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Whole Exome Sequencing in Patients With Developmental Delay/Intellectual Disability (DD/ID), Epilepsy and the First Turkish Patient Diagnosed With BCL11A-Related Intellectual Disability

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ABSTRACT

Introduction: Whole-exome sequencing (WES) is considered an important tool in investigating the etiology of developmental delay/intellectual disability (DD/ID) and epilepsy. Genetic diagnosis with WES has become an important tool in patients with DD/ID and epilepsy.

Methods: In this study, we present the findings of WES conducted between August 2021 and December 2024 on children with DD/ID and epilepsy. We evaluated clinically important variants identified by WES in 65 pediatric patients by retrospective analysis.

Results: Sixty-five patients with DD/ID were included in the study, 34 of whom (52.3%) were male. The most common symptom was epilepsy (45 patients, 69.2%), and the second most common symptom was DD/ID in 39 patients (60%). A total of 19 pathogenic/likely pathogenic variants (31.2%) with confirmation made in the parents and probands, 9 variants were determined to be de novo. In this study, the number of patients diagnosed was determined as 19 (31.2%). We detected a de novo likely pathogenic heterozygous c.142T>C (p.Cys48Arg) variant in the BCL11A gene in the first reported Turkish patient with BCL11A-related intellectual disability. Other previously unreported de novo variants identified: *ASXL3* gene, NM_030632.2 c.3613G>T p.(Glu1205Ter), *ANKRD11* gene, NM_001256182.2 c.4750G>T, *SHANK3* gene, NM_001372044.2 c.4711_4712del.

Conclusion: The cases we present contribute to the expansion of the spectrum of genetic variants in genetically heterogeneous patient groups such as DD/ID and epilepsy. These previously unreported variants advance our molecular understanding and broaden the clinical spectrum of these rare genetic disorders.

1 | Introduction

Developmental Delay/Intellectual Disability (DD/ID) and epilepsy present diagnostic challenges because they represent a genetically heterogeneous group of disorders. DD/ID patients, with a prevalence of approximately 1%–3% in the society, are a difficult patient group to diagnose, representing a diagnostically challenging cohort whose genetic etiology needs to be elucidated (Bowling et al. 2017; Yan et al. 2019). Epilepsy is a neurological disorder characterized by recurrent epileptic seizures that

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affects approximately 0.5%–0.8% of children. Although there are many causes in the etiology of epilepsy, such as infections, tumors, and brain anomalies, approximately 30% are thought to be genetic (Nouri et al. 2021; Manickam et al. 2021; Lindy et al. 2018).

As in many other patient groups, next-generation sequencing (NGS) increases diagnosis rates by providing the opportunity to analyze multiple genes simultaneously, accurately, and effectively in patients diagnosed with DD/ID and epilepsy. The ability to analyze many variants of many genes associated with clinical findings with a single test provides an effective diagnostic tool for DD/ID and epilepsy patients. Diagnosis rates have been reported to be 25%–65% when WES is used in patients diagnosed with DD/ID with high genetic heterogeneity. It is known that multiple clinical symptoms, autism spectrum disorder (ASD), epilepsy, hypotonia, facial dysmorphism and neuroimaging abnormalities in patients with DD/ID increase the diagnostic yield in WES analyses when evaluated together (Jo et al. 2024; Sun et al. 2022; Hiraide et al. 2021).

On the other hand, Chromosomal Microarray (CMA), which has a diagnostic rate of approximately 10%–25% in patients with DD/ID, was recommended as a first-line genetic test to determine chromosomal copy number variation in 2010 by the American College of Medical Genetics and Genomics. Patients with DD/ID were first subjected to karyotype, CMA, fluorescence-in situ hybridization (FISH), Fragile X test in boys, *MECP2* gene test in girls, and tests for specific single-gene disorders (Richards et al. 2015; Akkus and Cubuk 2024).

BCL11A-related intellectual disability (BCL11A-ID) is known as Intellectual Developmental Disorder with the persistence of fetal hemoglobin or Dias-Logan Syndrome. BCL11A-ID (OMIM: 617101) is a syndrome characterized by autosomal dominant inheritance, particularly delayed psychomotor development, intellectual disability, and hereditary persistence of fetal hemoglobin (HPFH). BCL11A-ID, identified by Dias et al., develops as a result of heterozygous mutations in the BCL11A gene with autosomal dominant inheritance in the 2p16 region (Dias et al. 2016; Shu et al. 2025). Furthermore, we report the first case of Dias Logan Syndrome within the Turkish population.

In this study, outcomes of 65 patients with DD/ID, global developmental delay, epilepsy, and multiple congenital anomalies were retrospectively reviewed using karyotype, CMA, and WES (Figure 1). The analysis included WES data for children with DD/ID and epilepsy collected between August 2021 and December 2024. We reported the frequency, type, and inheritance pattern of variants of uncertain significance (VUS), pathogenic or likely pathogenic (P/LP) variants in genes associated with clinical findings. Here in, we present several variants, including novel variants, in a group of 65 Turkish patients with DD/ID epilepsy, with major clinical findings detected by WES.

2 | Materials and Methods

We conducted a retrospective evaluation of clinically relevant variants identified by WES in 65 patients with DD/ID and epilepsy between August 2021 and December 2024. This retrospective study was approved by the Ethics Committee of the Faculty of Medicine of Tokat Gaziosmanpasa University (25-MOBAEK-130). Written informed consent was obtained from parents or legal guardians before the study commenced.

The inclusion criteria were as follows: DD/ID, epilepsy, and hypotonia.

On the other hand, the exclusion criteria were: Patients over 18 years of age and metabolic abnormalities.

Chromosome analyses were performed using the Giemsa banding technique in 550 bands for cytogenetic analysis of peripheral blood samples. Patient blood samples were examined using the Affymetrix Cytoscan Optima (315 K) CMA system, and the results were analyzed using the CHAS 4.3 analysis program.

