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Effects of the Missense Variants on Complete Phenotype and Splicing Variant on Severe Growth Retardation in the *BPTF* Gene

Gül Ünsel-Bolat[1] | Hamide Betul Gerik-Celebi[2] | Betül Diler Durgut[3] | Ayberk Türkyılmaz[4] | Hilmi Bolat[5]

[1]Department of Child and Adolescent Psychiatry, Balıkesir University Faculty of Medicine, Balıkesir, Turkey | [2]Department of Medical Genetics, Balıkesir Ataturk City Hospital, Balıkesir, Turkey | [3]Department of Pediatrics, Division of Child Neurology, University of Giresun, Giresun, Turkey | [4]Department of Medical Genetics, Karadeniz Technical University Faculty of Medicine, Trabzon, Turkey | [5]Department of Medical Genetics, Balıkesir University Faculty of Medicine, Balıkesir, Turkey

Correspondence: Gül Ünsel-Bolat (gul.unsel.bolat@gmail.com)

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ABSTRACT

Neurodevelopmental disorder with dysmorphic facies and distal limb anomalies (NEDDFL, OMIM no #617755) is an ultra-rare syndrome associated with heterozygous pathogenic variants in the *BPTF* gene. Haploinsufficiency of the *BPTF* gene, a chromatin remodeling gene that is related to epigenetic modification, is the cause of this disease.

BPTF gene variants were detected using whole-exome sequencing. Family segregation analysis was performed using sanger sequencing.

This study reported three variants, c.2812+1G>C, c.6022G>A, and c.6416G>A in the *BPTF* gene. The variations of the c.6022G>A and c.2812+1G>C have not been previously reported in variant types observed at the *BPTF* gene in sources including Genome Aggregation Database (gnomAD), Leiden Open Variation Database (LOVD), Human Gene Mutation Database (HGMD), and ClinVar.

We detected two novel missense variants in patients presenting all phenotypic characteristics of the *BPTF*-related NEDDFL syndrome severely, including severe ID, distinctive facial features, and anomalies of the hands and feet. Additionally, all four of our cases in this study had distal limb abnormalities such as syndactyly and clinodactyly that accompany severe intellectual disability. We suggest that distal limb abnormalities associated with the *BPTF* gene may accompany a more severe diagnosis of intellectual disability. Also, growth retardation may be more severe, especially for the cases with splicing variants of the *BPTF* gene variants.

1 | Introduction

Neurodevelopmental disorder with dysmorphic facies and distal limb anomalies (NEDDFL, OMIM No. #617755) is an ultra-rare syndrome associated with heterozygous pathogenic variants in the *BPTF* gene. This gene is in the 17q24.2 chromosomal region. The bromodomain PHD finger transcription factor (BPTF, OMIM No. 601819) gene encodes the largest subunit of the nucleosome remodeling factor (NURF), which is involved in the regulation of chromatin. The imitation switching (ISWI) family member

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NURF is a key evolutionarily conserved transcriptional activation regulator of a complex of five proteins that regulate the process of chromatin remodeling (Liang et al. 2023).

Epigenetics focuses on the accessibility of genetic information and related molecular mechanisms involved in the transcriptional activation of DNA (Stankiewicz et al. 2017). In light of technological advances, chemical epigenetic research, which uses probe molecules and chemical tools to elucidate the molecular mechanisms associated with epigenetic regulatory proteins, is also potentially promising for treatment (Zahid et al. 2021). Attempts to develop drugs that target this area are also promising. *BPTF* association studies are an important contribution to elucidate further the functional significance of the role of *BPTF* in the epigenetic mechanisms and etiopathogenesis of NEDDFL. There is a need for more detailed findings of the *BPTF*-gene related studies to provide broader implications for the medical and scientific community. This will contribute to the diagnostic and patient management processes for clinicians, inspire further research into the functional effects of the BPTF gene for researchers, and provide guidance for genetic counseling for affected families.

In this study, we present the clinical and genetic profiles of patients with variants detected in the *BPTF* gene from two different cohorts in Türkiye. Four patients ($n = 4$) with intellectual disabilities and various skeletal system findings were reported in the study.

2 | Material and Methods

2.1 | Patients

All cases were included if they met the criteria for developmental delay/intellectual disability (DD/ID) or autism spectrum disorder (ASD) in the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) (Blesson and Cohen 2020). We interviewed each participant and their parents and reviewed their medical records to collect their clinical information. This study was retrospective and cross-sectional.

