https://nmdprediction.shinyapps.io/nmdescpredictor/). The NCBI Constraint-based Multiple Alignment Tool (COBALT) server (version 1.22.0) was used for the analysis of conservation (https://www.ncbi.nlm.nih.gov/tools/cobalt/cobalt.cgi?CMD=Web). ACMG classification was performed by using the Varsome online tool (https://varsome.com/). The schematic view of the ZNF142 protein was provided by the Prosite protein database (https://prosite.expasy.org/).

TABLE 1 The primers sequences used for Sanger sequencing and co-segregation analysis.

Primer name	Sequence (5′ – > 3′)	Product size	Genomic coordinate (GRCh37)
Forward	5′- CGCTTCTGGTG GAGCCTTA –3′	406 bp	chr2:219507771–219508177
Reverse	5′- TTGAGCAGGGC AAGTTTCAC -3’		

3 | RESULTS

3.1 | Clinical findings

The proband is a 23-year-old girl with severe ID and speech disorder (Figure 1a-Individual IV-3). She was born at term after an uncomplicated pregnancy. She is the third child of a consanguineous family with Balouch ethnicity from Iran. Although birth parameters and neonatal adaption were normal, she had delayed in milestones. She lifts their head by 4 months old, sit with some support by 8 months, and started walking at 24 months. Her speech development was impaired; she spoke her first two- to three–3-word sentences at the age of five. She could not speak clearly and only used some unclear words at the time of this study. As described, she had a neurodevelopmental delay during infancy. She suffers from a learning disability that worsens with her age and is considered as a severe ID. She also suffered from enuresis since childhood. She did not encounter mobility challenges, seizures, and other medical problems. She shows no dysmorphic features. She had a normal number of chromosomes based on cytogenetics and normal aCGH test results. She has two younger siblings with the same conditions. Her younger brother is 17 years old (Figure 1a-Individual IV-4) and suffers from severe ID and speech impairment, he had a neurodevelopmental delay, learning disability, and enuresis. In general, he is similar in terms of signs and symptoms to the proband. They also have a younger 7-year-old brother (Figure 1a-Individual IV-5) with moderate ID and speech impairments. He is similar in conditions to his two elder affected siblings but did not show developmental delay. His phenotype is milder than his two siblings. There is a family history of the same conditions in their father's cousins that did not want to participate in the study (Figure 1a-Individual III-1,2,3).

3.2 | Molecular and in silico findings

Sanger sequencing and segregation analysis validated the NM_001379659.1 (*ZNF142*):c.3755dup homozygous frameshift insertion variant in the *ZNF142* gene (Gene Bank ID: GC02M218637) that was identified using WES (Figure 1b). The variant was found to be homozygous in the three afflicted individuals, and both parents were carriers for the variant. The variant is observed at an extremely low frequency in the gnomAD dataset (total allele frequency: <0.001%) and not found in the Iranome dataset (Table 2). Some in silico tools also demonstrated the variant negative influence on gene function, such as the NMDEscPredictor server which predicted to result in a loss or disruption of normal protein function through

