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Null variants and deletions in BRWD3 cause an X-linked syndrome of mild-moderate intellectual disability, macrocephaly, and obesity: a series of 17 patients

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Keywords:	BRWD3, intellectual disability, overgrowth, macrocephaly, X-linked

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Abstract

BRWD3 has been described as a cause of X-linked intellectual disability, but relatively little is known about the specific phenotype. We report the largest *BRWD3* patient series to date, comprising 17 males with 12 distinct null variants and two partial gene deletions. All patients presented with intellectual disability, which was classified as moderate (65%) or mild (35%). Behavioral issues were present in 75% of patients, including aggressive behavior, attention deficit/hyperactivity and/or autistic spectrum disorders. Mean head circumference was +2.8 SD (2.8 standard deviations above the mean), and mean BMI was +2.0 SD (in the context of a mean height of +1.3 SD), indicating a predominant macrocephaly/obesity phenotype. Shared facial features included a tall chin, prognathism, broad forehead, and prominent supraorbital ridge. Additional features, reported in a minority (<30%) of patients included cryptorchidism, neonatal hypotonia, and small joint hypermobility. This study delineates the clinical features associated with *BRWD3* null variants and partial gene deletions, and suggests that *BRWD3* should be included in the differential diagnosis of patients with an overgrowth-intellectual disability (OGID) phenotype, particularly in male patients with a mild or moderate intellectual disability associated with macrocephaly and/or obesity.

Keywords

BRWD3, intellectual disability, overgrowth, macrocephaly, X-linked

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1. Introduction

BRWD3 is an established X-linked intellectual disability gene, associated with a phenotype in males characterized by intellectual disability and macrocephaly (OMIM 300553; Mental retardation, X-linked 93; MRX93). Although *BRWD3* has been recognized as an intellectual disability gene since 2007 with reports of 27 affected males, limited clinical data have been published, and the *BRWD3* phenotype has been poorly understood *(Field et al., 2007; Grotto et al., 2014; Grozeva et al., 2015; Tatton-Brown et al., 2017; Tenorio et al., 2019)*. However, following the recent identification of seven unrelated patients with likely pathogenic *BRWD3* variants in a study to investigate overgrowth with intellectual disability (OGID), it has been suggested that the *BRWD3* phenotype should be considered an emerging member of the OGID syndrome family *(Tatton-Brown et al., 2017).*

BRWD3 (bromodomain- and WD repeat-containing protein 3, OMIM 300553) at chromosome locus Xp21.1 encodes a 1802 amino-acid protein containing eight N-terminal WD40 repeats and two C-terminal bromodomains (Figure 1A). BRWD3 was initially described as a putative transcription factor, and the *Drosophila* homologue was found to be a positive regulator of the JAK/STAT pathway *(Müller, Kuttenkeuler, Gesellchen, Zeidler, & Boutros, 2005)*. The protein has been shown to associate with transcriptionally-active chromatin *(D'Costa, Reifegerste, Sierra, & Moses, 2006)*, and may mediate its effects through histone H3.3 *(Chen et al., 2015)*.

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Here we report 17 patients with 12 distinct null variants and two partial gene deletions, we clarify the *BRWD3* phenotype, and we propose evidence-based management guidelines to optimize patient care.

2. Methods

The study was approved by the UK Research Ethics Committee (10/H0305/83), granted by the Cambridge South Research Ethics Committee and the London Multicenter Ethics Committee (MREC01/02/44 and 05/MRE02/17). Informed consent was obtained for all participants.

17 patients were included in the study (Table 1), including eight previously reported patients *(Field et al., 2007; Tatton-Brown et al., 2017)*. In order to generate robust clinical data, specific to *BRWD3,* we only included patients who were (1) male and (2) not found to have additional sequence or copy number variants that could potentially confound the phenotype.