All experimental procedures were conducted in accordance with the principles of the Declaration of Helsinki, and informed written consent was obtained from patients or their guardians. This was a retrospective clinical study approved by Balıkesir University Ethics Committee, Türkiye (approval number 2024/226/17.12.2024). The data of patients who underwent molecular genetic testing (whole-exome sequencing [WES] and chromosomal microarray analysis [CMA]) with a diagnosis of neurodevelopmental disorders were retrospectively evaluated in our cohort group. One more case from a different cohort group was added to our study to expand the phenotype.

2.2 | Clinical Data Acquisition

Demographic data (age, gender), family history, perinatal history, neurodevelopmental evaluation, and magnetic resonance imaging findings were obtained from the medical records of the patients. The mean age of four patients from three different families in this study was 13.2 years (1–38 years). All of the four cases were female. CMA analysis was performed as a first-tier genetic test for all patients. In the second tier, WES analysis was performed in patients who present no genetic variants explaining clinical phenotype following CMA analysis. WES analysis revealed three different variants (one pathogenic and two uncertain significance).

2.3 | Methods

2.3.1 | Whole Exome Sequencing

Genomic DNA (gDNA) was isolated from peripheral venous blood samples using the standard protocol. All variants were detected using WES. The missense variants were performed by capturing the coding regions and splice sites of targeted genes using the Illumina SureSelect V6 Exome (Agilent, Inc.)/Human Comprehensive Exome Panel (Twist Bioscience, South San Francisco) kit. After library enrichment and quality control, the samples were sequenced using the Illumina HiSeq4000 (Illumina, Inc.)/DNBSEQ-G400 (MGI Tech, China) instrument with 150-bp paired-end reads at an average sequencing depth of 80–100×. The splicing variant was detected using the QIAseq Human Exome Kit as per the manufacturer's instructions (Qiagen, Hilden, Germany). Paired-end sequencing (150 bp) was performed on the NovaSeq6000 system based on the manufacturer's guidelines (Illumina Inc., San Diego, CA, USA). We used the following filters to analyze the detected variants. All non-synonymous variants (missense, nonsense, frameshift, splice-site, no-stop, no-start, indels, and inframe variants in all protein-coding genes), synonymous or intronic variants affecting the consensus splice sites were investigated. Variants with minor allele frequency <1% in population studies (1000 Genomes, Genome Aggregation Database [gnomAD]) were evaluated. We evaluated the pathogenicity of novel variants using in silico prediction tools (SIFT, PROVEAN, GERP, CADD, PolyPhen2, and MutationTaster), segregation analysis, allele frequencies in population studies (1000 Genomes, gnomAD, Exome Aggregation Consortium), and the American College of Medical Genetics and Genomics (ACMG) criteria were used (Richards et al. 2015). Annotation of detected variants was performed using Online Mendelian Inheritance in Man (OMIM, https://www.omim.org/), the Human Genome Mutation Database (HGMD, http://www.hgmd.cf.ac.uk/ac/index.php), VarSome (https://varsome.com/), ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/), and PubMed. Family segregation analysis was performed using ABI 3130 Sanger sequencing (Applied Biosystems Inc.). In addition, the variants identified in the probands were confirmed by Sanger sequencing.

3 | Results

We detected c.2812+1G>C, c.6022G>A, and c.6416G>A variants of the BPTF gene in four cases from three families. Based on available literature and databases, clinical information about these specific variants was not previously reported. These c.6022G>A (p.Val2008Ile) and c.2812+1G>C variants have not been previously reported in public in silico variant analysis programs such as Leiden Open Variation Database (LOVD, https://www.lovd.nl), gnomAD (https://gnomad.broadinstitute.org/), ClinVar,

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TABLE 1 | Summary of *BPTF* gene variants detected in our study.

Family	Case No.	Sex	Age (year)	Nucleotide variation	Amino acid variation	Exon	Mutation type	ACMG classification	CADD score	Inheritance	Associated phenotype
1	1	F	1	**c.2812+1G>C (de novo)**	—	Intron 9	Non-coding	Pathogenic (PVS1, PM2, PS2)	32	AD	Dysmorphic facial findings, microcephaly, DD, cutaneous syndactyly on foot
2	2	F	2	**c.6022G>A (paternal)**	**p.Val2008Ile**	17	Missense	VUS (PM2, PP2)	24.1	AD	Dysmorphic facial findings, microcephaly ID/DD, speech delay, scoliosis, clinodactyly, small hands, pes planus
3	3	F	12	c.6416G>A (maternal)	p.Arg2139His	19	Missense	VUS (PM2, PP2)	29.1	AD	Dysmorphic facial findings, ID/DD, speech delay, clinodactyly
	4 (mother)	F	38								ID, clinodactyly, slender fingers