WES was performed using the Roche Kapa HyperExom Kit and the Illumina Novaseq 6000 platform. Raw data were analyzed via the Genomize-Seq variant analysis platform (Turkey). When filtering variants, we included nonsynonymous, nonsense, frameshift, splice, non-stop, non-start, and in-frame variants with frequencies between 30% and 100%, as well as synonymous or intronic variants affecting consensus splice sites. Variants with minor allele frequencies $<1.0\%$ in population studies (1000 Genomes, Exome Assembly Consortium database http://exac.broadinstitute.org/, Exome Sequencing Project, Genome Assembly Database) were included. We confirmed candidate variants in probands and their parents by NGS or Sanger sequencing. We assessed the pathogenicity of all novel variants using in silico prediction tools (MutationTaster http://www.mutationtaster.org, Human Splicing Finder https://www.genomnis.com/access-hsf, Provean http://provean.jcvi.org/index.php, SIFT http://sift.jcvi.org/, and PolyPhen2 http://genetics.bwh.harvard.edu/pph2/), DECIPHER (https://decipher.sanger.ac.uk/), ClinVar (https://www.ncbi.nlm.nih.gov/clinvar), HGMD (http://www.hgmd.cf.ac.uk/ac), OMIM (https://www.omim.org/), PubMed (http://www.ncbi.nlm.nih.gov/pubmed), and the American College of Medical Genetics and Association for Genomic and Molecular Pathology (ACMG-AMP) criteria (Richards et al. 2015).

2.1 | Variant Validation

In interpreting the variants, the patient's clinical findings, the inheritance model, the way the detected variant affects the gene function, and de novo detection are some of the important methods we used to confirm the diagnosis.

In the analysis of WES results, variants compatible with the phenotypes of the patients were reported. All genes related to the relevant Human Phenotype Ontology (HPO) terms, such as neurodevelopmental delay (HP:0012758), neurodevelopmental abnormality (HP:0012759), global developmental delay (HP:0001263), intellectual disability (HP:0001249), and nervous system abnormality (HP:0000707), were used in all analyzed patients. Other findings, such as the presence of seizures (HP:0001250), dystonia (HP:0001332), facial dysmorphism (HP:0001999), hypotonia (HP:0001252), etc. were used

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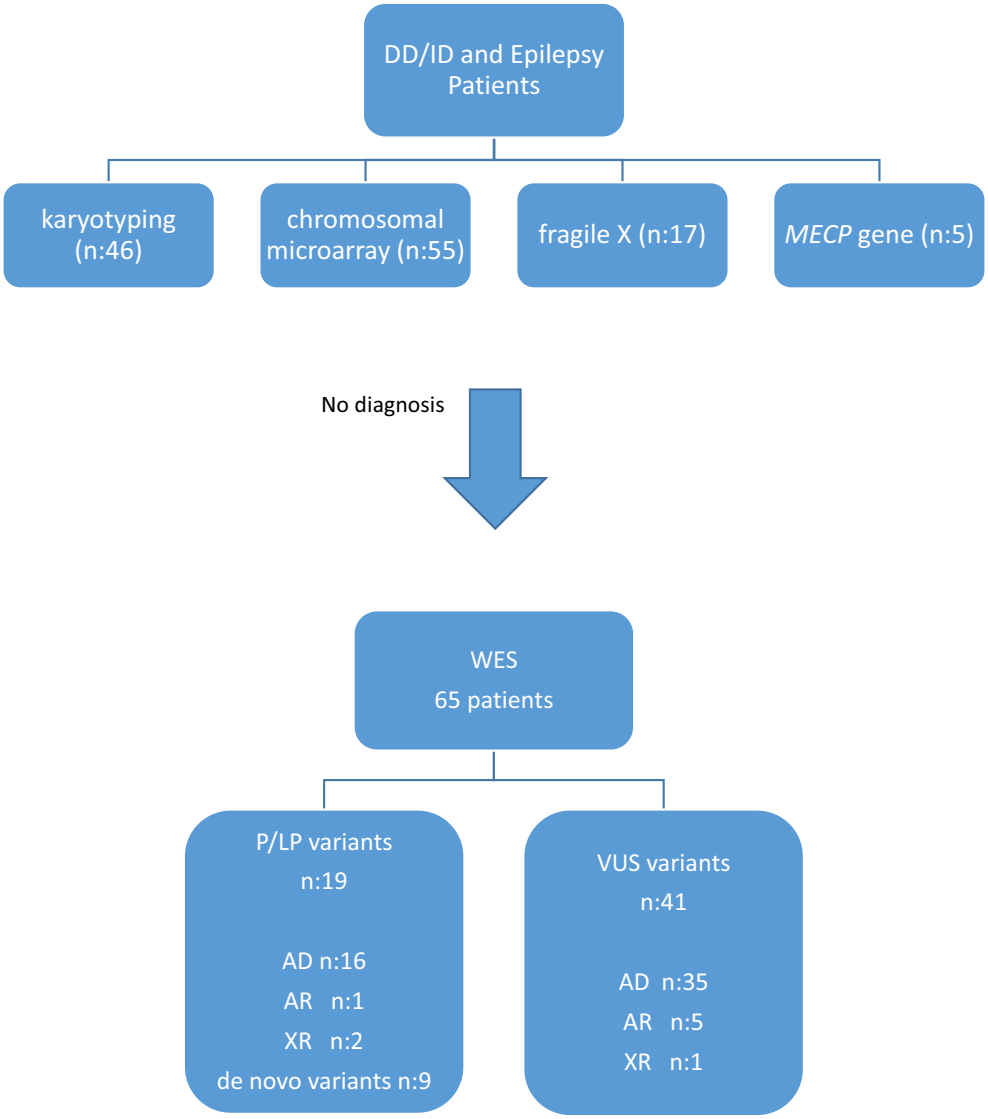


FIGURE 1 | Genetic analyses and results in patients with DD/ID, Epilepsy.

according to the complaints of the patients. Variants with minor allele frequencies below 0.05 were classified according to ACMG criteria (Richards et al. 2015).

2.2 | Statistical Analyses

The Chi-square test was conducted to analyse the results statistically via the IBM SPSS Statistics 27 program.

3 | Results

The WES results of 65 patients with DD/ID and epilepsy were evaluated retrospectively. Of the 65 patients, 36 were males and 29 were females, with an average age of 8 (1–18 years). The clinical findings of the patients are summarized in Figure 2.

The most common symptom was epilepsy, detected in 45 patients (69.2%), followed by DD/ID, which was detected in 39 patients (60%). The number of autosomal dominant variants was 51 (81%), the number of autosomal recessive variants was 6 (9.5%), and the number of X-linked variants was 3 (4.8%) (Figure 2).

Nineteen pathogenic/likely pathogenic (P/LP) variants were identified in 19 patients (31.2%), and with the confirmation made in the parents and probands, 9 variants were determined to be de novo (Table 1). Forty-one (65.1%) VUS variants were also identified (Figures 1 and 2 and Table 2).

Patients underwent additional genetic analyses before the WES study, including karyotyping (n:46), chromosomal microarray (n:55), fragile X (n:17), *MECP* gene (n:5), and MS-MLPA for Angelman/Prader Willi ($n = 2$), and all reports are summarized in Figure 1.

