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Genetic analysis of *BRPF1* exon deletion variant causing intellectual developmental disorder with dysmorphic facies and ptosis in a Chinese family

Qian Liu[1*], Feifei Li[1], Nana Wang[1] and Zhengjun Fan[1]

Abstract

Background Intellectual developmental disorders with dysmorphic facies and ptosis (IDDDFP) are rare neurological conditions caused by variants in the *BRPF1* gene. They primarily manifest as intellectual disabilities (ID) alongside distinctive facial features, particularly ptosis and blepharophimosis. This study aimed to investigate the molecular etiology and phenotype of the inaugural IDDDFP family documented in China.

Methods and results Clinical data were collected and validated through trio-based whole-exome sequencing of DNA from the proband and her parents, complemented by quantitative polymerase chain reaction (qPCR). The proband, a 10-month-old girl, presented with focal seizures and developmental delays. Notably, she exhibited facial features similar to those of her mother and sister, including ptosis and blepharophimosis. Both the proband's mother and sister also had mild ID. Genetic testing identified *BRPF1* deletion variants in all affected individuals, resulting in exon 2–14 heterozygous deletion. The qPCR verification confirmed the wild-type *BRPF1* in the proband's father and eldest sister. A review of 46 documented patients with *BRPF1* deficiency revealed that the primary clinical manifestations encompassed varying degrees of ID alongside special facial features, skeletal deformities, and ocular abnormalities. However, epilepsy was found to be rare in this syndrome. The syndrome has variable phenotypic features of neurodevelopmental disorders. Meanwhile, there seems to be a lack of correlation between phenotype and genotype.

Conclusion Our findings broaden the genotypic and phenotypic spectrum of individuals with genetically pathogenic variants of *BRPF1*. Moreover, they underscore the significance of recognizing ptosis and blepharophimosis associated with ID or seizures as potential signs of *BRPF1* variants.

Keywords BRPF1, IFFFPD, Neurodevelopmental disorder, Seizure, Gene testing

Background

Intellectual disability (ID) typically denotes significant cognitive impairment compared to individuals of the same age accompanied by apparent deficits in social adaptability [1]. The etiology of ID is complex and extensively heterogeneous, primarily influenced by genetic factors such as chromosomal variations, single-gene variations, and epigenetic abnormalities [2]. Specifically, a subset of gene variants contributes to ID by modulating epigenetic regulators, including lysine acetyltransferases,

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histone deacetylases, DNA methyltransferases, and ATP-dependent helicases [3]. The *BRPF1* gene encodes the bromodomain and plant homeodomain finger-containing protein 1, a chromatin reader that facilitates the histone acetylation process [4]. In 2017, two independent research teams concurrently discovered that defects in *BRPF1* cause hereditary ID syndrome characterized by identifiable features along with varying degrees of ID severity (typically mild). These features may include facial deformities, such as ptosis and blepharophimosis, skeletal deformities, and developmental delays [5, 6]. Consequently, ID syndrome associated with heterozygous variants in *BRPF1* and distinctive facial features was designated as an intellectual developmental disorder with dysmorphic facies and ptosis (IDDDFP; OMIM#617333).

Fewer than 50 cases of IDDDFP have been reported, highlighting the scarcity of essential research data regarding the correlation between disease phenotypes and genotypes [3, 5–13]. In this study, we present a case involving a Chinese family exhibiting typical IDDDFP features, with the proband also presenting with infantile epilepsy and developmental delay. Genetic testing confirmed *BRPF1* variants in all affected family members.

Materials and methods

Study participant

The proband was a 10-month-old female infant, the mother's fifth pregnancy, and the third delivery (Fig. 1; two uninduced spontaneous miscarriages). The proband was admitted to the hospital at 9 months of age owing to febrile convulsions. Patient medical history and clinical data, such as physical examinations, auxiliary examinations, imaging studies, and genetic testing, were collected to enhance data accuracy. Informed consent was obtained from the patient's parents and approved by the study's hospital (2024-03).