BRWD3 sequence variants were identified in 15 patients from 12 families. All 12 variants were unique to each family (Figure 1A). Nearly all of these patients (14/15) were recruited through the Deciphering Developmental Disorders (DDD) Study or the Childhood Overgrowth (COG) study, using a trio-based exome sequencing strategy and methods as previously described *(Firth, Wright, DDD Study, 2011; Tatton-Brown et al., 2017)*. One patient (patient 10) was diagnosed by exome sequencing in the NHS diagnostic laboratory. The sequence variants were reported relative to the canonical transcript (NM_153252.4), and all were classified as likely

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pathogenic according the American College of Medical Genetics and Genomics guidelines, as detailed in Supplementary Table 1 *(Richards et al., 2015)*. The 12 *BRWD3* sequence variants included six stop-gain, four frameshift and two canonical splice site variants (predicted to disrupt normal splicing), which were predicted to result in haploinsufficiency of a gene which exhibits a high degree of loss-of-function constraint (pLI 1.00, haploinsufficiency index 28.62%, PVS1). None of the reported variants were present in the gnomAD population database (PM2). Inheritance data were available for 12 patients with sequence variants; all were maternally inherited.

Two patients were found to have *de novo* partial deletions of *BRWD3* (see Figure 1B). Patient 16 had a deletion of approximately 80kb encompassing exons 1-13. Patient 17 had a deletion of approximately 97kb, spanning from exon 7 to the end of the coding sequence. The deletions did not extend into any other known genes.

Photographs, with accompanying consent to publish, were requested from all and received from the 11 patients shown in Figure 1C. Clinical data were obtained through face-to-face review by one of the authors, all experienced dysmorphologists, and a standardized proforma. Unfortunately, the majority of patients did not have detailed developmental and/or behavioral assessments, but for the purposes of our study, we asked the referring clinician to classify intellectual disability (if present) as mild, moderate or severe. Mild intellectual disability described an individual with delayed milestones who would attend a mainstream school with some support and live independently, with support, as an adult. Moderate intellectual disability described an individual who required high-level support in a mainstream school or special educational needs schooling and would

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live with support as an adult. Severe intellectual disability described an individual who required special educational needs schooling, had limited speech, and would not be anticipated to live independently as an adult.

Growth parameter Z-scores were calculated with reference to the World Health Organization Child Growth Standards (https://www.who.int/childgrowth/standards/en/), and are expressed in standard deviations above/below the mean (SD).

3. Results

Clinical data from all 17 male patients aged between 3 and 22 years at recruitment are summarized in Table 1. Detailed clinical data for 12 individual patients and, where relevant, their family members, are presented in the Supplementary Data. Unfortunately, detailed clinical data were not available for five of the patients: four had been lost to follow-up, and one restricted their consent to publication of limited data (variant details, growth measurements, general neurobehavioral phenotype).

All 17 patients (100%) presented with intellectual disability. The majority (11/17, 65%) were classified in the moderate range, and the remaining patients were mildly affected. Behavioral issues were common (12/16, 75% [data unavailable for one patient]) and are detailed in the Supplementary Data. Patients presented with combinations of aggressive behavior (6/16, 38%), attention deficit/hyperactivity disorder (4/16, 25%), and autistic spectrum disorder (3/16, 19%). Shyness in social situations was commonly reported (3/16, 19%).

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Detailed anthropometric data are presented in Figure 2, Table 1 and Supplementary Figure 1. The mean head circumference was +2.8 SD. Macrocephaly (head circumference ≥ +2 SD) was reported in 12/17 (71%), of whom 3/17 (18%) had extreme macrocephaly (> +4 SD). All patients had a head circumference greater than the age-adjusted mean. This suggests that the *BRWD3* phenotype encompasses a range of head circumferences, with the mean shifted to the right (+2.8 SD in our cohort).

The mean BMI was +2.0 SD. Nine of 17 (53%) patients had a BMI ≥ +2 SD. The BMI ranged from -1.1 SD to +6.6 SD.

The mean height was +1.3 SD. Only four (24%) patients had a height ≥ +2 SD. The heights ranged from -1.2 SD to +3.2 SD.

Shared facial features included a tall chin with associated horizontal skin crease, prognathism, broad forehead, and prominent supraorbital ridge (Figure 1C).

There were no additional consistently reported medical issues. Clinical features reported in multiple patients included cryptorchidism (5/17, 29%), neonatal hypotonia (4/17, 24%), and small joint hypermobility (4/17, 24%).

4. Discussion

It is over a decade since *BRWD3* disruption was first shown to cause an intellectual disability syndrome in males *(Field et al., 2007).* However, with only three clinical reports, we know surprisingly little about the *BRWD3* phenotype *(Field et al., 2007;*

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Grotto et al., 2014; Tenorio et al., 2019). The current clinical series, including 17 patients, represents the largest single *BRWD3* study to date and has enabled us to investigate this intellectual disability phenotype, to provide better clinical information to patients and their families, and to facilitate the development of evidence-based management guidance.

