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CASE REPORT Open Access

Intellectual developmental disorder with dysmorphic facies and ptosis caused by copy number variation including the *BRPF1* gene in Peruvian patient

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Abstract

Background: Intellectual developmental disorder with dysmorphic facies and ptosis (MIM #617333) is a very rare condition, characterized by more than 80% by language delay, intellectual disability, gross motor development delay, broad nasal bridge, hypertelorism, and hypotonia. This condition exhibits as autosomal dominant inheritance and is caused by a heterozygous variant in the *BRPF1* gene. Additionally, the copy number variation in the terminal region of chromosome 3p (MIM #613792) has been shown to manifest in most patients as intellectual disability, motor delay, and hypotonia.

Case presentation: We present an 18-year-old male patient with facial dysmorphism, intellectual disability, ptosis, and congenital heart disease. Using chromosomal microarray analysis, a previously unreported 90 kb deletion involving seven genes was found.

Conclusion: When comparing our findings with 39 previous reports, we found that the common clinical features of this syndrome, such as gross motor delay, hypotonia, and congenital spinal cord abnormalities, were not observed in this patient. From the seven genes implicated in the deletion, only *BRPF1* could be strongly correlated with the phenotype, according to its function and haploinsufficiency coefficients.

Keywords: *BRPF1*, Intellectual disability, Blepharoptosis, Blepharophimosis, Haploinsufficiency

Background

Intellectual disability (ID) manifests before the age 18 years and is defined as a limitation in two areas: intelligence or mental capability, and adaptive behavior in any of its three domains (conceptual, social, and practical) [1]. The global prevalence of ID is 1–3%, and the copy number variations (CNV) are the cause of ID in 36.1% of these cases [2]. To date, more than 2000 genes associated with ID have been reported (https://www.sysid.dbmr.unibe.ch). Of these, *BRPF1* gene (Bromodomain and PHD finger -containing 1) has been previously associated with an intellectual developmental disorder with dysmorphic facies and ptosis, or IDDDFP (MIM #617333), which is characterized by neonatal feeding disorder, hypotonia, gross and fine motor development delay, language delay, intellectual disability, epilepsy, brain abnormalities, flat and round face, broad nasal bridge, hypertelorism, small palpebral fissures, ptosis, blepharophimosis, joint hypermobility, and spinal anomalies [3]. To date, 39 patients with IDDDFP have been reported, most of them diagnosed in the USA and Europe with variants in the *BRPF1* gene detected by exome sequencing [3–10].

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The *BRPF1* (3p26-p25) has 14 exons and transcribes four isoforms. This gene code for a protein is called peregrin, which contains 1214 amino acids [11] and is a scaffolding subunit of several histone acetyltransferases, such as MOZ (KAT6A)/MORF(KAT6B) and the HBO1(KAT7) complex, having an acetyltransferase activity in the H3 histone [3, 12, 13]. Previous research suggests that MOZ/MORF, or HBO1 together with peregrin, EAF6, and ING5, bind transcription factors like Runx and p53, and intervenes in the embryonic development of hematopoietic and neuronal cells. Furthermore, variants in these molecules have also been related to leukemia, malignant neoplasms, and ID [14].

Here, we present the first Peruvian and Latin-American patient with a suspected case of IDDDFP caused by a CNV present in chromosome 3. The deletion includes the *BRPF1* gene, which adds evidence to the studies in animal models which show it is a haploinsufficient gene [15]. In addition, we highlight the importance of applying genome techniques, like CMA, to diagnose neurodevelopmental disorders in low- and middle-income countries.

