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SHORT REPORT

Understanding the new *BRD4*-related syndrome: Clinical and genomic delineation with an international cohort study

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Abstract

BRD4 is part of a multiprotein complex involved in loading the cohesin complex onto DNA, a fundamental process required for cohesin-mediated loop extrusion and formation of Topologically Associating Domains. Pathogenic variations in this complex have been associated with a growing number of syndromes, collectively known as cohesinopathies, the most classic being Cornelia de Lange syndrome. However, no cohort study has been conducted to delineate the clinical and molecular spectrum of *BRD4*-related disorder. We formed an international collaborative study, and collected 14 new patients, including two fetuses. We performed phenotype and genotype analysis, integrated prenatal findings from fetopathological examinations, phenotypes of pediatric patients and adults. We report the first cohort of patients with *BRD4*-related disorder and delineate the dysmorphic features at different ages. This work extends the phenotypic spectrum of cohesinopathies and characterize a new clinically relevant and recognizable pattern, distinguishable from the other cohesinopathies.

KEYWORDS
BRD4, BRD4-related syndrome, cohesinopathy, Cornelia de Lange syndrome, NIPBL

1 | INTRODUCTION

Bromodomain and extra-terminal domain (BET) proteins are chromatin readers with an important role in cell cycle progression.[1,2] BRD4 binds to hyperacetylated genomic regions that encompass promoters and enhancers, and BRD4 levels are particularly high at super-enhancers.[3] A recent study highlighted a novel interaction-mediated cooperation between BRD4 and NIPBL, including ChIP experiments supporting the co-location and mutual stabilization of these two proteins at the promoters of co-regulated genes, and transcriptome analysis indicating that NIPBL and BRD4 regulate a common set of genes.[1] Interestingly, Linares-Saldana et al. demonstrated that the role of BRD4-NIPBL on transcription is separate from its role on genome folding and loop extrusion.[4]

Pathogenic loss of function variants in *NIPBL* are the major cause of Cornelia de Lange Syndrome (CdLS).[5,6] NIPBL is part of a protein complex involved in loading of the cohesin complex onto DNA, a fundamental process required for cohesin-mediated loop extrusion and formation of Topologically Associating Domains (TADs).[7,8] Pathogenic variants in this complex have been associated with a growing number of syndromes, collectively known as cohesinopathies, the most classic being CdLS. However, even though certain overlaps exist, the clinical spectrum of cohesinopathies is very broad.[5]

Olley et al. recently reported the first three patients with *BRD4* single base-pair variants: two de novo frameshift variants and one de novo missense variant. They performed functional genomic analysis, suggesting that *BRD4* haploinsufficiency is associated with a CdLS-like condition.[9] These three first patients had a similar phenotype to previously reported patients with large deletions encompassing *BRD4*, consistent with the clinical spectrum associated with cohesinopathies.[4,5]

In this work, we report 14 new patients with *BRD4*-related disorder, to better define the phenotypic and molecular characteristics of this new syndrome.

2 | MATERIAL AND METHODS

To collect a cohort of patients with *BRD4* point variants or deletions encompassing this gene, we have organized an international collaborative project with the European Reference Network Ithaca (www.ern-ithaca.eu), reinforced by the collaboration of the French Cytogenetic Society network (ACLF, http://www.eaclf.org/). Eight patients with pathogenic or likely pathogenic point variants and six with large deletions were collected. All patients' families have agreed to a written consent after being informed during a specialized clinical genetics consultation, and all procedures performed for this study were done in accordance with the ethical standards of the institutional research committee and the Declaration of Helsinki.

Different chromosomal microarray platforms were used for copy number variations analysis: CGH 4x44 K, 6x60 K, 8x60 K, 4x180 K, Agilent microarrays®. Whenever possible, parental blood samples were obtained to test the inheritance using qPCR analysis and Fluorescence In Situ Hybridization. Single nucleotide variants were detected using Exome Sequencing, with different strategies depending on the inclusion center (single or trio analysis). The classification of variants was done according to the standards and guidelines for the interpretation of sequence variants published by the joint consensus of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology.[10]