The *BRWD3* phenotype, although sometimes non-specific with intellectual disability the only consistent feature, should be considered in a male who additionally has an X-linked intellectual disability family history, macrocephaly, obesity, and/or behavioral problems including autistic spectrum disorder, shyness, attention deficit/hyperactivity disorder and aggression.

A wide list of intellectual disability syndromes should be considered in the differential diagnosis of the *BRWD3* phenotype. However, if macrocephaly is present, other members of the OGID syndrome family should also be considered. For instance, the *PTEN* hamartoma tumor syndrome (OMIM 158350), *PPP2R5D* syndrome (OMIM 616355), Smith-Kingsmore syndrome, associated with MTOR gain-of-function mutations (OMIM 616638), and *AKT3* syndrome (OMIM 615937) should be considered where there is macrocephaly ≥ +3 SD. In addition, although tall stature (above +2 SD) is an infrequent finding in the *BRWD3* phenotype, other OGID syndromes including Sotos syndrome (OMIM 117550), Tatton-Brown-Rahman syndrome (OMIM 615879), Weaver syndrome (OMIM 277590), and the *CHD8* overgrowth syndrome (OMIM 615032) can present with isolated macrocephaly without tall stature.

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Relatively little is known about the biology of the *BRWD3* phenotype, and to our knowledge, there have been no reports of knockout models or functional studies in mammalian models. However, a possible mechanism of pathogenesis of the OGID phenotype is suggested by experiments in *Drosophila,* which found that loss of the *BRWD3* homologue leads to increased histone H3.3 levels and wide-ranging effects on gene transcription mediated through histone-dependent chromatin regulation *(Chen et al., 2015)*. We therefore speculate that *BRWD3* may eventually join the emerging family of genes with a role in epigenetic regulation and OGID (*Tatton-Brown et al., 2017)*. However, further work is required to investigate this and establish the specific mechanism by which *BRWD3* haploinsufficiency leads to overgrowth and intellectual disability.

In conclusion, this study presents the largest *BRWD3* patient series to date, and delineates the emerging phenotype associated with *BRWD3* null variants and partial gene deletions. Reassuringly, no consistent *BRWD3* clinical associations have emerged that require ongoing medical surveillance. However, we propose that patients receive support to optimize their cognitive and motor development, and may require physiotherapy and/or occupational therapy input for small joint hypermobility. In order to generate robust clinical data, we only included males with likely pathogenic or pathogenic *BRWD3* variants. However, for many of our patients, their mothers and/or sisters were carriers for the *BRWD3* variant. As genetic testing becomes more accessible, it is likely that greater numbers of patients (both male and female) with *BRWD3* variants will be identified, allowing further extension and clarification of the phenotype (in males and females), iteration of the proposed

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management guidance, and investigations of genotype-phenotype associations in this X-linked intellectual disability syndrome, which we believe should be considered a member of the OGID syndrome family.

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Acknowledgements

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Conflicts of Interest

The authors declare that they have no conflict of interest.

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Web resources

BRWD3 reference transcript, https://www.ncbi.nlm.nih.gov/nuccore/NM_153252.4

Online Mendelian Inheritance in Man, https://omim.org/

Genome Aggregation Database (gnomAD), https://gnomad.broadinstitute.org/

World Health Organization Child Growth Standards, https://www.who.int/childgrowth/standards/en/

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Table legends

Table 1. Molecular and clinical details of 17 patients with *BRWD3* sequence variants or partial gene deletions. Patients are numbered in order of sequence variant location (5' → 3'), followed by patients with deletions. Growth measurements are presented as Z-score (SD from the mean expected measurement for age/gender). DECIPHER identifiers are listed for patients with open-access records, in keeping with the DECIPHER publication policy.

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Figure legends

Figure 1. A: BRWD3 protein domains and location of the 12 sequence variants. W, WD40 domains. Br, bromodomains. **B:** Location of the two partial gene deletions. **C:** Patient photographs showing common facial features including tall chin with associated horizontal skin crease, prognathism, broad forehead, and prominent supraorbital ridge. Note Patient 11 was included in the original publication describing the *BRWD3* phenotype *(Field et al., 2007)*.