Case presentation

Clinical report

The patient is an 18-year-old male with non-consanguineous parents, without a family history of neurodevelopment disorders, and with an uneventful prenatal history. His mother presented with preeclampsia during pregnancy, causing the delivery to be carried out by cesarean section at 38 weeks of gestation, with a birth weight of 2.7 kg and an apparently normal Apgar score. However, the patient's height and head circumference were not recorded. Psychomotor development showed that he achieved head control at two months, sitting without support at six months, and walking at one year of age. Regarding his speech development, he said his first words at one year of age, and he began to form sentences at five years old, with a social smile at two months. The patient has a history of atrial septal defect (ASD) and a diagnosis of acquired hypothyroidism at ten years of age (under treatment with levothyroxine at 50 µg/day) with normal values of TSH and free-T4 at the last control. He underwent surgery for ASD twice (at 12 and 14 years of age) and tympanic membrane perforation (at 15 and 16 years of age). Additionally, he presented hyperglycemia and *acanthosis nigricans,* for which he is still medicated with metformin. In childhood, he was diagnosed with hyperactivity, and he reached eleventh grade with low performance. However, there is no family history of neurodevelopmental disorders or congenital anomalies (Fig. 1A).

Physical examination showed that the patient presented normal anthropometry, narrow forehead, blepharophimosis, palpebral ptosis, short and deep philtrum, thick vermilion of the lips, underdeveloped supraorbital ridges, brachydactyly, and limitation of the flexion of the fourth finger (Fig. 1B–D). Among the complementary evaluations, he had an IQ of 63.

Chromosomal microarray analysis (CMA)

For the molecular analysis and the publication of this article, informed consent of the parents was requested. According to the manufacturer, the chromosomal microarray analysis was performed using genomic DNA, which was amplified, labeled, and hybridized based on the *GeneChip CytoScan 750 K Array* (Affymetrix, USA ®) instructions. The DNA genomic was extracted from a blood sample using the *kit gSYNC™ DNA Extraction*, following the manufacturer's instructions. DNA concentration and purity were measured with spectrophotometer Nanodrop 2000 (Thermo Scientific, USA). Briefly, 250 ng of DNA was digested with restriction enzyme Nsp I and was then linked with adapters for the PCR amplification. The products of the PCR were analyzed with electrophoresis with agarose gel 2% *E-Gel ® EX* (Invitrogen, USA), and were posteriorly purified using magnetic beads. DNA purified was fragmented using DNAsa 1 and analyzed trough electrophoresis with agarose gel 4% *E-Gel®EX* (Invitrogen, USA). Fragmented products were labeled with biotin and hybridized for 18 h at the genechip; next, these were washed and colored with fluid station *Affymetrix 450*. The test included 550,000 non-polymorphic markers and 200,436 single nucleotide polymorphisms (SNP) markers. Finally, the gene chips were scanned with *Affymetrix 3000 GeneChip Scanner* and analyzed with *Chromosome Analysis Suite* (ChAS) v.4.2 (Affymetrix, USA®). The gains or losses were considered for analysis when at least 50/25 markers were compromised, respectively. In addition, the regions of homozygosity (ROH) were considered for analysis when the length was at least 5 Mb (ver Thermo Fisher Sc Inc, 2017).

The CMA result for the patient was arr[GRCh38] 3p25.3(9706732_9796589) × 1, with a ROH percentage of 0,69. The CNV, a 90 kb deletion, contained seven genes: *CPNE9, BRPF1, OGG1, CAMK1, TADA3, ARPC4,* and *ARPC4-TTLL3*. We did not perform another genomic test (i.e. whole exome sequencing) because CMA showed a variant related to the phenotype.

Discussion

Haploinsufficiency is the mechanism by which a gene in a hemizygous state causes a phenotype [16]. A likely cause of haploinsufficiency is that some genes that present conserved sequences during evolution with few functional coding variants are more likely to have a dose-sensitive effect [17]. The monoallelic expression occurs only when one allele needs to be expressed for a given function, and around 3000 genes have been established in humans.