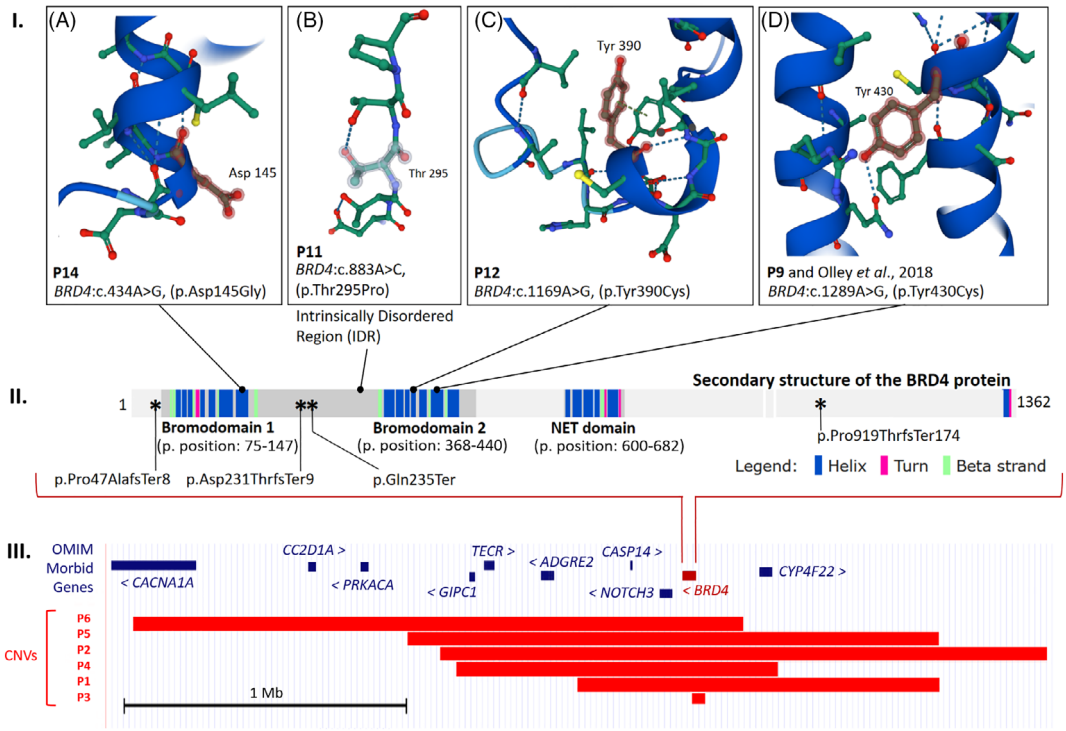

FIGURE 1 Single nucleotide variants and copy number variants identified in our study I. Localization of missense variants within the tertiary structure of the BRD4 protein. II. Localization of missense variants and null variants along the secondary structure of the BRD4 protein. *: null variants. NET = N-terminal Extraterminal domain. Note the location of the missense variants within the alpha helices of the bromodomains 1 and 2 (A, B, C). Missense variants in alpha helices of bromodomains are a known mechanism of loss of function through decreased binding to acetylated histones of promoters and superenhancers (Olley et al., 2018). III. Copy number variants reported in this study. P1, 2, 3, 4, 5, 6: patients 1, 2, 3, 4, 5, 6 [Colour figure can be viewed at wileyonlinelibrary.com]

3 | RESULTS AND DISCUSSION

3.1 | Molecular features

3.1.1 | Point variants

Detailed molecular results are described in Supporting Information S1. Among the eight-point variants identified, four were premature truncating variants (patients P7, P8, P10, P13), and four missense variants (P9, P11, P12, P14). Interestingly, the variant c.1289A > G, p.(Tyr430Cys) (P9) was already described in another patient by Olley et al., 2018.[9,11] This variant is located within one of the alpha helices of Bromodomain 2. Bromodomains 1 (BD1) and 2 (BD2) are responsible for binding to acetylated histones of promoters and superenhancers. Data from functional genomic experiments have demonstrated that this c.1289A > G, p.(Tyr430Cys) variant is responsible for a loss of function by decreased binding to acetylated histones of promoters and superenhancers.[9]

Figure 1 (I and II) indicates the position of our variants on the secondary and tertiary structures of the BRD4 protein. Interestingly, three missense variants are located within one of the alpha helices of BD1 or BD2, including the previously reported missense variant, whose loss-of-function mechanism has been validated by functional studies.[9] Further functional studies are needed to provide insight into the functional impact and mechanism of the new missense variants. The last missense variant, c.883A > C, p.(Thr295Pro), is located within an Intrinsically Disordered Region (IDR) (Figure 1). Recent molecular dynamics-based studies have explored the mechanism of disease-causing missense variants on IDRs, and propose that these variants could have a deleterious effect by reducing the conformational heterogeneity of IDRs which is quintessential for their multi-faceted cellular roles.[12]