In patient 19, a LP heterozygous c.142T>C (p.Cys48Arg) variant was detected in exon 2 of the BCL11A gene, causing BCL11A-associated intellectual disability (Figure 3). Moreover, the hemoglobin electrophoresis showed that the patient's HbF value was high whereas both parents exhibited normal results (Figure 4).

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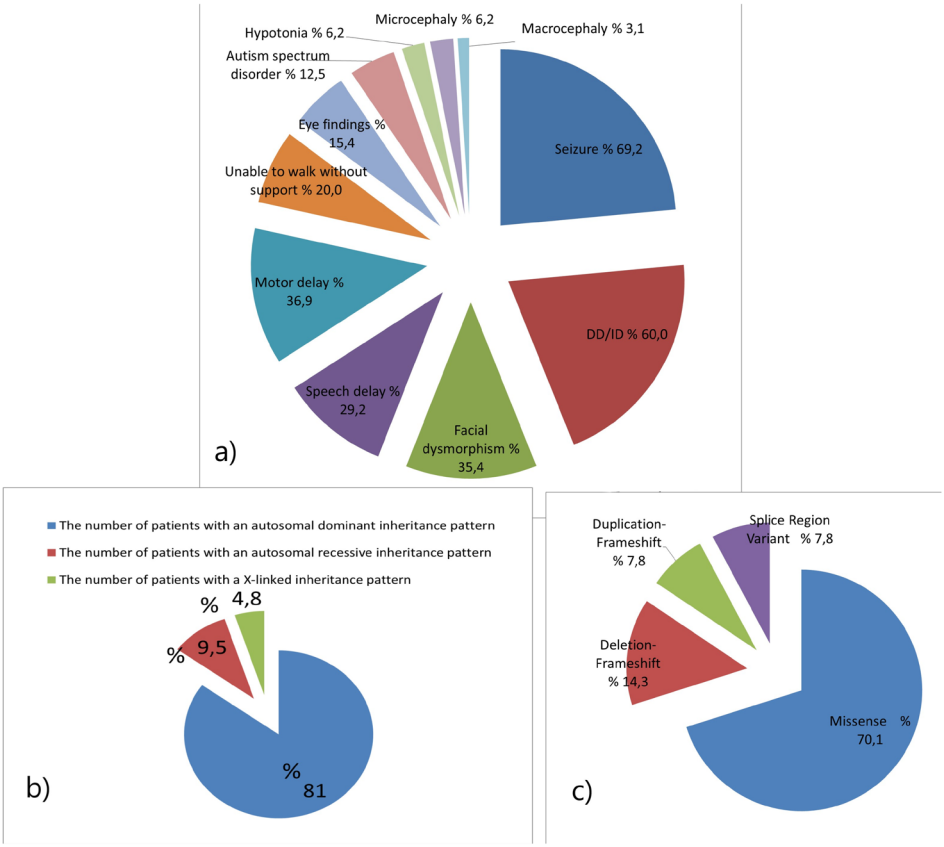


FIGURE 2 | (a) Clinical findings of the patients. (b) Inheritance patterns of the variants identified. (c) Types of mutations identified.

4 | Discussion

NGS is an important diagnostic tool with a 25%–65% diagnostic rate by parallel sequencing of a large number of genes, compared to a 21% diagnostic rate for standard genetic tests. In 2021, ACMG recommended genome-wide sequencing (exome/genome sequencing) as a first- or second-tier test for patients with DD/ID (Bowling et al. 2017).

The number of patients diagnosed in this study was determined as 19 patients (31.2%). Jo et al. (Jo et al. 2024) published a retrospective study involving 41 patients diagnosed with DD/ID, with a diagnostic rate of 48.8%. In another study, Ballesta-Martínez et al. (2023) reported a 34% diagnostic rate in 188 patients diagnosed with unexplained ID via WES analysis (Ballesta-Martínez et al. 2023).

BCL11A-ID is inherited as an autosomal dominant and occurs as a result of heterozygous variants in the BCL11A gene. BCL11A plays an important role in neurodevelopmental processes in the human brain. Moreover, BCL11A internal zinc finger domains selectively bind to g-globin promoter motifs, thus acting as a transcriptional repressor of fetal hemoglobin. A 9-year-old male patient, the third child of unrelated parents, was referred to our clinic due to language delay and ID. Clinical examination revealed microcephaly, DD/ID, hypermetropia, strabismus, scoliosis, and behavioral problems. The patient's first intelligible word was spoken at the age of 2, he can only form simple three-word sentences. In all patients diagnosed with BCL-11A-ID, HbF values were determined to be above the maximum reference for age in hemoglobin electrophoresis or high-performance liquid chromatography (HPLC) results. In light of this information, hemoglobin electrophoresis showed that our patient's HbF was high (Figure 1). This case (Patient 19) is the first Turkish patient diagnosed with BCL11A-ID with a heterozygous variant. c.143G>T (p.Cys48Phe) missense pathogenic variant occurring on another base affecting the same amino acid has been reported in patients previously diagnosed with BCL11A-ID. Microcephaly was not observed in the clinical findings of the patient with this variant reported by Dias et al. We expanded the clinical spectrum of 25 unique BCL11A pathogenic variants reported in the literature to date (14 frameshift, 4 missense, and 7 nonsense) with a missense variant (Dias et al. 2016; Shu et al. 2025). The patient underwent WES and then sanger sequence analysis for confirmation. This variant was not detected in the BCL11A gene in the segregation analysis performed with sanger sequence analysis (Table 1).

Another case (patient 17) diagnosed with a de novo variant was a 2-year-old boy with a diagnosis of epilepsy and hypotonia who was diagnosed using an additional sex comb-like 3 (ASXL3)-related disorder. The ASXL genes (ASXL1 on 20q11.21, ASXL2 on 2p23.3, and ASXL3 on 18q12.1) encode a regulator of the Drosophila additional sex comb (Asx) genes Polycomb group repressor complex (PRC). Pathogenic variants in ASXL1 and ASXL2, as well as in ASXL3, have been implicated in inherited neurological disorders, malignancies, and congenital heart disease (Srivastava et al. 2016). In most cases, loss-of-function variants in the ASXL3 gene have been reported and a dominant negative effect of functional haploinsufficiency has been observed to be responsible for pathogenicity. Bainbridge-Ropers

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TABLE 1 | Significant and diagnostic P/LP variations determined by WES.