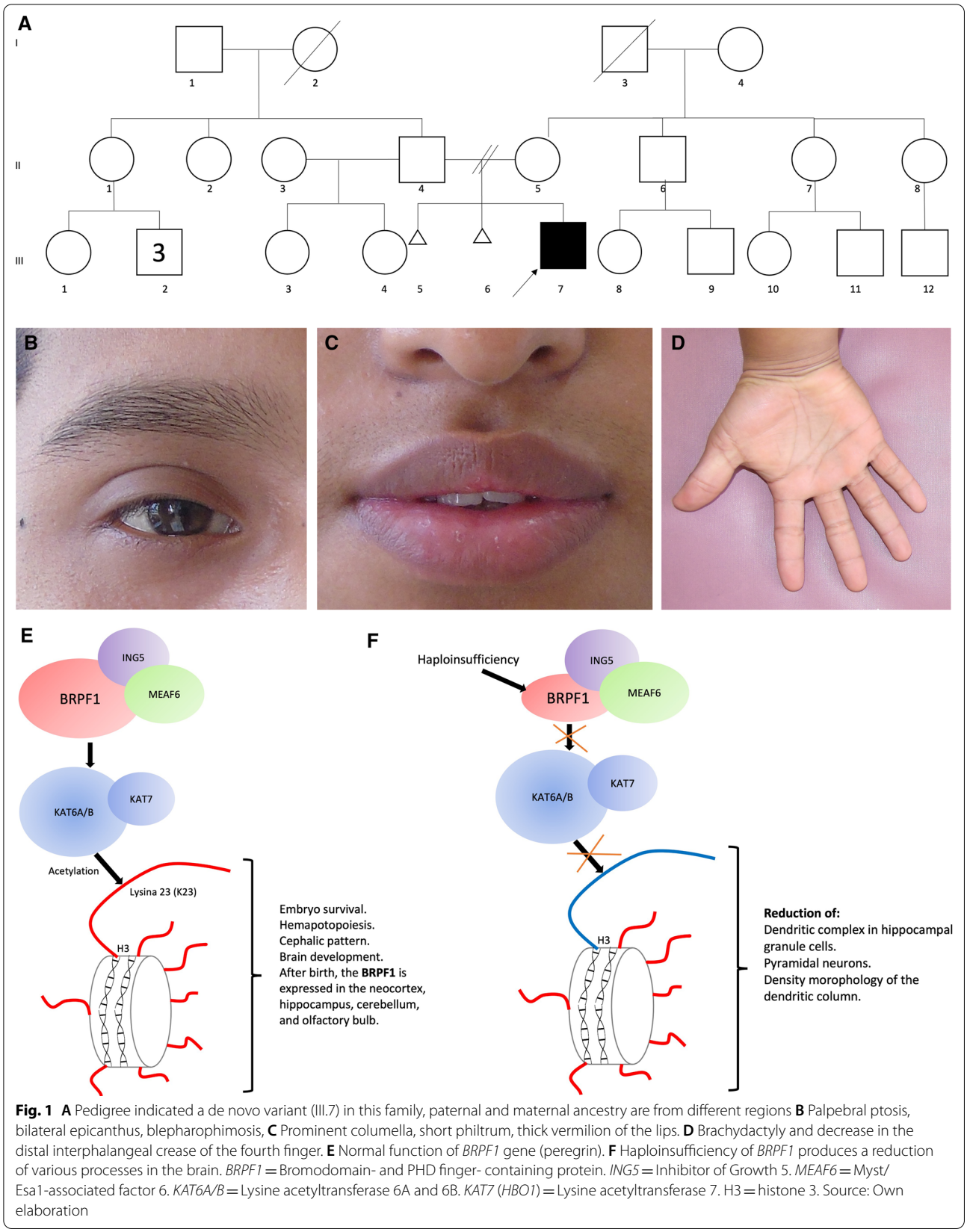

Fig. 1 **A** Pedigree indicated a de novo variant (III.7) in this family, paternal and maternal ancestry are from different regions **B** Palpebral ptosis, bilateral epicanthus, blepharophimosis, **C** Prominent columella, short philtrum, thick vermilion of the lips. **D** Brachydactyly and decrease in the distal interphalangeal crease of the fourth finger. **E** Normal function of *BRPF1* gene (peregrin). **F** Haploinsufficiency of *BRPF1* produces a reduction of various processes in the brain. *BRPF1* = Bromodomain- and PHD finger- containing protein. *ING5* = Inhibitor of Growth 5. *MEAF6* = Myst/Esa1-associated factor 6. *KAT6A/B* = Lysine acetyltransferase 6A and 6B. *KAT7* (*HBO1*) = Lysine acetyltransferase 7. H3 = histone 3. Source: Own elaboration

Conversely, in the biallelic expression, it is necessary that both alleles of a gene function simultaneously, and therefore the latter have a lower tolerance to loss in CNVs [18]. It has also been observed that in the process of evolution, during the complete genome duplication, some genes were retained, and others lost; the retained genes are called ohnologues, which are known to be involved in the embryonic development and are part of protein complexes [19].