Note: All nucleotide variants were transcribed according to the *BPTF* gene NM_182641.4 transcript. Novel variants are implicated as bold. Abbreviations: y, years; ID, Intellectual Disability; AD, autosomal dominant; DD, developmental delay; VUS, variant of unsignificance.

and HGMD. The c.6416G>A (p.Arg2139His) mutation is located within exon 19. This variant is not registered in the ClinVar database. However, $f = 0.00000398$ was recorded in the gnomAD Exomes (Version: 2.1.1) database. Furthermore, this missense variant affects a highly conserved amino acid residue and was not found in the Turkish Genome Project Data Sharing Portal, our public genetic database in the country. Information on detected variants and associated phenotypes for all cases is presented in Table 1.

3.1 | Family 1

Case #1, who had non-consanguineous parents, was born at the 38th gestational week with a weight of 2500 g (−1.94 SD) by cesarean delivery. The patient had a history of intrauterine growth retardation (IUGR). At 2 years and 7 months of age, the auxological parameters at the examination were head circumference: 45.5 cm (-– 1.96 SD), weight: 10.3 kg (−2.08 SD), and height: 88 cm (– 1.11 SD). She had mild microcephaly, dysmorphic facial findings (bulbous tip, pointed chin), developmental delay, poor overall growth, and cutaneous syndactyly of the foot. Brain MRI was normal. We identified a novel heterozygous non-coding variant in the *BPTF* (NM_182641.4): c.2812+1G>C through WES. This splice-site variant is likely to disrupt normal splicing of the *BPTF* gene, which could result in abnormal mRNA processing and produce a non-functional or truncated protein. It was previously unreported in databases, such as HGMD, LOVD (https://www.lovd.nl), gnomAD (https://gnomad.broadinstitute.org/), and ClinVar. The analysis of the familial segregation showed that the variant was de novo.

3.2 | Family 2

Case #2 was born to a 33-year-old mother by cesarean section at term. Birth weight was 2950 g (−0.84 SDS). Microcephaly, dysmorphic facial findings (bulbous nasal tip, thin upper lip,) scoliosis, clinodactyly, small hands, pes planus, delayed speech, autism spectrum disorder, and ID were noted. The patient had a history of hypotonia. Her parents are healthy non-related individuals of Turkish origin. In the chromosomal microarray analysis of Case#2, any pathogenic/likely pathogenic variants were not detected. In the WES analysis, the *BPTF*(NM_182641.4): c.6022G>A (p.Val2008Ile) variant was detected. The older sister had a history of ID, hyperactivity, and brachydactyly. Familial segregation analysis showed that the variant was paternally inherited.

3.3 | Family 3

Case #3 was a 12-year-old girl. She was born as the sixth child of a family of nine children. She had dysmorphic facial findings (upslanting palpebral fissures, thin upper lip,) clinodactyly, slender fingers, pes planus, DD/ID, and speech delay. Transthoracic

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echocardiography detected mild mitral insufficiency. Brain MRI was normal. Current anthropometry measured height: 146.3 cm (−1.34 SDS) and weight: 39.1 kg (−1.07 SDS). Chromosomal analysis performed from peripheral blood was evaluated as normal. In addition, microarray testing with Illumina CytoSNP-12 v2.1 was normal. In Case #3, WES also detected the variant NM_182641.4: c.6416G>A: p.Arg2139His in the *BPTF* gene. This variant was inherited from the mother. The mother, Case #4, was reported to have ID, clinodactyly, and slender fingers, but a detailed examination could not be performed because the mother did not attend. The c.6416G>A (p.Arg2139His) mutation is located within exon 19. This variant is not registered in the ClinVar database. However, $f = 0.00000398$ was recorded in the gnomAD Exomes (Version: 2.1.1) database. This change, p.Arg2139His, is classified as uncertain significance (PM2, PP2) in silico variant analysis databases according to the ACMG. Furthermore, this missense variant affects a highly conserved amino acid residue and was not found in the Turkish Genome Project Data Sharing Portal, our public genetic database in the country.

4 | Discussion

This study reported three variants, c.2812+1G>C, c.6022G>A, and c.6416G>A in the *BPTF* gene. This study provides detailed clinical information about novel variants of the *BPTF* gene. Clinical information on these specific variants of the *BPTF* gene was not previously reported in the literature and databases.