	Gene, zygosity, gender	Chromosomal position (hg38)	Accession number	Nucleotide alteration	Aminoacid alteration	Classification	Inheritance	Clinical features	Mother/ Father affected	Diagnosis
1	ERMARD, heterozygous, male	chr6:170176071 CTT->C	NM_018341.3	c.1432_1433del	p.Leu478AspfsTer7	LP	AD	DD/ID, Seizures, Autism, Delayed speech, motor delay	ND	OMIM# 615544 Periventricular Nodular Heterotopia 6; PVNH6
2	TSC1, heterozygous, male	chr9:132910576	NM_000368	c.1257del	p.Arg420GlyfsTer20	P	AD	DD/ID, Seizures, Delayed speech	De-novo	OMIM# 191100 Tuberous Sclerosis 1; TSC1
3	PRRT2, heterozygous, male	chr16:29813694	NM_145239	c.649dup	p.Arg217ProfsTer8	P	AD	Seizures	Paternal heterozygous	OMIM# 614386 Proline-Rich Transmembrane Protein 2; PRRT2
4	TUBA1A, heterozygous, male	chr12:49186833 G->A	NM_006009	c.4C>T	p.Arg2Cys	P	AD	DD/ID, Seizures	ND	OMIMD# 611603 Lissencephaly 3; LIS3
5	ANKRD11, heterozygous, male	chr16:89282151 TTC->T	NM_013275	c.4389_4390del	p.Lys1464ThrfsTer89	P	AD	DD/ID, Seizures, Hypotonia, Long curly eyelashes, Retrognathia	Maternal heterozygous	OMIM# 148050 KBG Syndrome; KBGS
6	SETD1B, heterozygous TMEM70, heterozygous, male	chr12:121825200 C->G chr8:73981196 AC->A	NM_001353345 NM_017866	c.5171C>G c.359del	p.Ser1724Cys p.Thr120AsnfsTer34	VUS P	AD AR	Seizures	Maternal heterozygous	# 619000 Intellectual developmental disorder with seizures and language delay; IDDSELD
7	SPR, heterozygous SCN1A, heterozygous, female	chr2:72891338 ATCCTCTAGG->A chr2:166073542 C->G	NM_003124 NM_001165963	c.596-_602del c.80G>C	p.Arg27Thr	LP VUS	AD AD	Seizures	Paternal heterozygous	OMIM# 604352 Febrile Seizures, Familial, 4; FEB4

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TABLE 1 | (Continued)

	Gene, zygosity, gender	Chromosomal position (hg38)	Accession number	Nucleotide alteration	Aminoacid alteration	Classification	Inheritance	Clinical features	Mother/ Father affected	Diagnosis
8	DCX, heterozygous, female	chrX:111410251 T->C	NM_001195553	c.148A>G	p.Lys50Glu	LP	XR	DD/ID, Seizures, Delayed ability to walk, Double Cortex	De-novo	OMIM# 300067 Lissencephaly, X-linked, 1; LISX1
9	ANKRD11, heterozygous, male	chr16:89348200 C->A	NM_001256182	c.4750G>T	p.Glu1584Ter	P	AD	DD/ID, Short stature, Triangular face	De-novo	OMIM #611192 KBG Syndrome
10	DLG3, hemizygous, male	chrX:70445397 AC->	NM_021120	c.201del	p.Thr68ProfsTer53	LP	XR	DD/ID, Hypotonia, Microcephaly	De-novo	OMIM# 300850 Intellectual developmental disorder, X-linked 90; XLID90
11	SCN1A, heterozygous, female	chr2:166894588 T->A	NM_001165963	c.2644A>T	p.Ile882Phe	LP	AD	Seizures	De-novo	OMIM# 607208 Dravet Syndrome; DRVT
12	PRRT2, heterozygous, male	chr16:29825657 C->T	NM_001256442	c.883C>T	p.Arg295Trp	LP	AD	Seizures	ND	OMIM#602066 Convulsions, familial infantile, with paroxysmal choreoathetosis OMIM#605751 Episodic kinesigenic dyskinesia 1 Seizures, benign familial infantile, 2
13	SCN1A, heterozygous, female	chr2-166009736 G>A	NM_006920.4	c.3952C>T	p.(Arg1318Ter)	P	AD	Seizures	De-novo	OMIM# 607208 Dravet Syndrome; DRVT

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TABLE 1 | (Continued)

	Gene, zygosity, gender	Chromosomal position (hg38)	Accession number	Nucleotide alteration	Aminoacid alteration	Classification	Inheritance	Clinical features	Mother/ Father affected	Diagnosis
14	RYR1, heterozygous, female	chr19:39075643 G->A	NM_000540.3	c.14707G>A	p.Glu4903Lys	LP	AD	DD/ID, Seizures, hypotonia, dysphagia	ND	OMIM# 117000 Congenital myopathy 1A, autosomal dominant, with susceptibility to malignant hyperthermia; CMYO1A
15	SHANK3, heterozygous, female	chr22-51160784-CG	NM_001372044.2	c.4711_4712del	p.Arg1571fs	LP	AD	Seizures, Autism, Delayed Speech	De-novo	OMIM#606232 Phelan-Mcdermid Syndrome; PHMDS
16	TTN, heterozygous DYNC1H1, homozygous, male	chr2-178678746 C>T chr14-102002911 A>G	NM_001267550.2 NM_001376.4	c.33826 + 1 G>A c.4829A>G		P VUS	AD AD	DD/ID, Seizures	Parents: Heterozygous	OMIM#614228 charcot–marie–tooth disease, Axonal, Type 2O
17	ASXL3, heterozygous, male	chr18:31323425 G->T	NM_030632.2	c.3613G>T	p.(Glu1205Ter)	P	AD	Seizures, Hypotonia	De-novo	OMIM# 615485 Bainbridge-Ropers Syndrome; BRPS
18	PRRT2, heterozygous BEST1, heterozygous, female	chr16:29813694 GCCC->G chr11:61958195 G->A	NM_145239 NM_004183	c.647_649del c.764G>A	p.Pro216del p.Arg255Gln	VUS LP	AD AD	Seizures, Cataract	ND	OMIM#614386 Proline-Rich Transmembrane Protein 2; PRRT2 OMIM# 607854 Bestrophin 1; BEST1
19	BCL11A, Heterozygous, male	chr2-60,546,214 A>G	NM_022893.4	c.142T>C	p.Cys48Arg	LP	AD	DD/ID, microcephaly, high HbF	De-novo	OMIM# 617101 Dias-Logan Syndrome. BCL11A-ID

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; LP, likely pathogenic variant; ND, not done; P, pathogenic variant; VUS, variant of uncertain significance; XR, X-linked recessive.