A CMA performed on the patient showed the deletion of a chromosome fragment that contained seven genes were present in a single copy and probably de novo. All these genes require both alleles to be present to function correctly. Of these, only *BRPF1* has been associated with a genetic disease (Additional file 1). This gene codes for peregrin, a multivalent protein chromatin reader that interacts with the histone acetyltransferase and activates them (epigenetic regulation), acting in a complex to promote the acetylation of lysine 23 of histone 3 [3]. Studies in mice and zebrafish indicate that *BRPF1* is essential for the embryo's survival, hematopoiesis, head pattern, and brain development. It is expressed in the neocortex, hippocampus, cerebellum, and olfactory bulb [20–22].

BRPF1 has a haploinsufficiency coefficient of 15.77%, and with a loss of function observed/expected upper bound fraction coefficient (LOEUF) of 0.176 [23, 24]. In mice, it has been observed that *BRPF1* haploinsufficiency causes reduction of the dendritic complex in hippocampal granulosa cells and the cortical pyramidal neurons, as well as reduction in the density and morphology of the dendritic column (Fig. 1E, F) [15].

To date, the other genes included in the CNV carried by the patient described in this paper (Additional file 1) have not been associated with a disease. For example, the *OGG1* gene (8-oxoguanine DNA glycosilase) encodes an enzyme related to transcriptional regulation and the maintenance of metabolic homeostasis, and heterozygous somatic variants have been associated with renal cell carcinoma (MIM #144700) [25, 26]. Two of the other implicated genes could nevertheless be eventually associated with the patient's phenotype: *Cpen9* and *ARPC4*. *Cpen9* (copine family member 9) has been related to calcium turnover, and it can be associated with cognitive performance. However, its probability of being loss-of-function intolerant (pLI) is very low (0.001), and the LOEUF is greater than 0.35 [27]. In this sense, the *ARPC4* has a pLI of 0.938 and a LOEUF of 0.265, and its function is to mediate actin polymerization through the stimulation by promoter factor nucleation and inhibition expression, which significantly attenuates the proliferation, migration, and the invasion in bladder cancer [28, 29].

Therefore, we believe that a considerable part of the described patient's phenotype is related to the intellectual development disorder with dysmorphic facies and ptosis, or IDDDFP (MIM # 617333) [7, 30]. It is characterized by microcephaly, short stature, brain abnormalities, seizures, strabismus, joint hypermobility, fusion of cervical vertebral bodies, camptodactyly, and short metacarpal, among other symptoms [7]. To date, 39 IDDDFP patients with 18 basic clinical characteristics have been described. The most common pathogenic variants in the *BRPF1* gene were substitution, followed by deletion and intragenic duplication; however, no variants with complete deletion of the gene have so far been registered (Table 1). The patient described in this study presents ten of the 18 clinical characteristics mentioned above. These include palpebral ptosis and blepharophimosis which was the main leading clinical features to suspect the presence of this disorder; however, according to the reported cases, blepharophimosis and ptosis are observed in 63.6% and 56.8% cases, respectively, while other nonspecific characteristics, such as language delay or intellectual disability, are the most frequently described characteristics. Therefore, it is difficult to establish a gestalt phenotype based on the cases reported so far. This highlights the importance of genomic diagnosis tools that allow the description of pathogenic variants.