Trio-whole-exome sequencing

For trio-based whole-exome sequencing, peripheral blood samples (3 mL) were collected from the patient and her parents. Genomic DNA was then extracted from these samples following the instructions provided by the DNA extraction kit (Qiagen, Inc.). xGEN Exom Research Panel v1.0 probe (IDT, Coralville, IA, USA) enriched exomes encoding proteins. Subsequently, the genome was sequenced using the second-generation high-throughput sequencing platform NovaSeq 6000 (Illumina, San Diego, CA). Fastp files were used to perform adapter trimming and filter low-quality reads. Burrows–Wheeler Alignment version 0.7.9a (http://bio-bwa.sourceforge.net) was used to align the GRCh/hg19 reference genome, and Genome Analysis Toolkit software V3.5 (https://gatk.broadinstitute.org/hc/en-us) was used to perform variant calling on single-nucleotide variants [14–16]. The filtered variant annotations included databases such as the dbSNP, 1000 Genomes Project, Exac, ESP, and gnomAD. Prediction algorithms, including Provean, SIFT, Polypen2, MutationTaster, M-Cap, and Revel software packages, were used to assess the potential pathogenicity of missense variants. Finally, all variants were evaluated for

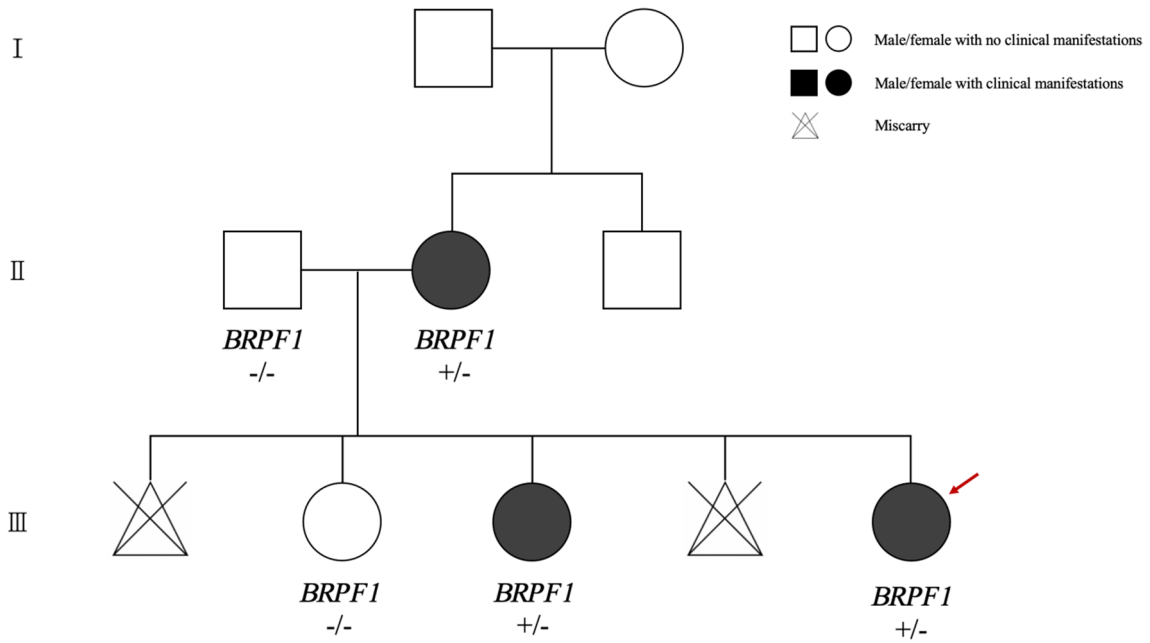

Fig. 1 Family diagram of the patient with intellectual disability. The red arrow indicates the proband

pathogenicity according to the guidelines of the American College of Medical Genetics and Genomics (ACMG) [17].

Quantitative real-time polymerase chain reaction

We conducted qPCR validation of the proband, her parents, and two sisters. The qPCR samples were analyzed using Takara SYBR Green reagent (Toyobo, Osaka, Japan), with *ALB* genomic content as an endogenous control for data normalization. The copy number was calculated using the ΔΔCt method, while two normal individual genomic DNA samples were employed as negative controls. Typically, the relative copy number of normal samples falls around 1 (normally ranging 0.8–1.2), whereas the relative copy number of heterozygous *BRPF1* exon deletion samples is approximately 0.5. Supplementary Table 1 lists the primer sequences.