We reported two missense and one splicing variant in our study. Fewer than 80 *BPTF* gene variants have been reported in HGMD Professional 2023.4, of which 41 are missense/nonsense and only three are splicing mutations. Although mostly missense variants of the *BPTF* gene were reported in the databases, clinical information about missense variants is very few in clinical reports. There is a lack of clinical information on missense variants of the *BPTF* gene.

Stankiewicz et al. demonstrated germline loss of function (LoF) *BPTF* gene variants in 10 unrelated individuals with autosomal dominant neurodevelopmental disorders. The authors discovered eight variants: four frameshifting indels, one splicing/frameshifting indel, one nonsense, and two missense variants. They suggested that these missense mutations (c.5770G>A and c.8558T>G) are likely to disrupt protein function (Stankiewicz et al. 2017). One of these cases with missense variants presented severe ID with clinodactyly and the other case showed mild ID without distal limb anomalies. Also in the same study, cases diagnosed with severe ID were accompanied by distal limb anomalies (such as clinodactyly) through eight *BPTF* gene variants. Glinton et al. reported one missense variant of the *BPTF* gene. They suggested that phenotypic characteristics were milder in the case of the missense variant compared to the other variant types in the study (Glinton et al. 2021). A study investigating growth retardation related to the BPTF gene reported another case with a missense variant of the *BPTF* gene. And, this case was presented for growth retardation without the diagnosis of ID (Wu and Chen 2023). In our study, both cases with the missense variants of the *BPTF* gene showed all phenotypic characteristics of the *BPTF*-related NEDDFL syndrome including neurodevelopmental disorders, dysmorphic facial findings, and distal limb abnormalities.

In HGMD Professional 2023.4, only three splicing *BPTF* gene variants have been reported. Reported splicing variants of the *BPTF* gene are rare in databases and clinical reports. Glinton et al. reported clinical information on the three splicing variants of the *BPTF* gene. Two of the three cases with splicing variants had severe feeding problems requiring gastrostomy (Glinton et al. 2021). In our study, all variants of the *BPTF* gene were associated with growth retardation and feeding problems. Similar to the cases in the previous reports, our case with the splicing variant had more severe growth retardation recognized earlier in the prenatal period with IUGR.

Furthermore, we aimed to add knowledge about the inheritance and penetrance of *BPTF*-related NEDDFL syndrome. In the literature, only one study described inherited *BPTF* gene variants (Glinton et al. 2021). These variants were frameshift, in-frame deletion, splicing, and nonsense variants. Two of our cases had inherited missense variants of the *BPTF* gene. Case #2 had a paternal inheritance pattern, and the father's clinical evaluation was unavailable. Case #3 had a maternally inherited *BPTF* gene missense variant from the affected mother. This mother presented ID, clinodactyly, and slender fingers.

In conclusion, the *BPTF* gene's missense variants were mostly associated with the milder phenotype in the previous reports. We detected two novel missense variants in patients presenting all phenotypic characteristics of the *BPTF*-related NEDDFL syndrome severely, including severe ID, distinctive facial features, and anomalies of the hands and feet. Additionally, all four of our cases in this study had distal limb abnormalities such as syndactyly and clinodactyly that accompany severe ID. We suggest that distal limb abnormalities associated with the *BPTF* gene may accompany a more severe diagnosis of ID. Growth retardation may be more severe, especially for the cases with splicing variants of the *BPTF* gene variants. Main limitations of our study were the limited number of patients and the need for larger cohort studies/collaborative studies. Additionally, more detailed findings of the *BPTF*-gene associated studies would provide broader implications for the medical and scientific community. We emphasized that this will contribute to the diagnostic and patient management processes for clinicians, inspire further research into the functional effects of the *BPTF* gene for researchers, and provide guidance for genetic counseling for affected families.

Author Contributions

Gul Unsel Bolat provided psychiatric evaluation. Betül Diler Durgut provided neurologic evaluation. Hamide Betul Gerik-Celebi, Hilmi Bolat, and Ayberk Turkyılmaz provided genetic evaluation. Gul Unsel Bolat, Hamide Betul Gerik-Celebi, and Hilmi Bolat designed the study and wrote the manuscript.

Ethics Statement

All procedures performed in this study were in accordance with the Declaration of Helsinki. This study protocol was reviewed and approved

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by the Balikesir University Faculty of Medicine Clinical Research Ethics Committee, approval number 2024/226 [dated 17.12.2024]. All the participants of the study gave their informed consent.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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