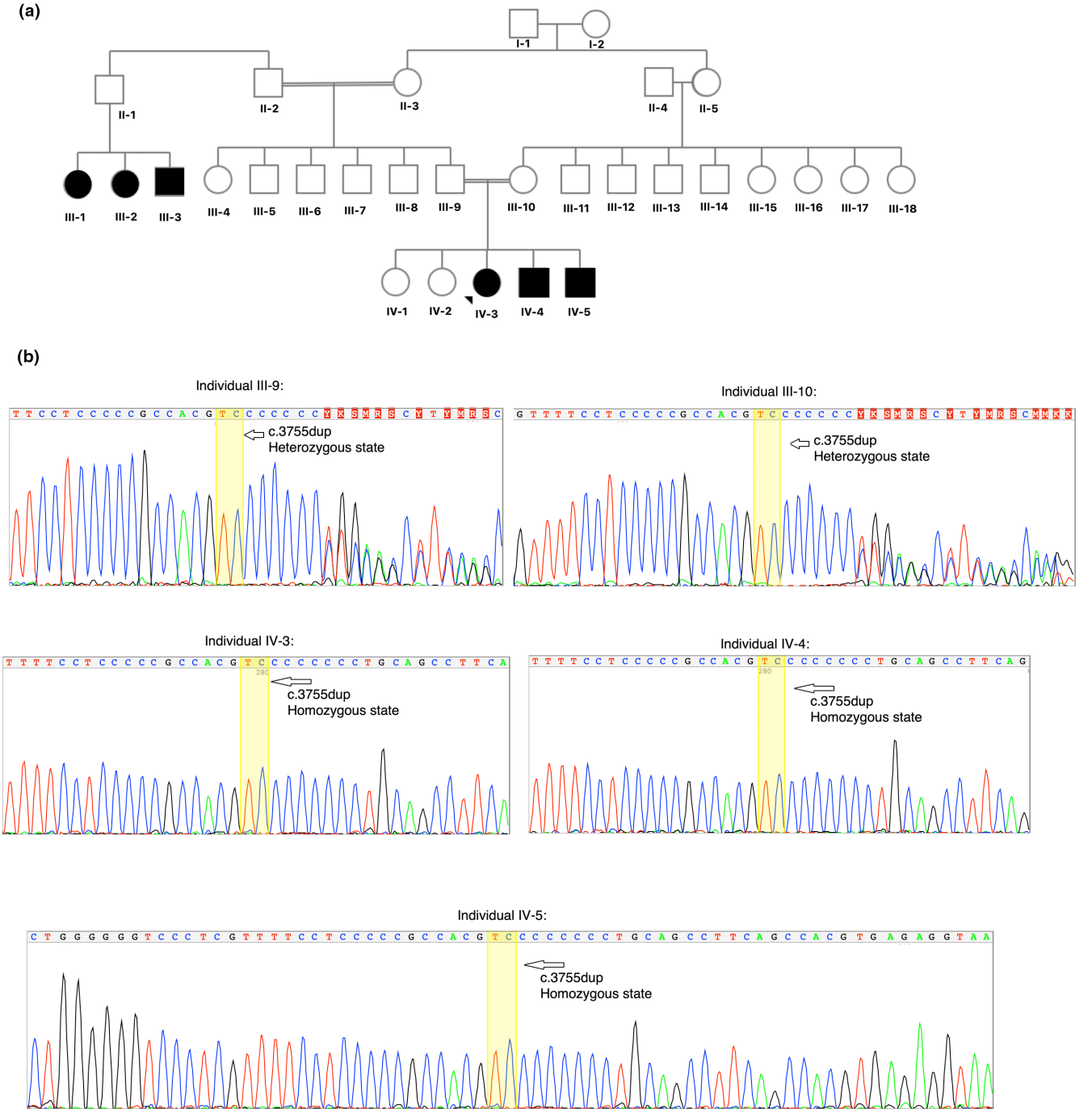

FIGURE 1 (a) The pedigree of the studied family: There are six patients with an intellectual developmental disorder and speech impairment in two generations. (b) The electropherograms of different members of the pedigree on mutation position.

TABLE 2 *In silico* findings of the c.3755dup variant.

Gene	Genomic position	cDNA position	Protein change	gnomAD frequency	Iranome frequency	Pathogenicity line of evidence based on ACMG
ZNF142	2-219,508,083-T-TC (GRCh37)	NM_001379659.1: c.3755dup	NP_001366588.1:p. Arg1253ThrfsTer15	<0.001%	Not found	PVS1 (null variant), PM2 (variant not found in gnomAD genomes), and PP1 (co-segregation with the disease in multiple affected members of the family)

nonsense-mediated decay (NMD) and protein truncation (Figure 2) and COBALT server showed the locus of the variant and downstream regions are highly conserved in multiple organisms (Figure 3) that their deletion could affect protein functions. ACMG classification of the variant was pathogenic based on PVS1 (null variant), PM2 (variant not found in gnomAD genomes), and PP1 (co-segregation with the disease in multiple affected members of the family) lines of evidence (Table 2).

4 | DISCUSSION

The *ZNF142* gene defect was first described by Khan et al. (2019) related to a specific neurodevelopmental condition. They discovered homozygous or compound heterozygous mutations in the *ZNF142* gene lead to "Neurodevelopmental Disorder with Impaired Speech and Hyperkinetic Movements" (NEDISHM; MIM: 618425). It is an autosomal recessive disorder characterized by global developmental delay apparent in infancy. Khan et al. studied seven patients with NEDISHM and autosomal recessive inheritance belonging to the four unrelated families (Khan et al., 2019). The majority of their studied patients have modest delays in walking and speaking, cognitive impairment, speech deficits, and motor impairment, in addition to hyperkinetic movement abnormalities such as dystonia, tremors, ataxias, and chorea. They found some individuals may develop seizures that gradually diminish (Table 3) (Khan et al., 2019). In 2021 Kameyama et al. described a Malaysian family with two affected members suffering from global developmental delay, epilepsy, dysmorphism, and typical facial features (Table 3) (Kameyama et al., 2022).