Results

Clinical features

This case involved a 10-month-old female patient delivered through a full-term breech presentation at 39 weeks of gestation. The child weighed 3600 g at birth, measured 50 cm in length, and experienced no prenatal or perinatal adverse events. At 8 months old, the child began experiencing intermittent convulsions due to a high fever of 40 °C, occurring approximately every 2 h. During these episodes, she exhibited confusion and right-sided staring, lasting a few min before resolving spontaneously. Subsequently, owing to an escalation in seizure frequency, the child was brought to our hospital. Shortly after admission, she experienced another convulsion characterized by confusion, staring eyes, foaming at the mouth, and limb twitching, lasting approximately 10 min. Physical examination revealed instability while sitting, delayed growth and development, and reduced limb muscle tone. Facial features included ptosis of the left eyelid (Fig. 2). Multiple seizures were captured during video electroencephalogram (EEG) monitoring, exhibiting head turning to the right, sluggish expression, and unresponsiveness to stimuli. Synchronous EEG showed medium–high amplitude slow spikes and polyspiny slow, complex waves in the left lead, with the frequency and amplitude gradually increasing (Fig. 3). Brain MRI showed no abnormalities (Fig. 4). Treatment primarily involved oral sodium valproate for antiepileptic therapy. At 2 months

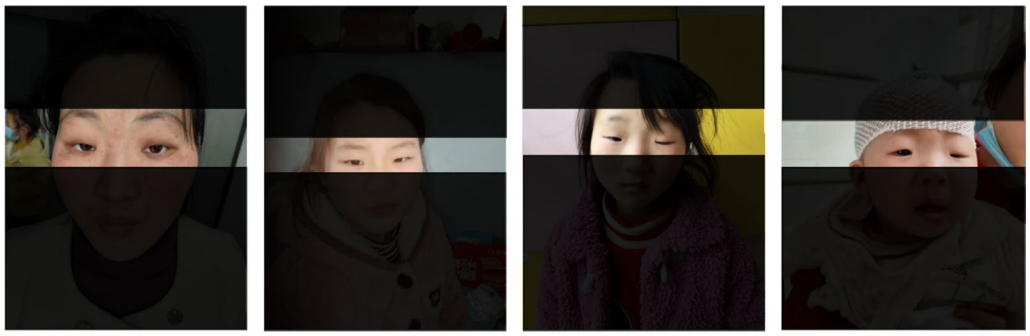

Fig. 2 Facial features of the family. Affected family members show ptosis and blepharophimosis, and the facial features of the proband's eldest sister are significantly different from those of the affected members

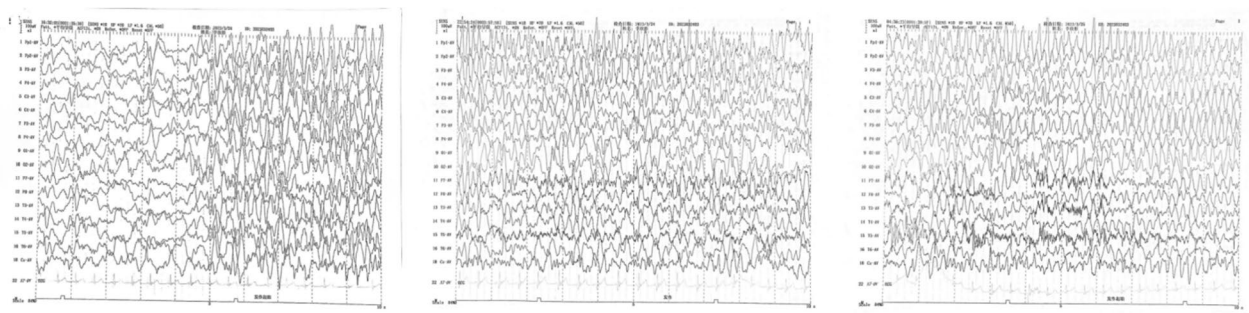

Fig. 3 Video electroencephalography monitors the proband's three seizures, with medium–high amplitude 2–3 Hz spike-slow and polyspiny-slow complex waves on the left lead, with the frequency and amplitude gradually increasing

