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ABSTRACT

Background: Since the first description of a *BRWD3*-associated nonsydromic intellectual disability (ID) disorder in 2007, 21 additional families have been reported in the literature.
Methods: Using exome sequencing (ES) and international data sharing, we identified 14 additional unrelated individuals with pathogenic *BRWD3* variants (12 males and 2 females, including one with skewed X-inactivation). We reviewed the 31 previously published cases in the literature with clinical data available, and describe the collective phenotypes of 43 males and 2 females, with 33 different *BRWD3* variants.

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Results: The most common features in males (excluding one patient with a mosaic variant) included ID (39/39 males), speech delay (24/25 males), postnatal macrocephaly (28/35 males) with prominent forehead (18/25 males) and large ears (14/26 males), and obesity (12/27 males). Both females presented with macrocephaly, speech delay, and epilepsy, while epilepsy was only observed in 4/41 males. Among the 28 variants with available segregation reported, 19 were inherited from unaffected mothers and 9 were *de novo*.

Conclusion: This study demonstrates that the *BRWD3*-related phenotypes are largely non-specific, leading to difficulty in clinical recognition of this disorder. A genotype-first approach, however, allows for the more efficient diagnosis of the *BRWD3*-related nonsyndromic ID. The refined clinical features presented here may provide additional diagnostic assistance for reverse phenotyping efforts.

1. Introduction

Intellectual disability (ID) is defined by the World Health Organization (WHO) as "a significantly reduced ability to understand new or complex information and to learn and apply new skills (impaired intelligence)". Incidence is estimated at between 0.6% and 1.6%. Genetic defects account for more than 45% of ID (Batshaw et al., 2013). Microarray analysis provides a diagnostic yield of ~12%, whereas exome sequencing (ES) increases this rate to more than 35% by detecting smaller SNVs and indels (Clark et al., 2018).

Since 2010, ES has helped to identify a significant number of new ID-associated genes (Wieczorek et al., 2018; Mir and Kuchay, 2019; De Luca et al., 2020). With more than 700 genes implicated in (often ultrarare) manifestations of ID to date, clinical recognition of these disorders by phenotype alone is often not possible, especially for rare diseases with few descriptions and for non-syndromic disorders with non-specific or variable features. At the current time, ES remains one of the most cost-effective and powerful tools for the diagnosis of ID and related disorders.

Causal variants in the *BRWD3* gene were first identified before ES was routinely used in clinical practice. In a cohort of 250 families with X-linked ID (XLID), which had normal FRAXA analysis and no variants in 61 genes known to be associated with syndromic XLID, two truncating *BRWD3* variants were identified in two families with nine affected males and one affected female (Field et al., 2007). A second cohort analyzed in the same study reported another family with a missense variant in the *BRWD3* gene. Both truncating variants were associated with developmental delay, mild to moderate ID, macrocephaly, prominent forehead and large cupped ears, while the missense variant was associated with a milder clinical phenotype (Field et al., 2007). Four additional families with ID were reported with *BRWD3* variants including two missense variants, one partial deletion of the last 30 exons, and one microduplication of 155 kb including the first 18 exons of *BRWD3* (Grotto et al., 2014; Dimassi et al., 2014; Hino-Fukuyo et al., 2015). ES also identified 7 *BRWD3* variants among 710 undiagnosed patients from the Childhood Overgrowth Study (Tatton-Brown et al., 2017). More recently, a series of sixteen new males with syndromic ID was reported with new loss-of-function *BRWD3* variants or partial gene deletions (Ostrowski et al., 2019).

In this study, we describe the phenotypes of 14 additional individuals with 13 different pathogenic variants in the *BRWD3* gene, including 12 males and 2 females, and provide a review of the literature.

2. Methods

Exome sequencing (ES) or screening using a macrocephaly panel was performed by all participants according to their own diagnostic protocols and platforms (See Supplemental data). Sanger sequencing was used to confirm *BRWD3* variants in DNA samples from the probands and relatives. *BRWD3* primers were designed based on RefSeq NM_153252.4 to confirm the identified variant and perform family segregation analysis. International data sharing platforms like GeneMatcher (see URL) were used to assemble the cohort.

The literature was also reviewed and only patients with phenotypic data available were included in our summary analysis.