Christensen et al. (2022) described 16 families containing 26 patients with NEDISHM and autosomal recessive inheritance (Table 3). The majority of the studied patients show intellectual disability, language impairments, and delay in developmental milestones, and some show seizures, hypotonia, behavioral problems, movement disorders, dystonia, tremor, and ataxia (Christensen et al., 2022). Kamal et al. (2022) reported an Iranian family with mutations in the *ZNF142* gene in an affected child with intellectual disability, developmental delay, hypotonia, and seizures (Table 3) (Kamal et al., 2022). Approximately 36 people in four studies have been diagnosed with NEDISHM to yet, and the present investigation identified another family with three afflicted siblings who have the *ZNF142* gene mutation and suffer from neurodevelopmental delay, severe intellectual disability, and speech dysfunction.

The NM_001379659.1 (*ZNF142*):c.3755dup homozygous variant was detected in all three sibs of the current study, whose parents were carrier heterozygous. The variant is located in exon 9 of 11 and in a region between two C2H2 domains. The identified variant is located in a region consisting of seven C nucleotide repeats, and

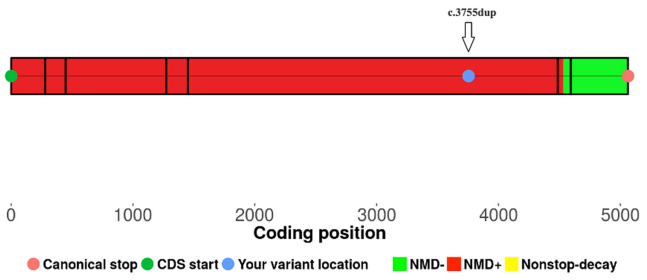

FIGURE 2 NMD prediction of the c.3755dup variant in the *ZNF142* gene using NMDEscPredictor server. The variant was located in the red-colored regions, and it is predicted to be targeted for NMD. Green-colored regions are not targeted for NMD.

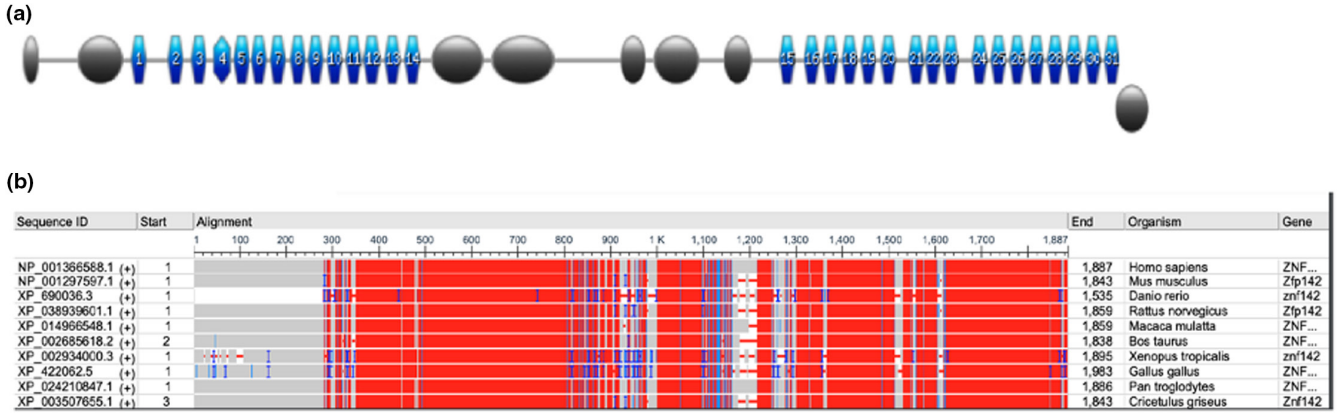

FIGURE 3 (a) Schematic view of the ZNF142 protein; blue shapes show C2H2 domains. (b) The protein alignment data of 10 organisms on the ZNF142 protein sequence to assess conservation domains; red-colored regions show high conservation between 10 organisms; gray-colored region are low conserved regions.