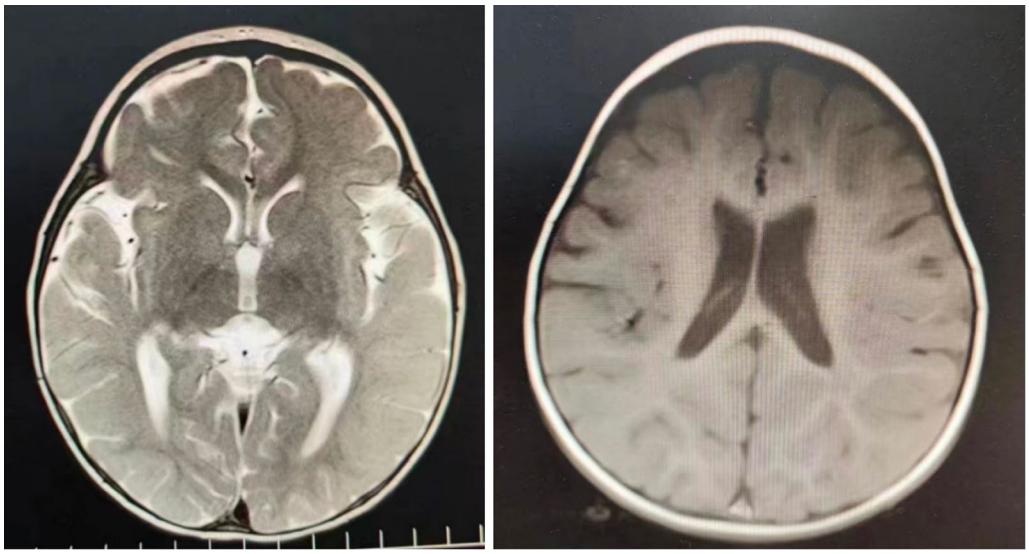

Fig. 4 The proband's cranial magnetic resonance imaging shows no structural abnormalities

of follow-up, the seizures ceased, effectively controlled by medication.

Family history

The proband's father, aged 29 years, and eldest sister, aged 8 years, were asymptomatic. The mother, aged 24 years, exhibited mild ID, with an IQ of 78 on the Wechsler intelligence scale test, and displayed bilateral eyelid ptosis. Similarly, her sister, aged 6 years, also had mild ID, with an IQ test score of 70, and presented with left eyelid ptosis akin to the proband (Fig. 2). Furthermore, neither the proband's mother nor her sister showed clinical manifestations of seizures, hypotonia, or global developmental delays.

Genetic studies

The proband and her parents underwent trio-based whole-exome sequencing, revealing no other single-nucleotide variants associated with seizures or ID. However, a heterozygous deletion of *BRPF1* (NM_001003694: loss1; exon2-exon14) was detected in the proband. The mother carried this variant, while the father had the wild-type variant (Fig. 5). This variant was rated as likely pathogenic based on the ACMG guidelines (PVS1 + PM2).

qPCR validation

qPCR revealed that the relative copy number of exons 2–14 of *BRPF1* in the proband, her mother, and sister was approximately 0.5. In contrast, those of her father and eldest sister fell within the normal range. This suggests that both the proband and her sister inherited the *BRPF1* variant from their mother (Fig. 6).

Discussion

In this study, we report a case involving a Chinese family exhibiting mild ID and facial dysmorphism. The proband, a 10-month-old child, not only displayed facial dysmorphisms but also experienced focal seizures and developmental delays. Genetic testing identified heterozygous deletion variants of *BRPF1 in* the proband, her mother, and her sister.

BRPF1 variations are associated with IDDDFP, with 46 patients documented across 10 studies (Table 1). The affected individuals typically present with varying degrees of ID (98%, 44/45) and facial deformities, mainly ptosis and blepharophimosis (72%, 32/44). Visual or ocular issues (64%, 25/39), such as strabismus, amblyopia, or refractive error, are relatively common. Additionally, some patients exhibit skeletal deformities (72%, 31/43), including hand (brachydactyly and brachymetacarpia) and foot (clubfoot or syndactyly) differences. However, a minority of patients with IDDDFP experience seizures (21%, 9/43) and structural brain abnormalities (50%, 10/20), often characterized by abnormal white matter signals under MRI and corpus callosum thinning [3, 5–13]. The affected family members in our report exhibited typical facial dysmorphisms of IDDDFP. Specifically, the proband, mother, and sister exhibited facial features consistent with hypoblepharoptosis. Owing to the proband's young age, an intelligence evaluation was not conducted. However, both her mother and sister exhibited mild ID without signs of developmental delay. While epilepsy is