3.1.2 | Copy number variants

The size of the deletions ranged from 46 kb to 2.2 Mb (Figure 1, III). Interestingly, the 46 kb deletion (P3) only overlaps the *BRD4* gene, and includes the exons 1 and 2, where exon 2 codes for part of BD1. Alesi et al. conducted a comprehensive review to assess the potential participation of contiguous genes in the phenotype of patients with microdeletions of the 19p13.12p13.11 region encompassing *BRD4*.[11] In complement, we specifically investigated the OMIM morbid genes encompassed by these deletions: *CACNA1A1*, OMIM 601011; *CC2D1A*, OMIM 610055; *PRKACA*, OMIM 601639; *GIPC1*, OMIM 605072; *TECR*, OMIM 610057; *ADGRE2*, OMIM 606100; *CASP14*, OMIM 605848; *NOTCH3*, OMIM 600276; *CYP4F22*, OMIM 611495. We assessed the probability of being a haploinsufficient (pHI) using

TABLE 1 Clinical features of the 14 new patients included in this study

Patient	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13	P14
Gender	M	M	F	F	M	F	M	M	M	F	M	M	F	M
Prenatal findings	IUGR	IUGR	NA	MA, IUGR	/	MA	/	IUGR	–	/	–	–	–	–
Age at assessment	3 year 9 month	10 week	14 year	38 WG	20 year	24 WG	16 year	10 year	29 year	18 year	10 year	19 year	32 year	4 year 9 month
Intellectual disability (ID)/Learning disability	LD	/	ID	/	ID	/	Normal IQ	ID	IQ 73	LD	Mild ID	LD	LD	Mild ID
Microcephaly (SD)	−6 SD	−3 SD	<−2 SD	<−2 SD	−4 SD	<−2 SD	−2 SD	−2 SD	−0.4 SD	−2 SD	+0.1 SD	−3.5 SD	−3.4 SD	−2.7 SD
Facial dysmorphism														
Synophris	+	/	/	–	+	–	–	+	+	+	–	/	/	/
Arched eyebrows	+	/	/	+	+	+	+	+	+	/	+	/	/	/
Sparse eyebrows	+	/	/	+	+	+	+	+	–	/	+	/	/	/
Downslanting palpebral fissures	+	/	/	–	–	–	–	–	+	/	–	/	+	/
Short nose	+	/	/	+	+	+	+	+	+	/	–	/	/	/
Anteverted nares	+	/	/	+	/	+	–	+	+	/	+	/	/	/
Strabismus	+	+	/	/	–	/	–	+	–	/	–	/	/	/
Large ears	+	+	/	+	+	–	–	–	–	/	–	/	/	/
Low set ears	–	+	/	–	–	–	–	–	–	/	–	/	/	/
Preauricular enchondroma	–	+	/	+	–	+	–	–	–	/	–	/	/	/
Low forehead	+	–	/	–	–	+	–	–	–	/	–	/	/	/
Frontal upsweep of hair	+	/	/	/	/	/	/	+	+	/	+	/	/	/
Proeminent incisors	+	/	/	/	/	/	/	+	+	/	+	/	/	/
Short philtrum	–	/	/	–	–	–	/	+	+	/	+	/	/	/
Skeletal abnormality	–	–	–	FPA	NSS	BS II–III	DBA	ES, 5FC	CFD, BHD, ES, FFC	–	PC	–	LNF	SH, BS II–III
Feeding specificities	NTF, GHH	CSD	HP	/	Severe GOR	/	–	–	>18 y: HP, O	–	–	–	–	–
Psychiatric disorder	–	/	–	/	HSB, TM	/	DMDD, IED, OCD	–	7 year: IP. 18 y: PD. Adult: S	DID, PPS	PPS	–	–	–
Brain MRI findings/ neuropathological examination	–	HCC	–	PC, HCC	–	–	–	–	–	–	–	/	/	–
Other	–	–	–	–	PA, VSD, LOP	AVSD, EFH	–	ECS	–	HS, SA	E	–	–	HS, MP
Variant (CNV: hg19/ SNV: NM_058243.2)	del 1.3 Mb	del 2.2 Mb	del 46 kb	del 1.1 Mb	del 1.9 Mb	del 2.2 Mb	c.703C > T, p.(Gln235Ter)	c.2753_2754insT, p.(Pro919ThrfsTer174)	c.1289A > G, p.(Tyr430Cys)	c.691del, p.(Asp231ThrfsTer9)	c.883A > C, p.(Thr295Pro)	c.1169A > G, p.(Tyr390Cys)	c.137dup, p.(Pro47AlafsTer8)	c.434A > G, p.(Asp145Gly)