3. Results

3.1. Molecular results

In this study, we assembled a cohort of 14 previously unreported individuals with 13 different *BRWD3* variants identified through ES (12 individuals) or macrocephaly panel screening (2 individuals) (Table 1). These 13 variants (NM_153252.4) included 3 nonsense, 4 frameshift, 2 splice site, and 4 missense variants. Human Splicing Finder (HSF v3.1) did not predict any significant splicing alteration for the c.473T>C missense variant, but did suggest the creation of an exonic splicing silencer site leading to a potential alteration of splicing for the c.574G>A variant. Five variants occurred *de novo* and 8 variants were maternally inherited. In one affected female (individual 5), X-inactivation analysis showed skewed X-inactivation (100%–0%).

All the new variants have been submitted in the ClinVar public database.

3.2. Clinical description

The assembled cohort included 12 males (one with a mosaic variant) and 2 females (Table 1). In order to compare and delineate their clinical phenotypes, we decided to separately describe males and females, and the male with the mosaic variant.

Among the 11 males (the one with the mosaic variant was excluded), 4/10 males had macrocephaly at birth, whereas all had macrocephaly at most recent examination suggesting that macrocephaly appears during infancy. The main dysmorphic facial features noted included high and prominent forehead present in 7/11 males and large, prominent ears in 5/11 males. Down-slanted palpebral fissures were reported in 4/11 males as well as hypertelorism/telecanthus. At clinical evaluation, 8 males had at least 2 growth parameters above the 97th percentile which suggested a possible overgrowth disorder. Regarding global development, 6/10 had muscular hypotonia and 6/11 had delayed walking. Speech delay was reported in 10/10 males, ID in 9/9 males, and epilepsy in 3/11 males. One 33-month-old male also presented with global developmental delay.

Focusing on the affected females with neurodevelopmental anomalies, one had macrocephaly, the other one had borderline occipital-frontal circumference (OFC). The female with macrocephaly had delayed speech acquisition and learning disabilities but no motor delay, whereas the other one had ID and borderline age of walking. Both had epilepsy. Skewed X-inactivation in favor of the mutated allele was reported in the female without macrocephaly.

The male with the mosaic variant had global developmental delay which had evolved into intellectual disability. Both weight and OFC were above 97th percentile.

3.3. Literature review

In our review of the literature, we identified 33 *BRWD3* variants including 9 frameshift, 11 nonsense, 6 missense, 4 splice site variants,

Table 1
Summary of the clinical and molecular features observed in individuals with BRWD3 variants (Table adapted from Grotto et al., 2014).