TABLE 3 Previous studies on variants of the *ZNF142* gene related to NEDSHM.

Family	Patient	Variant description	Variant type	Inheritance	Protein change	Protein domain
1	A B	NM_001105537.2: c.817_818del/ c.1292delG	Frameshift/ Frameshift	Compound heterozygote	p.(Lys273Glufs*32)/p. (Cys431Leufs*11)	C2H2-type 3/C2H2-type 9
2	A	NM_001105537.2: c.3175C > T	Nonsense	Homozygote	p.(Arg1059*)	Region
3	A	NM_001105537.2: c.3698G > T/c.4498C > T	Missense/ Missense	Compound heterozygote	p.(Cys1233Phe)/ p.(Arg1500Trp)	C2H2-type 18/C2H2-type 26
4	A B C	NM_001105537.2: c.4183_4185 delinsAT	Nonsense	Homozygote	p.(Leu1395*)	C2H2-type 23
5	A B	NM_001105537.4: c.1252C > T/c.1274-2A > G	Nonsense/ Nonsense	Compound heterozygote	p.(Arg418*)/ p.(Glu426*)	C2H2-type 8/-
6	A	NM_001105537.2: c.25C > T/c.2288C > G	Nonsense/ Missense	Compound heterozygote	p.(Gln9*)/ p.(Ser763Cys)	Region/Region
7	A	NM_001105537.2: c.527del/c.4030C > T	Frameshift/ Nonsense	Compound heterozygote	p.(Thr176Ilefs*93)/ p.(Arg1344*)	C2H2-type 1/C2H2-type 21
8	A B	NM_001105537.2: c.1165_1166del/ c.1910del	Frameshift/ Frameshift	Compound heterozygote	p.(Asp389Serfs*9)/p. (Pro637Leufs*23)	C2H2-type 7/Region
9	A B	NM_001105537.2: c.1252C > T	Nonsense	Homozygote	p.(Arg418*)	C2H2-type 8
10	A	NM_001105537.2: c.1456C > T	Nonsense	Homozygote	p.(Gln486*)	C2H2-type 11
11	A B	NM_001105537.2: c.1906C > T/c.3735del	Nonsense/ Nonsense	Compound heterozygote	p.(Arg636*)/p. (Leu1245Phefs*4)	Region/C2H2-type 18