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TABLE 2 | VUS variants identified by WES.

	Gene, zygosity, gender	Chromosomal position (hg38)	Accession number	Nucleotide alteration	Aminoacid alteration	Classification	Inheritance	Clinical features	Mother/ Father affected	OMIM
1	ADGRV1, heterozygous, female	chr5:90774294 C->G	NM_032119	c.12394C>G	p.Pro4132Ala	VUS	AD	Seizures	Paternal heterozygous	OMIM# 604352 Febrile Seizures, Familial, 4; FEB4
2	CACNA1H, heterozygous, female	chr16:1259078	NM_021098.3	c.3422_3442del	p.Arg1141_Ser1147d	VUS	—	Seizures	Maternal heterozygous	OMIM# 611942 Epilepsy, childhood absence, susceptibility to, 6; ECA6
3	NFIA, heterozygous, male	chr1:61818226	NM_001134673.4	c.940A>G	p.Thr314Ala	VUS	AD	DD/ID, Seizures, Autism	De-novo	OMIM# 613735 Brain malformations with or without urinary tract defects; BRMUTD
4	DLL1, heterozygous, female	chr6:170283376	NM_005618.4	c.1903C>T	p.Arg635Cys	VUS	AD	DD/ID, Seizures, Speech and motor delay	Maternal heterozygous	OMIM# 618709 Neurodevelopmental disorder with nonspecific brain abnormalities and with or without seizures; NEDBAS
5	GABRD, heterozygous, female	chr1:2019430	NM_00081	c.7G>T	p.Ala3Ser	VUS	AD	Seizures	ND	OMIM# 613060 Epilepsy, idiopathic generalized, susceptibility to, 10; EIG10
6	CACNA1E, heterozygous, female	chr1:181580630	NM_001205293	c.805G>A	p.Gly269Ser	VUS	AD	Seizures	Maternal heterozygous	
7	GABRD, heterozygous, female	chr1:2029753 G->A	NM_000815.5	c.1081G>A	p.Glu361Lys	VUS	AD	Seizures	ND	
8	SCN1A, heterozygous, female	chr2:166073542 C->G	NM_001165963	c.80G>C	p.Arg27Thr	VUS	AD	Seizures	Paternal heterozygous	OMIM# 604352 Febrile Seizures, Familial, 4; FEB4

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TABLE 2 | (Continued)

	Gene, zygosity, gender	Chromosomal position (hg38)	Accession number	Nucleotide alteration	Aminoacid alteration	Classification	Inheritance	Clinical features	Mother/ Father affected	OMIM
9	CHD2, heterozygous, female	chr15:92941956G->GT	NM_001271	c.826+2dup	—	VUS	AD	DD/ID, seizures	De novo	OMIM# 615369 Developmental And Epileptic Encephalopathy 94; DEE94
10	—	—	—	—	—	—	—	Seizures	—	—
11	HCN2, heterozygous, female	chr19:613899G->C	NM_001194	c.1873G>C	p.Asp625His	VUS	AD	Seizures	ND	OMIM# 602477 Epilepsy, Idiopathic Generalized, Susceptibility to, 17; EIG17
12	RELN, heterozygous, male	chr7:103650378T->C	NM_005045	c.1898A>G	p.Asn633Ser	VUS	AD	DD/ID, Seizures	ND	—
13	KMT2A, heterozygous, male	chr11:118373528G->C	NM_001197104.2	c.6921G>C	p.Lys2307Asn	VUS	AD	DD/ID, seizures, delayed speech, delayed ability to walk, strabismus, hypermetropia	ND	—
14	KIF26A, homozygous	chr14:104642436G->A	NM_015656.2	c.3311G>A	p.Ser1104Asn	VUS	AR	DD/ID, Seizures, hypotonia, dysphagia, microcephaly, cerebral cortical atrophy	Maternal and paternal heterozygous	
15	SMARCA4, heterozygous, male	ENST00000254250	NM_003072.5	c.3532T>C	p.Trp1178Arg	VUS	AD	DD/ID, delayed speech	De novo	OMIM#603254:Coffin-Siris Syndrome

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TABLE 2 | (Continued)

	Gene, zygosity, gender	Chromosomal position (hg38)	Accession number	Nucleotide alteration	Aminoacid alteration	Classification	Inheritance	Clinical features	Mother/ Father affected	OMIM
16	CNOT3, heterozygous, female	chr19:54152908 A->C	NM_014516	c.1946A>C	p.His649Pro	VUS	AD	DD/ID, Delayed speech, delayed ability to walk	De novo	
17	ARX, hemizygous, male	chrX:25013157 C->G	NM_139058	c.838G>C	p.Ala280Pro	VUS	XR	DD/ID, hypotonia, motor delay	Maternal heterozygous	OMIM #300382 Aristaless-Related Homeobox, X-linked; ARX
18	ATM, homozygous, female	chr11:108236087 G->A	NM_000051.3	c.9023G>A	p.Arg3008His	VUS	AR	DD/ID, ataxia, hypotonia, motor delay, telangiectasia, conjunctival	ND	OMIM#208900 Ataxia-telangiectasia; AT
19	MARCHF6, heterozygous	chr5:10390581 C->T	NM_005885	c.545C>T	p.Pro182Leu	VUS	AD	DD/ID, seizures, delayed speech, delayed ability to walk, right hemiplegia	ND	
20	MED13, heterozygous, female	chr17:60033044 G->C	NM_005121	c.5779C>G	p.Pro1927Ala	VUS	AD	Autism	ND	OMIM# 618009 Intellectual developmental disorder, autosomal dominant 61; MRD61
21	IRF2BPL, heterozygous, male	chr14:77493788 CTGCTGT>TTGCTGC	NM_024496	c.342_348delins GCAACAGC	p.Gln121_Gln127dup	VUS	AD	DD/ID, delayed speech, delayed ability to walk, motor delay	Paternal heterozygous	—
22	—	—	—	—	—	—	—		—	—
23	PRICKLE1, homozygous, male	chr12:42858443 T->C	NM_153026	c.1393A>G	p.Lys465Glu	VUS	AR	Seizures	ND	OMIM# 612437 Epilepsy, Progressive Myoclonic, 1B; EPM1B

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TABLE 2 | (Continued)