Abbreviations: AVSD, atrioventricular septal defect; BHD, bilateral hip dysplasia; BS II–III, bilateral syndactyly II–III; CFD, club feet deformity; CSD, central swallowing difficulties; DBA, delayed bone age; DID, dissociative identity disorder; DMDD, disruptive mood dysregulation disorder; E, epilepsy; EFH, early fetal hair and eyelashes; ECS, ear canal stenosis; ES, evolutive scoliosis; F, female; FFC, fifth fingers clinodactyly; FPA, fusion of posterior arches of 6th–7th ribs; GHH, giant hiatal hernia; GOR, gastro-esophageal reflux; HCC, hypoplasia of the corpus callosum; HP, hyperphagia; HS, hypospadias; HSB, hyper-sexualized behavior; ID, intellectual disability; IED, intermittent explosive disorder; IP, infantile psychosis; IUGR, intrauterine growth restriction; LD, learning difficulties without ID; LNF, long and narrow fingers; LOP, late-onset puberty; M, male; MA, medical abortion; MP, micropenis; NTF, nasogastric tube feeding; NSS, narrow, sloping shoulders; O, obesity; OCD: obsessive compulsive disorder; PA, pulmonary atresia; PC, pectus carinatum; PD, psychotic disorder; PPS, poor performance in socialization; PVC, paraventricular cysts; S, schizophrenia; SA, sleep apneas; SH, Short hands; TM, trichotillomania; VSD, ventricular septal defect; WG, weeks of gestation.

the classification method described by Huang et al., 2010.[13] None of the nine genes fulfilled the criteria to be classified as high rank (pHI: 0%–10%), with High Rank indicating that a gene is more likely to exhibit haploinsufficiency. Furthermore, haploinsufficiency of one of these genes has never been demonstrated in the medical literature: only investigation of single-gene deletions or point variants associated with a distinctive phenotype and functional research studies could clarify the potential contribution of contiguous genes.

3.2 | Clinical features

We report 12 new patients aged from 10 weeks to 32 years (mean age of 15 years) and two prenatal cases, resulting in medical termination of pregnancy due to severe intrauterine growth restriction (IUGR) and microcephaly with evidence of a large deletion by chromosomal microarray analysis (CMA) on amniotic fluid (Table 1).

Microcephaly, described as one of the cardinal features in previously reported patients, was present in 86% of our patients (12/14), including 100% of patients with large deletions (6/6) and only 75% (6/8) of patients with single base-pair variants. In particular, patients with null variants all had microcephaly (4/4) whereas microcephaly was inconstant in patients with missense variants (2/4).

An initial global developmental delay was present in 100% of the patients (12/12), but in patients over 3 years of age, intellectual disability was identified in only 45% (5/11), while 36% (4/11) had learning difficulties without intellectual disability, and two had an IQ within the normal range without learning difficulties. No correlation was identified between severity of neurodevelopment delay and type of variant (large deletion, null variant, missense variant): we report both patients with normal-range IQ and patients with ID for each of these alterations.

A previously unreported finding is the frequency of psychiatric disorders, identified in 46% of patients (5/11). Patient P9, whose neuropsychological assessment reported normal homogeneous IQ score at 7 years (total IQ 87) and heterogeneous IQ profile at adult age (WAIS-III: verbal IQ 82, Performance IQ 67), was first diagnosed with childhood psychosis from the age of seven, then with a psychotic disorder from the age of 18 and was subsequently diagnosed with schizophrenia. Patient P7, a 16-year-old boy with normal range intelligence, was diagnosed with disruptive mood dysregulation disorder, intermittent explosive disorder and obsessive–compulsive disorder. Patient P5 developed hyper-sexualized behavior from adolescence as well as aggression to property and people, requiring medication. He also developed trichotillomania. Patient P10 was diagnosed with dissociative identity disorder. We have identified these psychiatric disorders indifferently in patients carrying large deletions, null variants and missense variants.