Features	Ind. 1	Ind. 2	Ind. 3	Ind. 4	Ind. 5	Ind. 6	Ind. 7	Ind. 8	Ind. 9	Ind. 10	Ind. 11	Ind. 12	Ind.13	Ind. 14
Gender	M	M	F	M	F	M	M	M	M	M	M	M	M	M
Age at examination	6y	15y	13y	17mths	14y	7y 6mths	33mths	3y 4mths	7.5y	7.5y	8mths	14.5y	5.5y	3y 7mths
Family history	–	–	–	–	–	–	+	+	+	–	+	+ (brother Ind.14)	+ (Brother Ind. 13)	+
Birth measurements (term/WG)	38	32	NA	36	39	Full term	38 + 5d	39 + 2d	39	37	39 + 1d	40	Full term	36
Birth weight (g)	3,680 (66th)	NA	NA	3,486 (40th)	3290 (58th)	3,175 (3rd-25th)	4,080g (84th)	3,700 (75–90th)	3,995 (82nd)	3,606 (90th)	3,850 (72nd)	4,200 (90th)	3,850 (78th)	3,271 (90th)
Birth length (cm)	51 (60th)	NA	NA	53 (91st)	50.5 (70th)	NA	–	54 (>97th)	54 (95th)	54 (>97th)	–	52 (62nd)	53 (91st)	50.5 (94th)
Birth OFC (cm)	37 (92nd)	>95th	NA	36.5 (92nd)	35 (75th)	NA	NA	38 (>97th)	37.5 (94th)	37 (97th)	39.5 (>99th)	41 (>99th)	37 (92nd)	33 (44th)
Facial features														
Long face	–	–	–	–	–	–	–	–	–	–	–	–	–	–
High and prominent forehead	+	+	–	+	–	–	–	–	+	+	+	–	+	–
Frontal bossing	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Large prominent ears	–	+	–	–	–	–	+	+	+	–	–	–	–	+
Pointed chin	–	–	–	–	–	–	–	–	+	–	–	–	–	–
Other features	Triangular face, large mouth with thick lips, macrognathia, epicanthal folds	Hypertelorism, thin lips		Bitemporal widening, hypertelorism, downslanting palpebral features, round face	Facial asymmetry, flat profile, bulbous nose with protruding root, thin lips, dental malposition	–	synophrys, peri-orbital fullness, minimal down slant of his eyes, high palate	–	Dolichocephaly, long eyelashes	Mildly down slanting palpebral fissures, low set fleshy ears	Hypertelorism, flat nose consistent with right cleft	Deep-set eyes, downslanting palpebral fissures	–	Asymmetric face, telecanthus, hypoplastic midface, long and full philtrum, almond shaped eyes, synophrys, tubular nose, broad mouth with downturned corners, tented upper lip, stuck-on chin
Measurements at last follow-up														
Weight (kg)	22 (70th)	NA	64 (93rd)	14 (>98th)	60 (80th)	39.8 (>99th)	16.7 (94th)	20 (>99th)	40.8 (>99th)	62.5 (>99th)	10.435 (82nd)	82.2 (>97th)	22.3 (85th)	20.1 (98th)
Height (cm)	121 (85th)	NA	158 (84th)	89.5 (>99th)	169 (90th)	128 (70th)	101 (97th)	102.6 (86th)	137.5 (>97th)	146.5 (>97th)	79.5 (>97th)	168 (58th)	115.5 (71st)	108 (98th)
Body Mass Index	15 (25th-50th)	NA	25.6 (>97th)	17.5 (50th-75th)	19.6 (50th-75th)	24.3 (>97th)	16.4 (71st)	18.9 (>97th)	21.6 (>99th)	29.1 (>99th)	16.5 (38th)	29.1 (>99th)	16.7 (84th)	17.2 (91st)
OFC (cm)	55 (>97th)	60 (>97th)	56.7 (>97th)	53 (>99th)	57 (95th-97th)	55.5 (>97th)	51.8 (97th)	55 (>99th)	60 (>97th)	60 (>97th)	50.6 (>97th)	59 (>97th) at 8years	60 (>97th)	55.6 (>99th)
Hand and foot	–	Clinodactyly of the fifth finger	–	–	Small and inverted toenails	–	–	–	Broad fingers and toes	–	2/3 syndactyly feet	Bilateral valgus pedis	–	Unusual creasing on the right palm
Pubertal development	–	NA	–	–	Early puberty at 8 years	–	NA	NA	NA	–	NA	Tanner 1	–	NA
Other morphological features	Pectus excavatum, wide spaced nipples	Hypospadias	–	Mild submucosal cleft palate Snoring Nasal sounding voice GERD	Cutaneous brown stains	Poor sleep Recurring vomiting	Mild pectus excavatum, joint laxity, small penile (<10th), shawl scrotum, CALM, pharyngo-laryngomalacia	–	Cryptorchidism Scoliosis	–	Mild hypospadias	Inverted papilla mammaria	–	Large anterior fontanel, slightly advanced bone age, ankyloglossia
Developmental features														
Muscular hypotonia	–	NA	–	+	+	+	–	+	+	–	+ (poor head balance)	+	–	+
Age of walking	18mths	19mths	15mths	17mths	18mths	24mths	22mths	18mths	2-3y	19mths	No independent walk at 19mths	16mths	11mths	30mths
Speech delay	+	+	+	+	+	+	+	NA	+	+	+	+	+	+

(continued on next page)

Table 1 (*continued*)