	Gene, zygosity, gender	Chromosomal position (hg38)	Accession number	Nucleotide alteration	Aminoacid alteration	Classification	Inheritance	Clinical features	Mother/ Father affected	OMIM
24	RANBP2, heterozygous, female	chr2:109345615 A->C	NM_006267	c.100A>C	p.Lys34Gln	VUS	AD	DD/ID, seizures	Maternal heterozygous	OMIM# 608033 Encephalopathy, Acute, Infection-Induced, Susceptibility To, 3; IIAE3
25	NEDD4L, heterozygous, female	chr18:56050547 A->ATT	NM_001144967	c.2423_2424insTT	p.Asp809SerfsTer3	VUS	AD	DD/ID, seizures, delayed speech, delayed ability to walk, hypotonia, hydrocephalus	Paternal heterozygous	OMIM# 617201 Periventricular Nodular Heterotopia 7; PVNH7
26	CACNA1E, heterozygous, female	chr1:181687263 G->A	NM_001205293	c.1598G>A	p.Arg533His	VUS	AD	Seizures	Paternal heterozygous	
27	USP25, heterozygous, male	chr21:17250269 T->C	NM_001283041	c.3164T>C	p.Met1055Thr	VUS	AD	Seizures	ND	OMIM# 621064 Epilepsy, Idiopathic Generalized, Susceptibility To, 19; EIG19
28	RELN, heterozygous, female	chr7:103141316 T->C	NM_005045	c.8543A>G	p.Asp2848Gly	VUS	AD	Seizures	Paternal heterozygous	OMIM# 616436 Epilepsy, Familial Temporal Lobe, 7; ETL7
29	RELN, heterozygous, male	chr7-103498074 T>G	NM_005045.4	c.8843+3A>C		VUS	AD	DD/ID, seizures, hypotonia, delayed speech, delayed ability to walk, dysphagia	ND	OMIM# 616436 Epilepsy, Familial Temporal Lobe, 7; ETL7
30	SBF1, homozygous, female	chr22:50893287 T->C	NM_002972	c.4768A>G	p.Thr1590Ala	VUS	AR	Seizures, miyopati	Parents: heterozygous	OMIM# 615284 Charcot–Marie–Tooth Disease, Demyelinating, Type 4B3; CMT4B3

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TABLE 2 | (Continued)

	Gene, zygosity, gender	Chromosomal position (hg38)	Accession number	Nucleotide alteration	Aminoacid alteration	Classification	Inheritance	Clinical features	Mother/ Father affected	OMIM
31	KCNT1, heterozygous, female	chr9:138649062 C->T	NM_020822	c.661C>T	p.Pro221Se	VUS	AD	DD/ID	De novo	OMIM# 614959 Developmental and Epileptic Encephalopathy 14; DEE14
32	PACS1, heterozygous, female	chr11:65983614 G->A	NM_018026	c.685G>A	p.Ala229Thr	VUS	AD	DD/ID, delayed speech	ND	OMIM# 615009 Schuurs-Hoeijmakers Syndrome; SHMS
33	TBC1D24, heterozygous, male	chr16-2496299 C>T	NM_001199107.1	c.151C>T	p.(Arg51Trp)	VUS	AD	DD/ID, delayed speech, cafe au late, deafnes	Maternal heterozygous	—
34	SOX11, heterozygous, female	chr2:5833298	NM_003108	c.456_467dup	p.Gly153_Gly156dup	VUS	AD	Microtia, preauricular skin tags, postaxial polydactyly, elbow flexion contractures, camptodactyly of finger	ND	—
35	FRRS1L, homozygous, female	chr9:111899801 GA->G	NM_014334	c.968del	p.Phe323SerfsTer9	VUS	AR	DD/ID, hypotonia, delayed speech, delayed ability to walk	Parents heterozygous	OMIM#616981 Developmental and Epileptic Encephalopathy 37; DEE37
36	TCF12, heterozygous, female	chr15:57574709 C->A	NM_207037	c.2045C>A	p.Ser682Ter	VUS	AD	Hypotonia, microcephaly	Paternal heterozygous	OMIM#615314 Craniosynostosis 3; CRS3
37	KMT2C, heterozygous, male	chr7:151878169 G->A	NM_170606	c.6776C>T	p.Pro2259Leu	VUS	AD	DD/ID, delayed speech, hypermetropia	Maternal heterozygous	—

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TABLE 2 | (Continued)

	Gene, zygosity, gender	Chromosomal position (hg38)	Accession number	Nucleotide alteration	Aminoacid alteration	Classification	Inheritance	Clinical features	Mother/ Father affected	OMIM
38	ADGRL1, heterozygous, male	chr19:14273961 C->T	NM_001008701	c.667G>A	p.Val223Ile	VUS	AD	DD/ID, myopia	ND	OMIM#620065 Developmental delay, behavioral abnormalities, and neuropsychiatric disorders; DEDBANP
39	KCNB1, heterozygous, male	chr20:48098758 C->T	NM_004975	c.260G>A	p.Arg87His	VUS	AD	DD/ID, autism	ND	—
40	HNRNPU, heterozygous, male	chr1:245026995 C->G	NM_031844.3	c.615G>C	p.Gln205His	VUS	AD	DD/ID, seizures	Maternal heterozygous	—

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; LP, likely pathogenic variant; ND, not done; P, pathogenic variant; VUS, variant of uncertain significance; XR, X-linked recessive.

syndrome (OMIM #615485) develops as a result of de novo truncation or nonsense mutation in the *ASXL3* gene located on chromosome 18q12.1 (Balasubramanian et al. 2017; Orphanet 2021; Yang et al. 2020). This case is the first Turkish patient reported so far, but the number of BRPS cases in the literature is 124, and a total of 92 separate variants have been identified in the ASXL3 gene. A de novo heterozygous pathogenic loss-of-function mutation in the ASXL3 gene in patient NM_030632.2 c.3613G>T p.(Glu1205Ter) has been previously reported in the literature (Ling et al. 2024). The patient underwent WES and then sequence analysis for confirmation. This variant was not detected in the *ASXL3* gene in the segregation analysis performed with sequence analysis (Table 1).