Clinical findings	Method	References
Mild ID, Speech impairment, Developmental delay, Ataxia, Tremor, Dystonia, Dolichocephaly, Torticollis	Whole exome sequencing	Khan et al. (2019)
Mild ID, Speech impairment, Developmental delay, Ataxia, Tremor, Dystonia, Dolichocephaly, Torticollis, Seizure, Behavior problems, Facial dyskinesia, Movement disorder	Whole exome sequencing	
Moderate ID, Speech impairment, Developmental delay, Ataxia, Seizure, Hypotonia, Signal intensities in brain MRI, Dystonia, Choreatic movements, excessive beta activity in EEG, Torticollis, Excessive crying	Whole exome sequencing	Khan et al. (2019)
Mild ID, Speech impairment, Developmental delay, Brain MRI: Mild thinning of the posterior aspect of the body of the corpus callosum with an associated mild reduction in white matter volume, brisk reflexes, Increased tone and reflexes in lower limbs	Whole exome sequencing	Khan et al. (2019)
Severe ID, Speech impairment, Seizure, Dolichocephaly	Whole exome sequencing	Khan et al. (2019)
Severe ID, Speech impairment, Developmental delay, Ataxia, Tremor, Seizure	Whole exome sequencing	
Severe ID, Speech impairment, Developmental delay, Tremor, Dolichocephaly, Seizure	Whole exome sequencing	
Severe ID, Speech impairment, Developmental delay, Seizure, Hypotonia, Bilateral mesial temporal sclerosis in brain MRI, Autistic features, Dolichocephaly, Prominent eyes, Micrognathia, Flat nasal bridge, Thick lips, Accessory nipple, Arachnodactyly	Whole exome sequencing	Kameyama et al. (2022)
Moderate ID, Speech impairment, Developmental delay, Seizure, Delayed myelination in brain MRI, Autistic features, Atonia, Dolichocephaly, Prominent eyes, Micrognathia, Flat nasal bridge, Prominent Forehead, Caf e au lait spot	Whole exome sequencing	
Mild ID, Seizures, Abnormal EEG, Broad nasal bridge, Wide nose, Narrow palpebral fissures, Syndactyly of 2nd and 3rd toe, Amenorrhea	Trio whole genome sequencing	Christensen et al. (2022)
Neurodevelopmental delay, Speech impairment, Moderate ID, Behavioral problems, Dystonia, Tremor, Ataxia, Hypotonia, Hyperkinetic Movements, Seizures, Thick lips, Faunal ears, Oblic palpebral fissures, Overlapping teeth, Narrow palate, Strabismus, Long and bulging chest, Nipples apart, Scoliosis and kyphosis, Hands and feet laxity, Clinodactyly on feet	Whole exome sequencing	Christensen et al. (2022)
Neurodevelopmental Delay, Speech Impairment, Moderate ID, Autistic behavior, Seizure, MRI: Small degree of cranial asymmetry, Hypotonic facies with open mouth, Pes planus, Joint laxity, Ataxia	Targeted exome sequencing	Christensen et al. (2022)
Neurodevelopmental Delay, Speech Impairment, Mild ID, Autistic behavior, Seizure, Hypotonic facies with open mouth, Pes planus, Joint laxity	Sanger sequencing	
Neurodevelopmental Delay, Speech Impairment, Severe ID, Autistic behavior, Tremor, Mild hypotonia, Complex movement disorder, Dysarthria, Dysphagia, Salivation, Axial rigor, Brady diadochokinesia, Mild postural instability. Stereotypic hand movements, Seizure, Abnormal EEG, Hypomimia, Macrocephaly (56 cm), Dwarfism, Mild thoracic scoliosis. Pes planus, Male-pattern hypertrichosis (face, legs, genital region)	Sanger sequencing	Christensen et al. (2022)
Neurodevelopmental Delay, Speech Impairment, Moderate ID, Mildly ataxic gait, Mild hypotonia, Seizure, Joint laxity, Renal involvement	Whole exome sequencing	
Neurodevelopmental Delay, Speech Impairment, Moderate ID, Unexplained laughing, Dysonia, Tremor, Ataxia, MRI: Thin corpus callosum, deep white matter dysmyelination around the occiptial horn of lateral ventricles, mild cortical involution with deep Sylvian fissures and deep interhemispheric fissure (3 years), High forehead, Wide palpebral fissures, Braod nose, Long philtrum, Thin Upper lip, Everted lower lip, Pointed chin, Low set ears	Whole exome sequencing	Christensen et al. (2022)
Neurodevelopmental Delay, Speech Impairment, Autism, Mild Hypotonia, Cerebral visual impairment, Delayed myelinization parieto-occipital, Thick eyebrows, Mild synophrys, Broad nasal bridge, Epicantal folds, High nasal bridge, Long and broad philtrum, Hair on upper lip, Ears are normally implanted, folded but posteriorly rotated, Proximal thumbs, Hockey stick palmar crease unilaterally, Long and broad first rays of the feet; inspection of the mouth, nek, upper body is normal, Primary amenorrhea	Trio exome sequencing	Christensen et al. (2022)
Neurodevelopmental Delay, Speech impairment, ADHD, Cerebral visual impairment, Small cyst with surrounding gliosis at the tip of the anterior horn of the left lateral ventricle with contiguous prominent vascular structure in the caput Nuclei caudati, crus anterior of capsule interna right down to the nucleus lentiformis, Thick eyebrows, Mild synophrys, Broad nasal bridge, Hypertelorism, Epicantal folds, Mild bilateral ptosis, High nasal bridge, Long and broad philtrum, Ears are normally implanted, folded but posteriorly rotated	Direct analysis of the familial variant	