Fig. 5 Schematic diagram of exon deletions/duplications in the proband and parents based on next-generation sequencing results. The red dotted lines indicate normal reference values

observed in a minority of patients with *BRPF1* defects, onset typically occurs in childhood [5, 6, 10]. Notably, only one case involving a 3-month-old infant with fever-induced multiple seizures has been documented, similar to the seizure characteristics in our proband, suggesting the involvement of *BRPF1* in the mechanism of epilepsy [10].

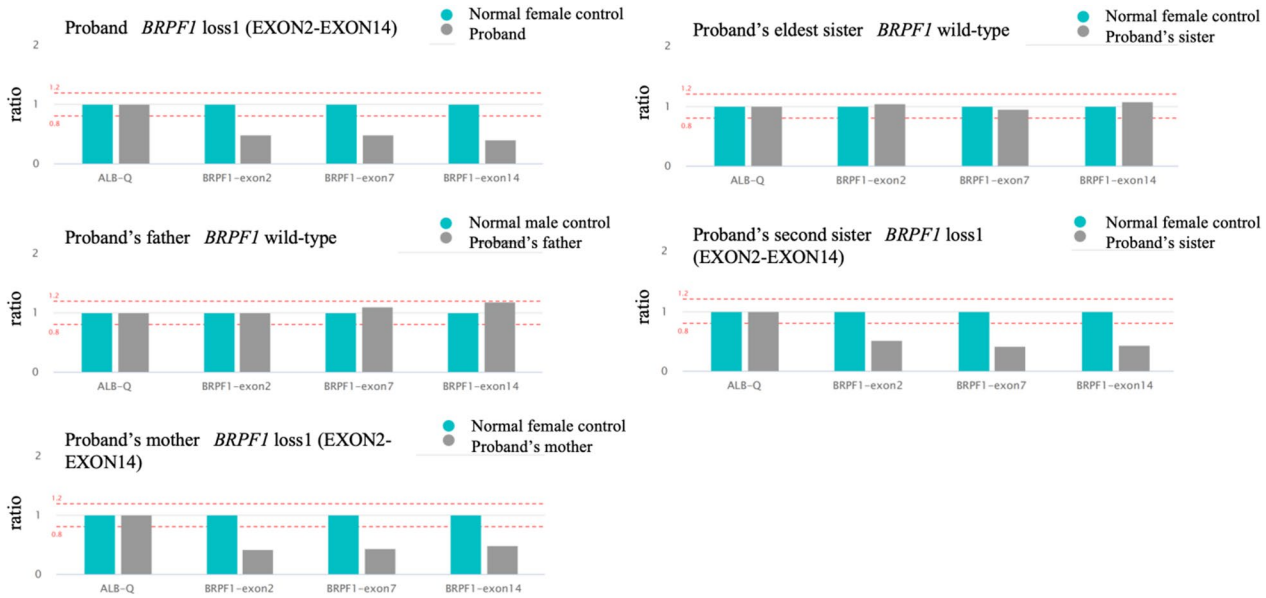

Fig. 6 Quantitative polymerase chain reaction shows the *BRPF1* exon deletion in the proband, her parents, and two sisters. The red dotted lines indicate normal reference values