A pathogenic variant was detected in the *ANKRD11* gene in another patient (patient 9) diagnosed with DD/ID and short stature, a 4-year-old boy with dysmorphic findings such as hyperopia, strabismus, macrocephaly, and a triangular face, pointed nose structure, and slightly protruding ears (Table 1). KBG syndrome (OMIM#148050), which is characterized by extensive phenotypic findings, shows an autosomal dominant inheritance pattern with craniofacial findings and skeletal findings such as short stature, delayed bone age, and various rib and spine abnormalities, in addition to intellectual disability (Martinez-Cayuelas et al. 2023; Gao et al. 2022). A novel de novo heterozygous mutation in the *ANKRD11* gene (NM_001256182.2 c.4750G>T) was identified, which has not been previously reported in the literature. The case we present contributes to the expansion of the spectrum of genetic variants associated with KBG syndrome with a previously unreported variant and also broadens the clinical approach to this rare genetic syndrome. The patient underwent WES and then sequence analysis for confirmation. This variant was not detected in the *ANKRD11* gene in the segregation analysis performed by sequence analysis in the patient's parents. In another patient (patient 5) with DD/ID, seizures, hypotonia, long curly eyelashes, and retrognathia findings, the pathogenic variant NM_013275 c.4389_4390del, previously reported in the literature, was detected in the ANKRD11 gene (Table 1; Alfieri et al. 2019).

Additionally, we identified a variant in the *SHANK3* gene in a 9-year-old male patient (patients 15) diagnosed with epilepsy and ASD (Table 1). Phelan-McDermid Syndrome (OMIM#606232) is a disease characterized by neonatal hypotonia, absence or severe delay in speech, developmental delay, and mild dysmorphic facial features (Coo et al. 2023; Frank 2021). In the analyses performed, a novel de novo likely pathogenic heterozygous mutation was detected in the *SHANK3* gene, NM_001372044.2 c.4711_4712del, which has not been previously documented in the literature. The patient underwent WES and then sequence analysis for confirmation. This variant was not detected in the *SHANK3* gene in the segregation analysis performed with sequence analysis.

DLG3 has been identified as one of the causes of X-linked intellectual disability (XLID-90; OMIM# 300850). Synapse-associated protein 102 (SAP102), encoded by the DLG3 gene (OMIM #300189), plays a role in the proliferation and regulation of neurons in the brain, particularly in the cortex. N-methyl-D-aspartate receptor (NMDAR) genes are known to be associated

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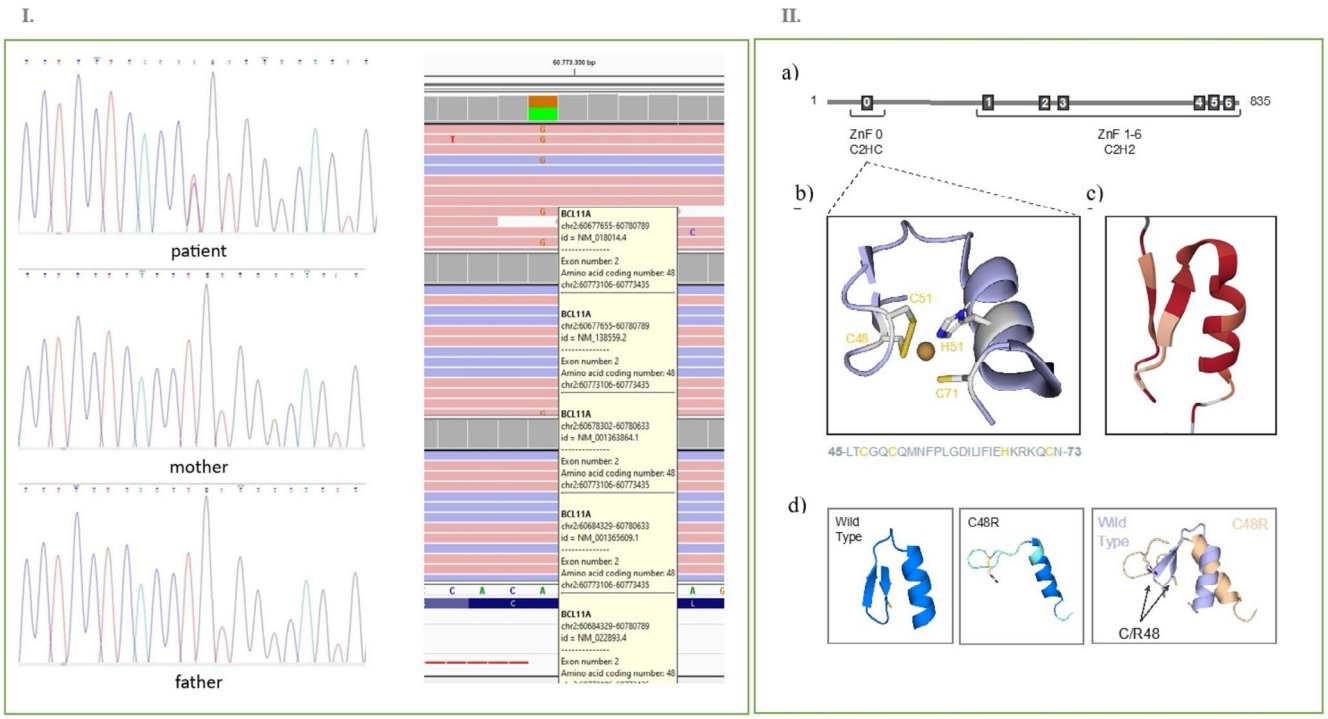


FIGURE 3 | (I) NGS and Sanger sequencing results in the patient and his parents. The likely pathogenic variant in the BCL11A gene (c.143G>T) is illustrated in the IGV figure of the BAM file of the proband and his parents. (II) In silico analysis of p.Cys48Arg (C48R) mutation in BCL11A. (a) Relative positions of zinc finger domains in BCL11A. Single C2HC (ZnF 0) and six C2H2 (ZnF1-6) domains represented. (b) NMR structure of ZnF0 (9BV0), functional residues of zinc finger domain shown as sticks and highlighted with yellow in the sequence. (c) ZnF 0 domain residues colored according to pathogenicity scores predicted by AlphaMissence. Benign, uncertain, and pathogenic scores colored in blue, white, and red, respectively. (d) Structure predictions of wild type (left) and mutant (middle) ZnF 0 domain, colored according to confidence scores provided by AlphaFold3. Superposition of wild type and mutant ZnF 0 (left).

with NDD and epilepsies. Furthermore, several studies have investigated whether DLG3 is classified among the NMDAR genes and its effect on phenotype (Alavanda and Çıkı 2025). We identified a novel pathogenic variant in the DLG3 gene in a 1-year-old boy with DD/ID, microcephaly, and hypotonia (patient 10) (Table 1). In the analyses performed on our patient, a new de novo pathogenic heterozygous mutation, named NM_021120 c.201del, was detected in the DLG3 gene, which has not been previously reported in the literature. The patient with the DLG3 variant had findings of DD/ID but no diagnosis of epilepsy. We present this case, which will contribute to the genotype–phenotype spectrum of DLG3 variants.