From the CNV perspective, 31 patients with interstitial and terminal deletions in chromosome 3p have been previously described with phenotypic characteristics like those presented by this patient. The characteristics of the 3p deletion syndrome (MIM #613792) are ID, motor delay, microcephaly, micrognathia, ptosis, long philtrum, polydactyly, hypotonia; heart, renal, and gastrointestinal anomalies; hypothyroidism, epilepsy, short stature, and risk of tumors [7, 31–33]. However, as it is a contiguous gene syndrome, the clinical characteristics will be variable and depend on the number of genes involved. Out of the ten most important characteristics of the 3p deletion syndrome, our patient has only four (Additional file 1): ID, broad nose, palpebral ptosis, and heart anomalies.

Considering all the available information and results, we believe that our patient's diagnosis is more similar to IDDDFP de novo than the 3p deletion syndrome, primarily because the CNV found involves only one gene that could be related to the clinical manifestations, either by function, its pLI, or the haploinsufficiency coefficient. Nevertheless, studies on issues such as RNA or proteins expression of the other six genes contained in the deletion (*CPNE9, OGG1, CAMK1, TADA3, ARPC4,* and *ARPC4-TTLL3*) should be carried out to know specifically how haploinsufficiency in these genes affect the phenotype of the patient.

Although parental consanguinity was not declared and the maternal and paternal grandparents come from different regions of Peru, the ROH was 0.69%, corresponding to a parental consanguinity relationship of the fifth degree.

Table 1 Clinical characteristics observed in patients with pathogenic variants in the *BRPF1* gene. *Source*: Own elaboration

Summary of the relevant clinical characteristics of the patients with variants in *BRPF1*	*N* = 39				Present case Abarca et al. 2021
	Positive	Not described	Negative	%*	
Global development delay or intellectual disability	38	1	0	100.0	+
Gross motor delay	28	10	1	96.6	−
Delayed language	27	9	3	90.0	+
Hypotonia	22	14	3	88.0	−
Fine motor delay	16	18	5	76.2	+
Round face	8	27	4	66.7	+
Blepharophimosis	21	6	12	63.6	+
Congenital spinal cord anomalies	5	31	3	62.5	−
Downslanted palpebral fissures	10	23	6	62.5	+
Broad nasal bridge	14	16	9	60.9	+
Joint hypermobility	6	29	4	60.0	−
Ptosis	21	2	16	56.8	+
Flat face	8	23	8	50.0	−
Hypertelorism	11	16	12	47.8	+
Neonatal feeding difficulties	10	18	11	47.6	−
Congenital brain anomalies	10	18	11	47.6	−
Epilepsy	11	3	25	30.6	−
Short stature	5	19	15	25.0	−
Variants in the BRPF1 gene					
Substitution	18	0	21	46.2	−
Partial deletion	13	0	26	33.3	−
Duplication	5	0	34	12.8	−
Total deletion	0	0	39	0.0	+

* Excluded to not described patients

Conclusions

To summarize, we suggest that dysmorphic features such as ptosis or blepharophimosis, if present from early years, could be considered as sufficient signs for the search for DNA pathogenic variants. Furthermore, our approach shows how imperative it is to use the molecular diagnosis in patients with these clinical features and how necessary it is to make these technologies more accessible. These tests can assist for determine of both the etiology and the prognosis, as well as the risk of recurrence.

Abbreviations

CMA: Chromosomal microarray analysis; IDDDFP: Intellectual developmental disorder with dysmorphic facies and ptosis.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s43042-022-00356-z.

Additional file 1. Supplemental information about compromised genes in the patient's CNV and related diseases to date; and frequent clinical manifestations in patients with 3pter-3p25 deletion syndrome.

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Author contributions

HHAB, FCV and RPL interpreted the CMA's data. HHAB wrote and edited the manuscript. FCV and RPL reviewed the document. All authors read and approved the final manuscript.

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Availability of data and materials

Data such as chromosomal microarray analysis or medical history supporting the findings of this study are available and may be obtained from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

All procedures performed in this study were under the ethical standards of the institutional research committee of Instituto Nacional de Salud del Niño and the 1964 Helsinki Declaration and its later amendments.

Consent for publication

The written informed consent was obtained from the family for this publication.

Competing interests
The authors declare no competing interest.

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