The primary reported variants comprised frameshift (47%, 16/34), nonsense (26%, 9/34), and three deletion (9%) variants, suggesting haploinsufficiency of *BRPF1* as a pathological mechanism [3, 5–13]. However, phenotypic variations exist among affected individuals within the same family. For instance, in the family reported by Pode-Shakked et al., all affected offspring exhibited ID despite their mothers carrying the same variants without showing cognitive impairments [3]. Similarly, in the family reported by Mattioli et al., the patients' offspring exhibited agenesis of the corpus callosum and attention deficit hyperactivity disorder; however, their mother lacked such symptoms [6]. Including the family with ID reported in this study, only the proband exhibited seizures and developmental delay. This emphasizes that *BRPF1* defects have variable phenotypic characteristics in neurodevelopmental disorders, suggesting no definitive correlation between the *BRPF1* genotype and phenotype. For clinical diagnosis, consideration should be given to IDDDFP in patients with facial deformities, particularly ptosis and blepharophimosis, alongside ID. However, the differential diagnosis should also include Arboleda–Tham syndrome (OMIM#616268) or Say–Barber–Biesecker–Young–Simpson syndrome (OMIM#603736), stemming from *KAT6A* or *KAT6B* gene defects, respectively. Patients with *KAT6A* or *KAT6B* deficiency may exhibit more severe neurodevelopmental disorders and multisystem malformations [18, 19]. It is also worth noting that *CDK13* gene defects lead to congenital heart defects, dysmorphic facial features, and intellectual developmental disorder (OMIM#617360), which is accompanied by facial features such as a wide eye distance, epicanthus, ptosis, and ear deformities; different degrees of nervous system abnormalities; and characteristics of congenital heart disease with high penetrance [20].

BRPF1, located in the p25.3 region of chromosome 3, encodes the BRPF1 protein, comprising 1,214 amino acids. This protein exhibits ubiquitous expression, particularly in the testis and spermatogonia, where it attains the highest expression level [21]. Structurally, the BRPF1 protein comprises three main domains: a bromodomain, a plant homeodomain finger, and a chromo/tudor-related Pro-Trp-Trp-Pro (PWWP) motif [22]. Serving as a crucial component of the KAT6A (also known as MOZ or MYST3)/KAT6B (also known as MORF or MYST4) histone acetyltransferase (HAT), the BRPF1 protein functions as both a scaffolding subunit and transcriptional regulator [23]. Notably, *KAT6A* and *KAT6B* defects can result in neurodevelopmental disorder phenotypes similar to those observed in IDDDFP [24, 25]. Previous studies have shown that BRPF1 primarily controls H3K23 acetylation through KAT6A/KAT6B, thereby influencing epigenetic regulation and developmental programs [26, 27]. In a study by Yan et al., BRPF1-deficient patients with neurodevelopmental disorders exhibited disrupted propionylation processes in addition to H3K23 acetylation regulation [10]. This finding suggests that BRPF1 deficiency may regulate the H3K23 acylation process through KAT6, contributing to the pathogenesis of neurodevelopmental disorders. The heterozygous deletion of

Table 1 The phenotypes and genotypes of the three patients in this study are related to those reported in patients with IDDDFP

	Diagnostic age/Sex	DD/ID	Ptosis and blepharophimosis	Seizure	Brain	Ocular abnormality	Skeletal	Hypotonia	Variation (NM_001003694.1)	References
#1	61 y/F	+	+	–	NA	–	NA	NA	c.556C > T(p.Glu186*)	[3]
#2	42 y/M	+	+	–	NA	–	NA	NA	c.556C > T(p.Glu186*)	[3]
#3	30 y/M	+	+	–	NA	–	NA	NA	c.556C > T(p.Glu186*)	[3]
#4	24 y/F	+	+	–	NA	–	+	NA	c.556C > T(p.Glu186*)	[3]
5	NA/F	+	+	–	WM hyperintensity	+	+	+	c.362_363delAG(p.Glu121Glyfs*2)	[5]
#6	NA/M	+	–	+	decreased WM and thin CC	+	+	+	c.942_955del(p.Trp315Leufs*26)	[5]
#7	NA/F	+	+	+	–	+	+	NA	c.942_955del(p.Trp315Leufs*26)	[5]
8	NA/M	+	–	+	–	–	–	+	c.1108C > T(p.Pro370Ser)	[5]
9	NA/F	+	+	+	–	–	+	+	c.1363C > T(p.Arg455*)	[5]
10	NA/M	+	+	–	NA	+	+	+	c.1688_1689del(p.His563Profs*8)	[5]
11	NA/M	+	+	+	NA	–	+	NA	c.1883_1886dup(p.Gln629Hisfs*34)	[5]
12	NA/F	+	–	–	NA	+	+	–	c.2497C > T(p.Arg833*)	[5]
13	NA/F	+	–	+	decreased WM	+	+	+	c.2915dupC(p.Met973Asnfs*24)	[5]
14	NA/F	+	+	–	–	–	–	+	c.3298C > T(p.Arg1100*)	[5]
#15	5 y 9 m/M	+	+	–	ACC	+	+	+	c.1052_1053del(p.Val351Glyfs*8)	[6]
#16	32 y/F	+	+	–	NA	+	+	NA	c.1052_1053del(p.Val351Glyfs*8)	[6]
#17	34 y/F	+	+	–	NA	+	+	NA	c.1052_1053del(p.Val351Glyfs*8)	[6]
#18	6 y 10 m/F	+	+	–	–	+	+	+	c.1052_1053del(p.Val351Glyfs*8)	[6]
#19	30 y/F	+	+	–	NA	+	+	NA	c.1052_1053del(p.Val351Glyfs*8)	[6]
20	6 y 6 m/M	+	+	–	NA	NA	+	–	deletion of chr3: 9,724,693–9,896,683	[6]
#21	3 y 8 m/F	+	+	–	NA	+	–	+	deletion of chr3: 9,632,462–9,813,339	[6]
#22	37 y/F	+	NA	NA	NA	NA	NA	NA	deletion of chr3: 9,632,462–9,813,339	[6]
23	10 y/M	+	+	+	+	+	+	+	c.2982C > G(p.Tyr994*)	[6]
24	3 y/M	+	+	–	NA	NA	+	–	c.567delT(p.Asp190Metfs*24)	[6]