Figure 2. Standardized growth parameters (Z-scores) in *BRWD3* patients (n=17). Bars represent mean ± SD. Solid horizontal line indicates the population average for age/gender (Z-score = 0 SD); dashed horizontal lines indicate Z-score cut-offs of ±2 SD. Solid red points indicate parameters with a mean Z-score of ≥ +2 SD (head circumference, body mass index); circles indicate parameters with a mean Z-score of < +2 SD (height).

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Supplementary material

Supplementary Table 1. Sequence variant classification according to the ACMG criteria *(Richards et al., 2015)*.

Supplementary Figure 1. Relationship between age and growth parameters (Z-scores). Solid horizontal line indicates the population average for age/gender (Z-score = 0 SD); dashed horizontal lines indicate Z-score cut-offs of ±2 SD. Note that each data point represents a distinct patient at the age of recruitment, rather than longitudinal growth measurements. There were no significant correlations between age and growth parameters.

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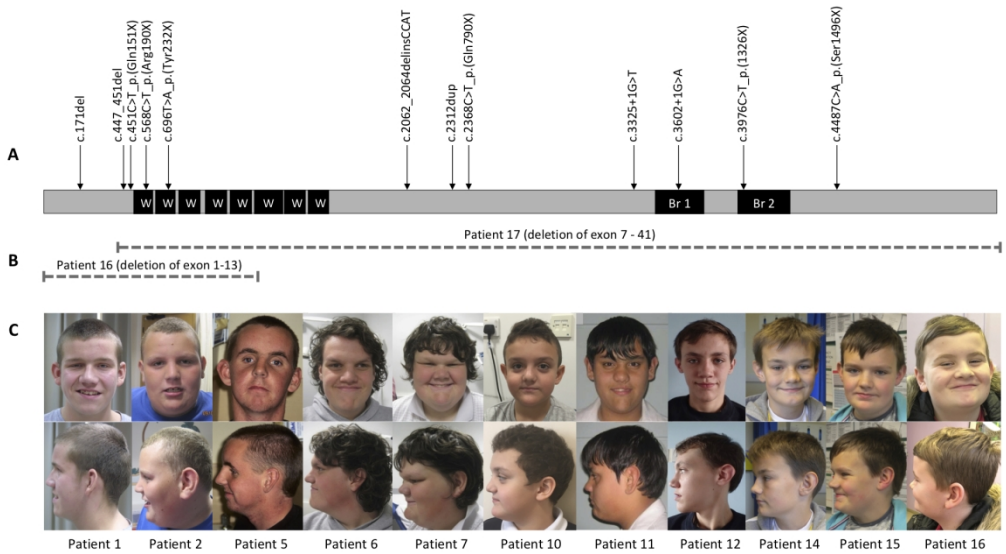

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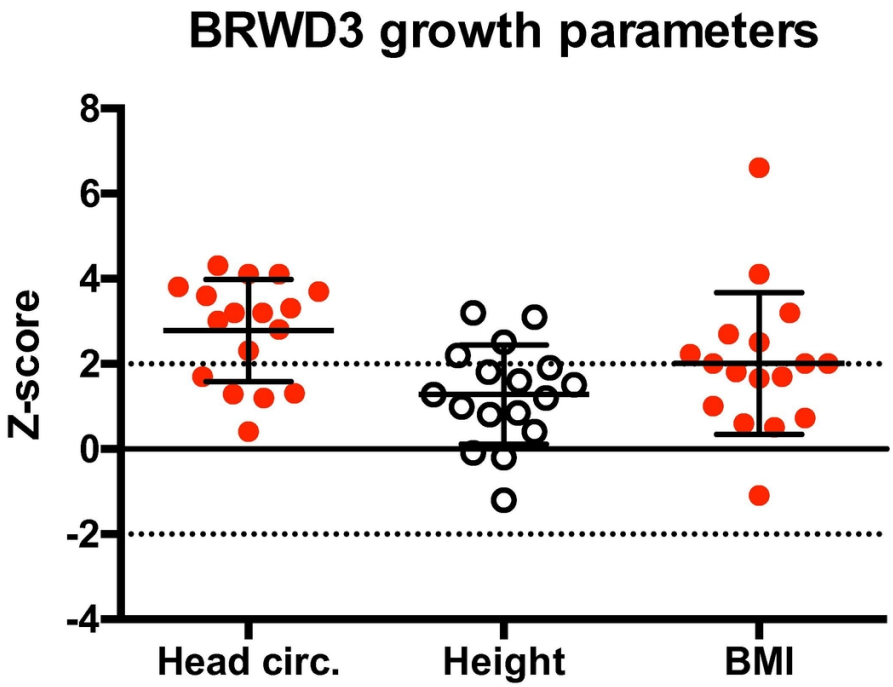
338x190mm (150 x 150 DPI)