Features	Ind. 1	Ind. 2	Ind. 3	Ind. 4	Ind. 5	Ind. 6	Ind. 7	Ind. 8	Ind. 9	Ind. 10	Ind. 11	Ind. 12	Ind.13	Ind. 14
Intellectual disability	+	+	Learning disability	+	+	+	−	+	Mild	Mild	NA	+	+	+
Shyness	+	−	−	−	−	−	−	NA	−	−	NA	−	+	−
Other features	Atypical epilepsy with centro-temporal spikes	ASD, spastic paraplegia and lower limbs' pyramidal features	Primary generalized epilepsy	−	ADHD, anxiety, seizures	ADHD	Impulsive/compulsive features, ADHD, echolalia, aggression, obsessive eating, high pain threshold	−	Anger outburst, difficulties with tandem gait and balance, myopathic changes on electromyography	Autism, ADHD, impulsivity and anger		ASD, frontal epilepsy		ASD, aggressive behavior, seizures, tight Achilles tendons
BRWD3 genomic variant	c.2801G > C	c.568C > T	c.1247delC	c.473T > C	c.574G > A	c.2598_260ldupAAAT mosaic	c.778C > A	c.5017A > T	c.4620delA	c.3264-1G > A	c.5248A > T	c.1521+1G > A	c.1521+1G > A	c.2462_2465delACAG
BRWD3 aminoacid variant	p.Arg934Pro	p.Arg190*	p.Ser416Leufs*11	p.Phe158Ser	p.Gly192Arg	p.Leu868Lysfs*15	p.Leu260Ile	p.Arg1673*	p.Lys1540Asnfs*70	NA	p.Arg1750*	NA	NA	p.Asp821Valfs*16
Type of variants	Missense	Nonsense	Frameshift	Missense	Missense	Frameshift	Missense	Nonsense	Frameshift	Splice site variant	Nonsense	Splice site variant	Splice site variant	Frameshift
Familial segregation	Maternally inherited	De novo	De Novo	Maternally inherited	De Novo	De Novo	De novo	Maternally inherited	Maternally inherited	Maternally inherited	Maternally inherited	Maternally inherited	Maternally inherited	Maternally inherited

ADHD: Attention Deficit Hyperactivity Disorder; ASD: Autism spectrum disorder; CALM: Café-au-lait macules; d: day; mths: months; NA: not available; OFC: Occipital-frontal circumference; GERD: Gastroesophageal reflux disease; WG: weeks of gestation; y: year.

and 3 large deletions including *BRWD3*. Three nonsense variants (p. Gln151*, pArg190* and p.Tyr232*) have been reported in at least two unrelated individuals (Fig. 2) (Field et al., 2007; Grotto et al., 2014; Tatton-Brown et al., 2017; Tenorio et al., 2019; Ostrowski et al., 2019). Within these studies, only 31 individuals had associated clinical data available for analysis. As part of the "Spanish Overgrowth Registry", using targeted sequencing with two "overgrowth panels", OGLYVAS V1.0 (183 genes) and Overgrowth v2.3 (212 genes), 4 *BRWD3* variants were identified, but clinical data were not reported in detail (Tenorio et al., 2019). Therefore, these individuals were not included in our summary review which included phenotypic information from 31 reported individuals with 21 *BRWD3* variants (Table 2).

4. Discussion

We present a large series of 14 individuals with 13 novel *BRWD3* variants in addition to 31 individuals with 20 pathogenic variants that have been reported to date (Field et al., 2007; Grotto et al., 2014; Tatton-Brown et al., 2017; Tenorio et al., 2019; Ostrowski et al., 2019). Including the individuals previously published, we summarized the clinical findings in 45 individuals (43 males and 2 females) from 34 different families harboring 33 different *BRWD3* variants, thus expanding and refining the *BRWD3*-related phenotypic spectrum. While 9 variants occured *de novo* in 7 males and 2 females, 16 other variants are maternally inherited with an X-linked inheritance pattern (for the others segregation remains unknown).

Phenotype data are available or partially available for 39/44 individuals, including 37 males (one with a mosaic variant) and 2 females. In males (excluding the case with the mosaic variant), the phenotype is characterised by ID (39/39 males), facial dysmorphism (24/25 males), macrocephaly (28/35 males), overgrowth (20/35 males), and obesity (12/27 males) (Table 1). Macrocephaly was present at birth in 12/20 males, but also developed postnatally in 28/35 males (among the others, one had borderline OFC measured around the 90th-95th percentile, one has an OFC at the mean, and for the others no data were available). Dysmorphic facial features included a high and prominent forehead (18/ 25 males), large and prominent ears (13/25 males), and prominent pointed chin (12/25 males), giving these individuals an appearance of a long triangular face (Fig. 1). More than one third of the males also presented with large fingers and/or toes (11/31 males). Additional features included cleft palate (3/25 males), scoliosis (3/25 males), kyphosis (2/25 males), pectus excavatum (3/25 males), and seizures (4/ 36 males). Hypospadias or cryptorchidism have also been reported in a few individuals. ID is a consistent feature (39/39 males) and is often associated with behavioral disturbances (23/36 males), including shyness (10/36 males), attention deficit hyperactivity disorder (ADHD; 8/36 males), and autism spectrum disorder (ASD; 6/36 males). The male with a mosaic variant presented with ID, ADHD, and macrocephaly (+2.1SD), but lacked dysmorphism including skeletal and congenital anomalies. Coexistence of at least two growth parameters >+2SD including OFC, height, and weight (20/35 males) may be suggestive of an overgrowth syndrome. Sotos syndrome appears to be the main differential diagnosis, because of the association of macrocephaly, high forehead, and long chin (Tatton-Brown et al., 2017). The association of hypospadias/cryptorchidism and obesity could also suggest the genital-obesity-ID syndromes.