Table 1 (continued)

	Diagnostic age/Sex	DD/ID	Ptosis and blepharophimosis	Seizure	Brain	Ocular abnormality	Skeletal	Hypotonia	Variation (NM_001003694.1)	References
25	12 y/M	+	+	+	NA	+	+	NA	c.104dupA(p.Tyr35)	[6]
26	3 y 9 m/M	+	+	–	–	+	+	+	c.1165 T > C(p.Cys389Arg)	[6]
27	NA/M	+	–	–	Hypoplasia of CC	+	–	–	c.655G > T(p.Glu219*)	[7]
28	3 y/M	NA	+	NA	NA	NA	+	NA	c.1182_1183delAG(p.Ala396Leufs*69)	[8]
29	6 y/F	+	+	–	–	–	+	+	c.1054G > C(p.Val352Leu)	[9]
30	NA/M	+	–	–	decreased WM, CC dysmorphic, HME	–	–	+	c.277C > T(Pro76Leu)	[10]
31	NA/F	+	–	–	NA	NA	+	–	c.286C > T(p.Gln96*)	[10]
32	NA/M	+	+	+, febrile, starting at 3 months of age	–	+	+	–	c.558_570del13ins11(p.Asp187Glyfs*29)	[10]
#33	NA/F	+	-	–	NA	–	+	+	c.883_884del(p.Met295Valfs*17)	[10]
#34	NA/F	+	–	–	NA	–	+	–	c.883_884del(p.Met295Valfs*17)	[10]
35	NA/M	+	–	–	NA	+	–	–	c.953G > A(p.Arg318 His)	[10]
36	NA/F	+	+	–	decreased WM and thin CC	+	–	–	c.1229A > G(p.His410Arg)	[10]
37	NA/F	+	+	–	NA	+	NA	+	c.1300delA(p.Thr434Profs*61)	[10]
38	NA/NA	+	NA	NA	NA	NA	NA	NA	c.1420dupG(p.Glu474Glyfs*3)	[10]
39	NA/M	+	–	+, age 1.5 years	NA	–	+	+	c.1622_1626dup(p.Tyr543Thrfs*6)	[10]
40	NA/M	+	+	–	Pituitary shortening	+	–	–	c.2497C > T(p.Arg833*)	[10]
41	NA/M	+	–	–	Mega cisterna magna and thin CC	NA	+	+	c.3459_3461delCTT(p.Phe1154del)	[10]
42	16 y/M	–	+	–	–	+	+	+	c.964C > T(p.Gln322*)	[11]
43	18 y/M	+	+	–	–	–	–	+	arr[GRCh38]3p25.3(9706732_9796589) × 1	[12]
#44	5 m/M	+	+	–	NA	+	+	+	c.1433G > A(p.Trp478*)	[13]
#45	21 y/F	+	+	–	NA	+	+	–	c.1433G > A(p.Trp478*)	[13]
#46	2 m/F	+	+	–	NA	+	+	+	c.1433G > A(p.Trp478*)	[13]
Our study	10 m/F	+	+	+	–	–	–	+	deletion of chr3: 9,775,824–9,789,033	
	6 y/F	+	+	–	NA	–	–	–	deletion of chr3: 9,775,824–9,789,033	