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99x70mm (300 x 300 DPI)

Table 1

Patient ref	Sex	Age (yrs)	Variant	ID	Behavior	BW	Ht	HC	Wt	BMI	Additional medical problems	PMID / published patient ref
1	M	13.5	c.171del	Mod.	Shy	0.0	-0.2	3.2	2.0	2.7	Hypotonia	-
2	M	12.2	c.447_451del	Mod.	ASD	-0.3	3.1	3.8	4.3	4.1	Congenital dislocation of the hips, long-sighted, hypospadias	28475857/ COG1785
3	M	4.6	c.451C>T_p.(Gln151X)	Mod.	-	0.3	0.4	2.8	1.4	1.8	-	28475857/ COG1976
4	M	3.3	c.451C>T_p.(Gln151X)	Mod.	-	1.0	-0.1	3.7	1.6	2.5	-	-
5	M	22.0	c.568C>T_p.(Arg190X)	Mild	-	1.5	1.5	4.1	1.3	0.6	Hypotonia, bilateral cryptorchidism, seizures, migraine, dental crowding	28475857/ COG0222
6	M	18.7	c.696T>A_p.(Tyr232X)	Mild	Aggressive	0.5	2.5	3.6	3.0	2.0	Unilateral cryptorchidism, small joint hypermobility	-
7	M	16.0	c.696T>A_p.(Tyr232X)	Mod.	ASD, aggressive	1.4	1.2	3.2	3.9	3.2	Small joint hypermobility	28475857/ COG1291 DDD276611
8	M	6.8	c.2062_2064delinsCCAT	Mild	nk	0.4	1.8	2.3	1.4	0.5	nk	28475857/ COG0055
9	M	6.5	c.2312dup	Mild	-	2.3	2.2	4.3	6.3	6.6	Ventricular septal defect, advanced bone age	28475857/ COG0091
10	M	8.0	c.2368C>T_p.(Gln790X)	Mild	Attention deficit	-2.2	1.0	1.3	2.2	2.2	Bilateral mild hearing loss, fetal finger pads	-
11	M	17.0	c.3325+1G>T	Mod.	Shy	0.1	1.9	3.0	1.9	1.0	Unilateral cryptorchidism, hypotonia, cleft lip, pes planus	17668385/ 322 III-6
12	M	6.5	c.3602+1G>A	Mod.	Shy	-0.1	3.2	1.7	3.0	2.0	-	28475857/ COG0800
13	M	9.5	c.3976C>T_p.(Arg1326X)	Mod.	ASD, attention deficit	0.0	-1.2	0.4	-1.4	-1.1	Unilateral cryptorchidism, small joint hypermobility, hypotonia, Chiari malformation, macrotia, bilateral inguinal	-/DDD259794
14	M	8.4	c.4487C>A_p.(Ser1496X)	Mod.	Aggressive, attention deficit	1.0	0.8	4.1	1.9	2.0	Bilateral cryptorchidism, small joint hypermobility, pectus carinatum	-/DDD287029
15	M	6.4	c.4487C>A_p.(Ser1496X)	Mod.	Aggressive, attention deficit	0.5	1.6	3.3	2.1	1.7	Haemangioma	-/DDD287030
16	M	11.4	80kb del (exon 1-13)	Mod.	Aggressive	1.4	1.3	1.3	1.6	1.7	-	-/DDD257570
17	M	4.8	97kb del (exon 7-41)	Mild	Aggressive	0.7	0.9	1.2	1.0	0.7	Seizures, pes cavus, abnormal dentition, abnormal hair pattern	-

Abbreviations: Patient ref, Patient reference; M, male; yrs, years; -, feature absent; nk, not known; ID, intellectual disability; mod, moderate; ASD, autistic spectrum disorder; BW, birthweight; Ht, height; HC, head circumference; Wt, weight; BMI, body mass index; PMID, PubMed identifier

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