The *BRWD3*-related disorder shows some phenotypic similarities in males and females, such as ID (1/2 females) and macrocephaly (1/2 females) (Table 1). However facial dysmorphisms were absent in both females described in this report, whereas epilepsy (present in both females) is only reported in 4/36 males. One female presented with syndromic ID and ADHD (individual 5), while the developmental phenotype in the other female (individual 3) appears less severe with only learning difficulties without behavioral disturbances. This syndromic phenotype includes facial dysmorphism, supernumerary nipples, partial agenesis of the corpus callosum, foot anomalies, and early

puberty. Individual 5 had a heterozygous missense variant with complete skewing of X-inactivation in favor of the *BRWD3* mutant allele which may explain the more severe phenotype.

ID, speech delay, macrocephaly, and facial dysmorphism, with high forehead, long face, and large prominent ears, appear to be the main features described in individuals with *BRWD3* variants. These non-specific characteristics make it difficult to diagnose a *BRWD3*-associated disorder in the absence of corresponding genotype information. Indeed, in 13 of 14 newly described individuals, *BRWD3* variants were detected by untargeted next generation sequencing (i.e. ES). Reverse phenotyping therefore plays an important role in the decision process of validating those variants. Moreover, for medical follow-up, particular attention must be paid to possible sensory disorders that might mask autism-associated behaviors, as well as abnormalities in growth and stature including possible scoliosis, kyphosis, and pectus excavatum. Physical and occupational therapy exercise approaches can be beneficial for patients especially in case of hypotonia and/or muscle weakness. Studies in *Drosophila* have suggested that dBRWD3 may function as a tumor suppressor and is disrupted in leukemia. However, no signs of pancytopenia, preleukemia, or hemihypertrophy with tumor predisposition have been found in the patients with germline loss-of-function variants in *BRWD3*.

To date, more than 30 different *BRWD3* variants have been identified, including 24 truncating and 6 non-truncating variants, as well as 3 large deletions including the gene (Fig. 2). The phenotypic severity was initially suspected to be correlated with the type of pathogenic variant, with truncating variants leading to more severe phenotype (Field et al., 2007; Grotto et al., 2014). Additional data does not appear to support

this hypothesis, as ID, speech delay, and behavioral abnormalities are described in individuals with both frameshift and missense variants. Facial dysmorphism also does not appear to be less marked in patients with missense variants. Moreover, *BRWD3* variants follow an X-linked mode of inheritance. While X-linked genes account for 5–10% of ID in males (Lubs et al., 2012), there is more limited data on the overall contribution to ID in females.

BRWD3 was initially identified on the X chromosome through study of t(X;11)(q13;q23) translocations identified in B-cell chronic lymphocytic leukemia (B-CLL) patients (Kalla et al., 2005). In *Drosophila*, several experiments suggest a role for dBRWD3 in the Janus tyrosine kinase/signal transducer and activator of transcription (JAK/STAT) pathway, a signalling cascade whose evolutionarily conserved roles include cell proliferation and regulation of hematopoesis. Indeed, a transposon insertion in the fourth intron of its ortholog CG31132 (hereafter termed dBRWD305842) was responsible for late embryonic lethality in *Drosophila* (Müller et al., 2005). Interestingly, in loss-of-function JAK/STAT mutant brains, the neuroepithelial cells lose epithelial cell characteristics and differentiate prematurely, while ectopic activation of this pathway is sufficient to induce neuroepithelial overgrowth in the optic lobe (Wang et al., 2011). Further investigation of the role of the JAK/STAT signaling pathway may be warranted including its role in clinical overgrowth and macrocephaly in males with *BRWD3* pathogenic variants.

In conclusion, this study defines the core clinical phenotype associated with alterations in *BRWD3*, including ID with frequent macrocephaly and additional variable features including obesity and behavioral disturbances, that may be non-specific and difficult to

Table 2
Clinical and molecular features observed in the 43 males with *BRWD3* variants from the present series and the literature.