Table 1 (continued)

	Diagnostic age/Sex	DD/ID	Ptosis and blepharophimosis	Seizure	Brain	Ocular abnormality	Skeletal	Hypotonia	Variation (NM_001003694.1)	References
	24 y/F	+	+	–	NA	–	–	–	deletion of chr3: 9,775,824–9,789,033	
Total	49	47/48	35/47	11/46	10/21	25/42	31/43	23/36		

M male, *F* female, *y* year, *m* month, *NA* not applicable, *DD/ID* developmental delay/intellectual disability, *HME* hemimegalencephaly, *WM* white matter, *ACC* agenesis of the corpus callosum, *CC* corpus callosum, *Ref* references, # family members

exons 2–14 in *BRPF1* identified in our study impairs the biological functions of the various domains of the BRPF1 protein.

Currently, no effective treatment is available for IDDDFP. However, research by Yan et al. suggested that *BRPF1* variation contributes to H3K23 acylation defects. They revealed that valproate, vorinostat, propionate, and butyrate can enhance H3K23 acylation at the cellular level. Specifically, propionate has been shown to enhance H3K23 propionylation in embryonic fibroblasts in mouse models [10]. Understanding these mechanisms and further pharmacological studies may provide potential treatment strategies for patients with IDDDFP. In addition, patients with IDDDFP may be subjected to potential social discrimination due to their ID and appearance, and their quality of life is often low, necessitating special education and psychological counseling.

Conclusions

In conclusion, we may be the first to report a Chinese family affected by IDDDFP, wherein the proband shares similar facial features with her mother/sister and exhibits additional symptoms of seizures and developmental delay. However, this study had limitations, primarily the lack of more detailed clinical investigations of affected family members and the need to expand variant verification to other maternal relatives. Overall, IDDDFP is a phenotypically variable genetic disorder characterized by ID and accompanied by ptosis, blepharophimosis, or seizures. Genetic testing actively used to identify *BRPF1* variants is crucial for guiding genetic counseling.

Abbreviations

IDDDFP	Intellectual developmental disorder with dysmorphic facies and ptosis
ID	Intellectual disabilities
BRPF1	Bromodomain and plant homeodomain finger-containing protein 1
PCR	Polymerase chain reaction
qPCR	Quantitative polymerase chain reaction
EEG	Electroencephalogram
MRI	Magnetic resonance imaging
ACMG	American College of Medical Genetics and Genomics
OMIM	Online Mendelian inheritance in man
KAT6A	Lysine acetyltransferase 6A
KAT6B	Lysine acetyltransferase 6B
HAT	Histone acetyltransferase
WES	Whole-exome sequencing
DNA	Deoxyribonucleic acid
IQ	Intelligence quotient
SNP	Single-nucleotide polymorphism
ESP	Exome Sequencing Project
PVS1	Pathogenic very strong
PM2	Pathogenic moderate
H3K23	Histone H3 lysine 23
PWWP	Pro-Trp-Trp-Pro
HME	Hemimegalencephaly
CC	Corpus callosum

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s43042-024-00539-w.

Supplementary Material 1.

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We thank the members of family for their participation in this study.

Author contributions

QL contributed to conceptualization, writing—original draft preparation, project administration, and methodology; QL and FL contributed to software and writing— review and editin; QL, FL and NW contributed to investigation; NW and ZF contributed to data curation; and FL supervised the study. All authors have read and agreed to the published version of the manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding authors upon request.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee of Taihe Hospital Affiliated to Wannan Medical College (protocol #03 from March 2024).

Consent for publication

Consent to publish from the father of the proband has been taken.

Competing interests

The authors have no relevant fnancial or non-fnancial interests to disclose.

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