TABLE 3 Continued

Family	Patient	Variant description	Variant type	Inheritance	Protein change	Protein domain
12	A	NM_001105537.2: c.1906C > T/c.3885C > A	Nonsense/ Missense	Compound Heterozygote	p.(Arg636*)/p.(Phe1295Leu)	Region/C2H2-type 20
13	A	NM_001105537.2: c.2650del	Frameshift	Homozygote	p.(His884Thrfs*3)	–
14	A B	NM_001105537.2: c.2851del/c.3167dup	Frameshift/ Frameshift	Compound heterozygote	p.(Glu951Lysfs*66)/p.(Gly1057Argfs*11)	Region/region
15	A B C	NM_001105537.2: c.3155dup	Frameshift	Homozygote	p.(Arg1053Thrfs*15)	Region
16	A	NM_001105537.2: c.3175C > T	Nonsense	Homozygote	p.(Arg1059*)	Region
17	A	NM_001105537.2: c.3346del	Frameshift	Homozygote	p.(Glu1116Asnfs*4)	–
18	A B C	NM_001105537.2: c.3514C > T	Nonsense	Homozygote	p.(Gln1172*)	C2H2-type 16
19	A	NM_001105537.2: c.4261C > T	Nonsense	Homozygote	p.(Gln1421*)	–
20	A B	NM_001105537.2: c.4436del	Frameshift	Homozygote	p.(Pro1479Leufs*45)	–
21	A B	NM_001105537.2: c.4440C > G	Nonsense	Homozygote	p.(Tyr1480*)	C2H2-type 26
22	A	NM_001105537: c.25C > T/c.1741C > T	Nonsense/ Missense	Compound heterozygote	p.Gln9*/p.Arg581Cys	Region/C2H2-type 14
23	A B C	NM_001379659.1: c.3755dup (NM_001105537.2: c.3155dup)	Frameshift	Homozygote	p.Arg1253ThrfsTer15	Region

therefore replication slippage mechanism can lead to the insertion of additional C nucleotides in that position (Viguera et al., 2001). The variation alters the Arginine residue at residue 1253 of the protein at the protein level. After 15 amino acids, a premature stop codon is formed, resulting in a shortened protein lacking highly conserved domains (Figure 3b). Therefore, the last two exonic regions of the gene encoding the critical C2H2 domains are lost. Hence, multiple pathogenic variants were reported downstream of this variant. In addition to the missed functional domains, the transcript could be exposed to the nonsense-mediated decay process, which shortens the half-life of the transcript (Holbrook et al., 2004). Moreover, the identified deleterious variant, NM_001379659.1 (*ZNF142*):c.3755dup, was recently reported from Iran on the same ethnicity group related to the same condition (Christensen et al., 2022), which might implicate it as a variant of the founder

Clinical findings	Method	References
Speech impairment, Episodic ataxia, Neonatal hypertonia, Seizure, High-arched palatum, Systolic cardiac souffle	Whole exome sequencing	Christensen et al. (2022)
Speech impairment, Moderate ID, Dystonia, Tremor, High forehead, Thick eyebrows, Epicanthus, Thick lips, Posteriorly rotated ears	Whole exome sequencing, Sanger sequencing	Christensen et al. (2022)
Neurodevelopmental Delay, Speech Impairment, Moderate ID, Behavior problem, Sleep disorder, Hypotonia, Seizure, Mild hypertelorism, Overfolded helices, Narrow palate, Overlapping toe, Clinodactyly	Whole exome sequencing	Christensen et al. (2022)
Neurodevelopmental Delay, Speech Impairment, Mild ID, Mild peripheral hypertonia, Axial hypotonia, Seizure, Bilateral epicanthus, Wide nasal bridge, Anteverted nares, Pronounced philtrum, Overfolded helices, Left single palmar crease	Whole exome sequencing	
Speech impairment, Moderate ID	Whole exome sequencing	Christensen et al. (2022)
Speech impairment, Severe ID, Narrow forehead, Short philtrum, Thick lips	Sanger sequencing	
Speech impairment, Moderate ID, Narrow forehead, Long face, Long nose, Thick lips	Sanger sequencing	
Neurodevelopmental Delay, Speech Impairment, Global developmental delay, Broad-based walking, Seizure, Facial hypotonia, Thick lips, Dolicocephaly, Retrognathia, Curled ears	Whole exome sequencing	Christensen et al. (2022)
Speech impairment, Moderate ID, Social disorder, Behavior problems, Seizure, Macrocephaly, Long face, Epicanthus, Low-set ears, Joint laxity, Arachnodactyly, Long and narrow feet, Long toes, Unilateral cryptorchidism	Trio exome sequencing	Christensen et al. (2022)
Neurodevelopmental delay, Speech impairment, Mild ID, Aggressive Behavior, Seizure, Abnormal EEG, Kyphosis	Sanger sequencing	Christensen et al. (2022)
Neurodevelopmental delay, Speech impairment, Moderate ID, Pes planus	Whole genome sequencing	
Neurodevelopmental delay, Speech impairment, Moderate ID, Tremor, Seizure, Pes planus	Whole genome sequencing	
Neurodevelopmental delay, Speech impairment, Mild ID, Anxiety, Aggressive behavior, Ataxia, Hypotonia, Seizure, Abnormal EEG, High forehead, Thick lips, Scoliosis, kyphosis, Strabismus, Hypermetropia	Whole exome sequencing	Christensen et al. (2022)
Neurodevelopmental delay, Speech impairment, Mild ID, Dystonia, Hypotonia, Seizure, Long thin face, Broad nasal root and tip, Narrow palate	Whole exome sequencing	Christensen et al. (2022)
Neurodevelopmental delay, Speech impairment, Mild ID, Some immature behaviors	Whole exome sequencing	
Neurodevelopmental delay, Speech impairment, Moderate ID, Dystonia, Hypotonia, Seizure, Abnormal EEG, Narrow forehead, Thick eyebrows, Narrow palpebral fissures, Hanging upper eyelids, Broad nasal bridge, Prominent nose with hypoplastic nares, Very short philtrum, Everted lower lip, Prominent incisors, Hyperlordosis and scoliosis, Slender and long arms, Short stature, Myopia, Pubertas tarda	Whole exome sequencing	Christensen et al. (2022)
Neurodevelopmental delay, Speech impairment, Moderate ID, Hypotonia, Seizure, Long face, Medial flaired eyebrows, Thick eyebrows, Short philtrum, Thick lips, Prominent incisors, Uvula bifida (lower part), Dental crowding, Low set ears	Whole exome sequencing	
ID, Speech impairment, Developmental delay, Seizure, Hypotonia	Whole exome sequencing	Kamal et al. (2022)
Severe ID, Speech disorder, Developmental Delay	Whole exome sequencing	Present Study
	Sanger sequencing	
	Sanger sequencing	