Features	Field et al. (2007)	Grotto et al. (2014)	Tenorio et al. (2019)	Ostrowski et al. (2019)	Present study	Total
Gender (n=)	4 M	5 M	5 M	17 M[a]	12 M[b]	43 M
Median age at examination (Range)	15y (9–38)	24y (19–27)	13y (6y 9mths-25)	8.2y (3.3–22)	6.75y (0,8–15)	–
Family history	4/4	4/5	3/5	5/11	7/11	23/36 (63.8%)
Birth measurements						
Birth weight >+2SD	0/3	1/5	2/4	1/4	0/10	4/26 (15.4%)
Birth length >+2SD	NA	1/5	2/4	1/2	2/8	6/19 (31.6%)
Birth OFC >+2SD	2/3	1/1	2/4	2/2	4/10	12/20 (60%)
Facial features						
Long face	2/4	0/5	0/5	NA	0/11	2/25 (8%)
High and prominent forehead	1/4	5/5	5/5	NA	7/11	18/25 (72%)
Frontal bossing	2/4	0/5	0/5	1/1	0/11	3/26 (11.5%)
Large prominent ears	3/4	2/5	3/5	1/1	5/11	14/26 (53.8%)
Pointed chin	4/4	3/5	3/5	0/1	1/11	11/26 (42.3%)
Other features	2/4	5/5	5/5	2/2	9/11	23/27 (85,2%)
Measurements at last follow-up						
Weight >+2SD	0/4	2/5	3/5	6/8	6/10	17/32 (53%)
Body Mass Index >+2SD	0/4	2/5	2/4	4/4	4/10	12/27 (44.4%)
Height >2SD	0/4	1/5	1/5	4/10	5/10	11/34 (32.4%)
Overgrowth	1/4	2/5	3/5	6/10	8/11	20/35 (57,1%)
OFC >+2SD	4/4	4/5	4/5	6/10	11/11	28/35 (80%)
Hand and/or foot anomalies	1/1	5/5	3/3	5/6	5/11	14/26 (53.8%)
Other morphological features	3/3	5/5	3/3	7/8	8/11	26/30 (86.7%)
Developmental features						
Muscular hypotonia	2/2	1/5	1/5	2/3	6/10	12/25 (0.48%)
Walking delay	1/3	0/5	1/2	1/3	6/11	9/24 (37.5%)
Speech delay	3/3	5/5	3/3	3/4	10/10	24/25 (96%)
Intellectual disability	4/4	5/5	5/5	16/16	9/9	39/39 (100%)
Shyness	1/3	4/5	1/5	3/11	1/9	10/33 (30.3%)
Type of variants						
Missense	0/2	0/1	1/4	0/11	3/10	4/28 (14.3%)
Frameshift	1/2	0/1	0/4	3/11	2/10	6/28 (21.4%)
Nonsense	0/2	1/1	2/4	7/11	3/10	13/28 (46.4%)
Splice site variant	1/2	0/1	1/4	1/11	2/10	5/28 (17.9%)
Other	–	1 partial deletion	–	2 partial deletions	–	3 partial deletions
Familial segregation						
De Novo	0/2	1/2	0/3	6/8	2/10	9/25 (36%)
Maternally inherited	2/2	1/2	3/3	2/8	8/10	16/25 (64%)

[a] One was excluded from analysis because already reported in Field et al. (2007).

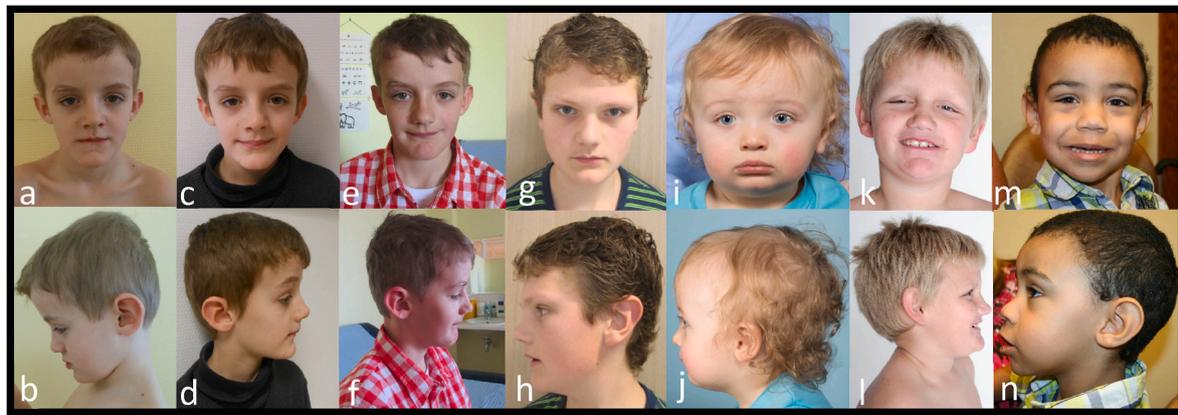[b] One male with mosaic variant was excluded from analysis.