Broader genomic approaches such as WES, a broad genotyping tool, help to discover clinically relevant disease-causing and particularly novel variants. Therefore, WES enables the identification of genetic heterogeneity conditions, rare syndromes, and newly identified genes such as DD/ID and epilepsy that cannot be detected by other conventional genetic tests (Ankala et al. 2015). When evaluated in conjunction with the clinical findings of the patients, P/LP and VUS variants were assessed in the diagnosis based on segregation results and according to the ACMG criteria. Given the high number of VUS variants and the evolving nature of genomic interpretation, scheduled follow-up and re-reporting may facilitate reanalysis for updates on phenotypic evolution and possible variant reclassification.

This study has limitations. Firstly, the inability to perform sequence analysis verification and segregation analyses on all patients. Additionally, the limited cohort size was another limitation. For this reason, we suggest that functional investigations should be conducted in larger patient populations to ascertain the pathogenicity of variants of uncertain significance.

5 | Conclusion

The use of WES in the diagnosis of DD/ID and epilepsy patients, a group of genetically heterogeneous diseases with etiologies, was validated. In this study, the patient population was carefully selected from cases suspected of genetic disorders which is believed to have contributed to the observed increase in the rate of genetic diagnosis obtained using WES. WES analyses can be crucial for patients with DD/ID and epilepsy, a genetically heterogeneous group with syndromes identified in the etiology. WES analyses will enhance our understanding of the diagnosis of rare syndromes and facilitate genetic counseling, patient access to accurate information, and prenatal diagnosis. In cases of highly prevalent disorders such as DD/ID and epilepsy, determining the genetic diagnosis of patients is of great importance in providing accurate information to families and enabling appropriate interventions for patient follow-up and management (Ankala et al. 2015; Xiang et al. 2021).

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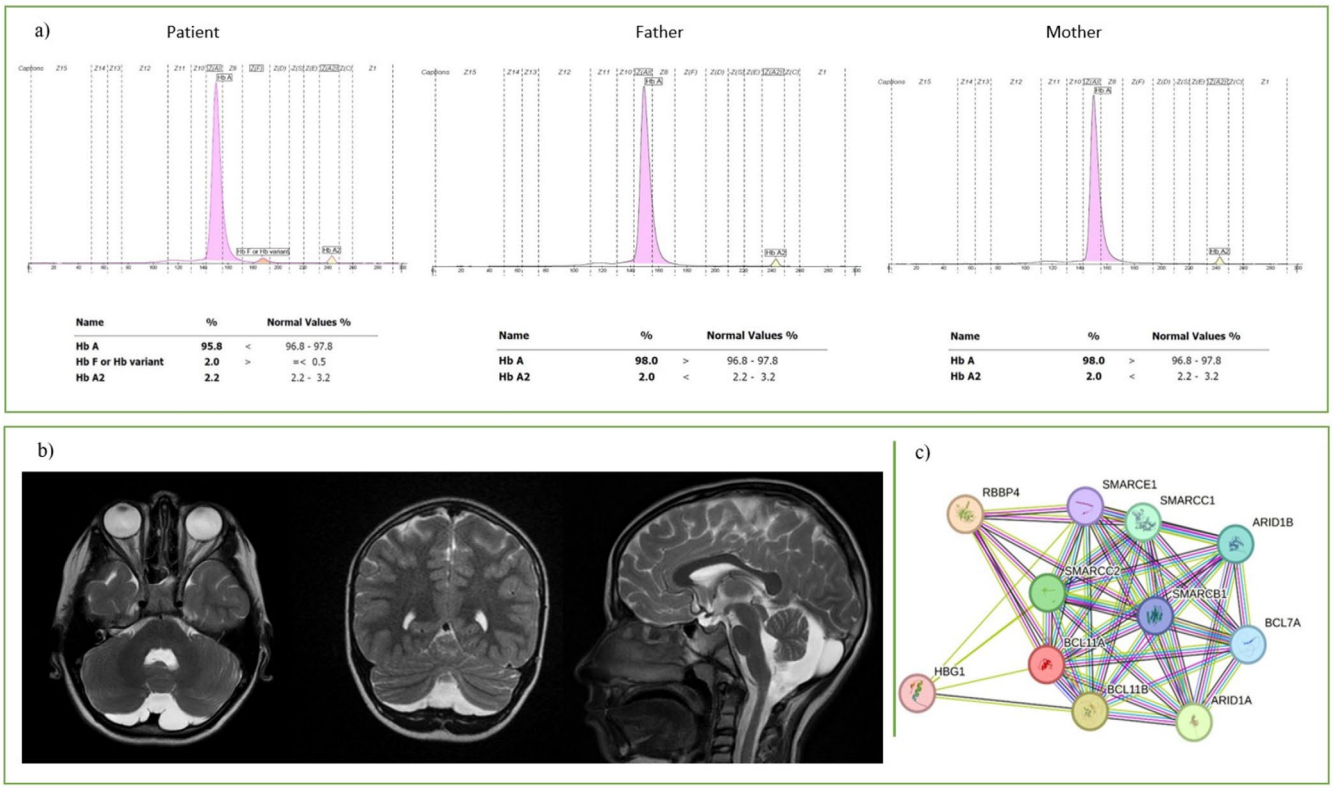


FIGURE 4 | (a) As a result of hemoglobin electrophoresis, the patient's HbF levels are high, and both parents have normal values. (b) T2-weighted images show congenital changes in the mega cistern magna from the retrocerebellar cisternal distance and mild hypoplasia in the lower cerebellar vermis. The 4th ventricle is slightly dilated. Cerebellar sulci were widened secondary to mild cerebellar atrophy. There is slight elongation in the sagittal T2A image. (c) Connections of the BCL11A gene with the HBGB1 gene and other genes.

Author Contributions

N.A., A.C., S.G., E.G., P.D., I.B.: conceptualization, methodology, software, validation, formal analysis, investigation and data collection, writing – original draft preparation, writing – review and editing. All authors have read and approved the published version of the article.

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The authors have nothing to report.

Ethics Statement

This study was approved by the Medical Ethics Committee of the Faculty of Medicine of Tokat Gaziosmanpasa University (Approval No: 25-MOBAEK-130). All procedures were performed in accordance with the ethical standards of the Declaration of Helsinki.

Consent

Informed consent was obtained from all participants' familiars in the study.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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