effect. In general, along with the current study, about 29 variants in this gene have been reported, which are related to neurodevelopmental delay conditions (Table 3). Based on HGMD non-professional, 16 out of the 29 variants are base substitutions and 14 are INDELs. Thus, the frequency of point substitution and small insertion/deletion variants are almost equal. Therefore, loss-of-function (LOF) is a known mechanism of disease (gene has 15 reported pathogenic LOF variants). Besides, compound heterozygous variants should be considered in the *ZNF142* gene variants analysis (Table 3) (Schaaf et al., 2012).

According to previous studies, pathogenic variants in this gene resulted in a spectrum of clinical presentations including intellectual disability, speech impairment, developmental delay, hyperkinetic movements, ataxia, tremor, dystonia, dolichocephaly, torticollis, seizure, deficits in social and executive functions, Facial dyskinesia,

movement disorder, hypotonia, atonia, some facial features. Along with other studies, the patients in current study show intellectual disability, neurodevelopmental delay, delayed milestones, and speech impairments. Nevertheless, despite the chosen term for the linked disorders, hyperkinetic movements were not seen in the current investigation or the majority of prior studies. Table 3 presents comparing of reported variants and their detailed clinical manifestations with the current study. It is concluded that different types of mutations, either homozygous or compounds heterozygous on C2H2 and regions could lead to various phenotypes. However, more studies are needed to conclude a genotype–phenotype correlation.

5 | CONCLUSION

In conclusion, this study revealed a recurrent deleterious variant in the *ZNF142* gene (NM_001379659.1 (*ZNF142*):c.3755dup), identified by WES, and described clinical findings in the family. The results broaden the mutational and clinical spectrum of the *ZNF142* gene.

AUTHOR CONTRIBUTIONS

Atefeh Mir: Patient identification and provision of clinical data, exome data analysis, and mutation screening, performing experiments and segregation analysis in families by Sanger sequencing, and writing the first draft of the manuscript. **Yongjun Song**: Performing whole exome sequencing and data analysis. **Hane Lee**: Performing whole exome sequencing and data analysis. **Mostafa Montazer-Zohouri**: Recruitment of patients and family members and sampling, performing experiments. **Marziyeh Reisi**: Recruitment of patients and family members and sampling, performing experiments. **Mohammad Amin Tabatabaiefar**: Design and supervision of the research, review and editing the first draft of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article and the raw data that support the findings of this study are available from the corresponding author upon reasonable request. In addition, the identified variant during the current study has been submitted in the ClinVar repository with accession number; VCV001705330.1.

ETHICS STATEMENT

The research was performed in accordance with the approval of the ethics board of the Medical University of Isfahan (Ethics code: IR.MUI.MED.REC.1400.042).

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