Fig. 1. Facial pictures of individuals with *BRWD3* variants showing facial dysmorphism with mainly high and prominent forehead, large prominent ears, and prominent pointed chin (a, b, c, d, e, f: individual 1 at different ages; g, h: individual 2; i, j individual 4; k, l: individual 13; m, n: individual 14).
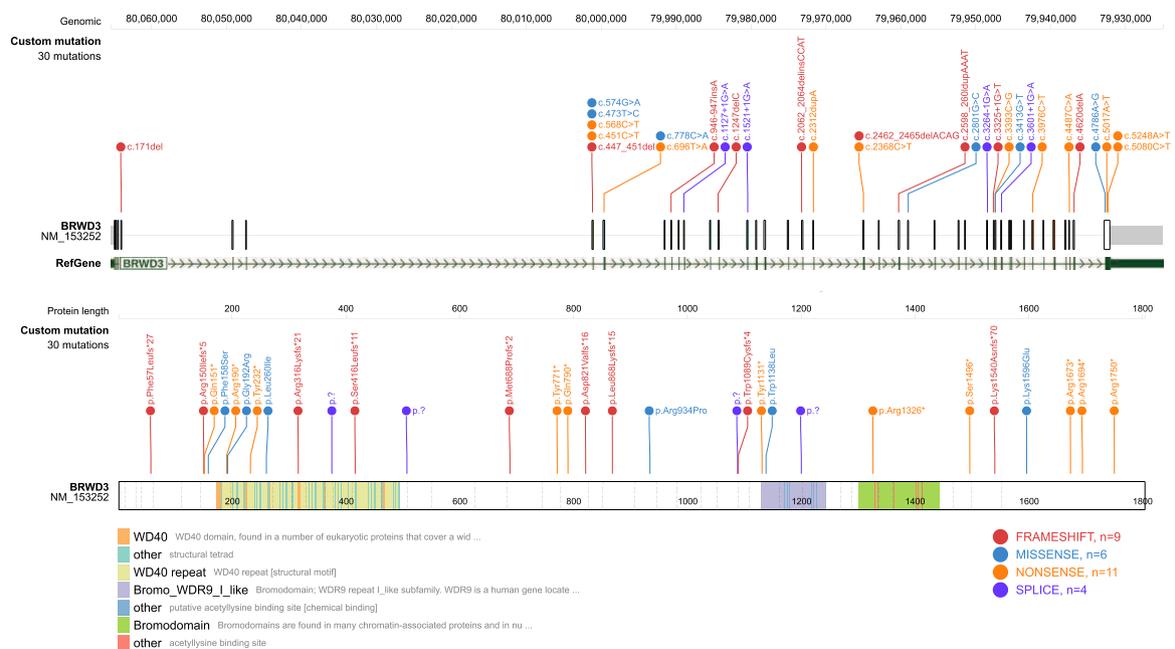

Fig. 2. Diagram of the BRWD3 transcript (NM_153252.4) (upper panel) and protein (NP_694984.4) (lower panel) with WD40 containing repeat domain and bromodomains, showing the location of the different *BRWD3* SNV/indel variants generated using ProteinPaint: https://pecan.stjude.cloud/home. The large *BRWD3* deletions/duplications are not included in the figure. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

recognize for clinicians. Thus, we suggest a genotype-first approach is better suited for the diagnosis of this disorder.

URLs

http://genome.ucsc.edu
http://evs.gs.washington.edu/
http://exac.broadinstitute.org/
https://genematcher.org
http://www.ncbi.nlm.nih.gov/clinvar.

CRediT authorship contribution statement

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Declaration of competing interest

The authors declare no conflict of interest.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmg.2022.104670.

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