The morphological features and facial dysmorphism of the patients are illustrated in Figure 2 and Supporting Information S2. We delineated a characteristic and recognizable pattern, consisting of arched eyebrows, often sparse, sometimes with synophris, with a frontal upsweep of hair, prominent incisors, and a short nose with anteverted nostrils, present in 6/7 patients. These dysmorphic features seem to evolve with age: patient P9, who developed hyperphagia from 18 years of age, and then truncal obesity with a weight of 124 kg at 29 years, had an adult facial dysmorphism suggestive of Cohen syndrome, with a Cohen-like grimacing smile with small mouth and short philtrum, frontal upsweep of hair, and a narrow palate.

Interestingly, none of the 14 patients presented a Classic CdLS phenotype, neither regarding the facial morphology, nor regarding extra-facial CdLS findings: in particular growth failure, marked facial and extra-facial hypertrichosis, radial and limb anomalies, were absent in our patients.

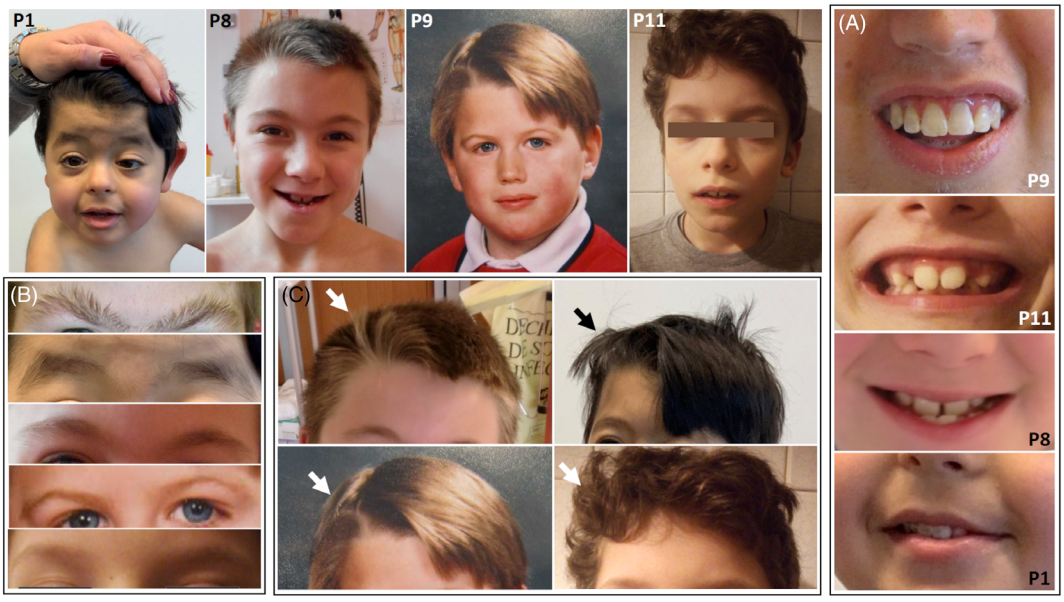

FIGURE 2 Dysmorphic features. (A) Note the Cohen-like appearance of the smile and the prominent incisors. (B) Note the arched appearance of the eyebrows, often thick and sparse, sometimes associated with a synophris. Arrow: upswept frontal hair pattern [Colour figure can be viewed at wileyonlinelibrary.com]

In several syndromes, the initial phenotype during infancy may be suggestive of the CdLS-like spectrum, and then evolve into a different core phenotype: this is especially the case for *KMT2A*, *ANKRD11*, or *SETD5*-related disorders.[8,9,11] Long-term follow-up of patients and the identification of new adult cases will allow us to determine whether this also applies to *BRD4*, and to further characterize its core phenotype.

4 | CONCLUSION

This work presents the first cohort of patients with the newly described *BRD4*-related disorder through a collection of 14 cases, broadening the phenotype with particular emphasis on a new clinically relevant and recognizable core pattern, distinguishable from the other cohesinopathies and especially different from the Classic CdLS phenotype. We report eight-point variants and six deletions encompassing *BRD4*. Interestingly, three missense variants are located within one of the alpha helices of BD1 or BD2, including a previously reported missense variant, whose loss-of-function mechanism has been validated by functional studies. This study allows a first clinical delineation of this new neurodevelopmental syndrome with remarkable clinical expressivity. Future descriptions of new patients and their molecular data will be valuable to investigate potential genotype–phenotype correlations.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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