A novel partial de novo duplication of JARID2 gene causing a neurodevelopmental phenotype

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Case Report

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Title

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Running title

A novel partial *de novo* duplication of *JARID2*

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Conflict of Interest Statement

The authors have no conflict of interest to report.

Data Availability Statement

The patient phenotype and duplication data has been submitted to the DECPIHER database (ID: 345282) (Firth et al., 2009). Genomic sequencing read data are available from the corresponding authors with permission of the Helsinki and Uusimaa Hospital district Ethics Committee. National and institutional

regulations prohibit deposition of these data in public repositories. The authors confirm that data supporting the findings of this study are available within the article and its supplementary materials.

Abstract

Deletions covering the entire or partial *JARID2* gene as well as pathogenic single nucleotide variants leading to haploinsufficiency of *JARID2* have recently been shown to cause a clinically distinct neurodevelopmental syndrome phenotype. Here, we present a previously undescribed partial *de novo* duplication of the *JARID2* gene in a patient displaying a phenotype associated with known *JARID2* loss-of-function variant carriers. The phenotype of the index patient included coordination problems, clumsiness, language delay, unclear speech, problems with behavior and attention as well as difficulties with social contacts and daily activities. The patient has markedly dark infraorbital circles and slightly prominent supraorbital ridges. The phenotype shares a notable resemblance to previously characterized *JARID2* deletion patients. Genetic analyses from the samples of the index patient and the parents were performed. Whole-genome sequencing and array comparative genomic hybridization revealed a novel disease-causing variant type, a partial tandem duplication of *JARID2,* covering the exons 1-7. Furthermore, RNA sequencing validated increased expression of these exons. Expression alterations were also detected in the target genes of PRC2 complex, in which JARID2 acts as an essential member. Our data adds to the variety of different pathogenic variants causing the *JARID2* specific neurodevelopmental syndrome phenotype.

Keywords:

JARID2, duplication, de novo, pathogenic variant, whole genome sequencing, RNA sequencing

Introduction

The *JARID2* gene (Jumonji and AT-rich interaction domain 2, OMIM *601594) encodes an ARID transcription factor that is widely detected across human tissues (Bergé-Lefranc et al., 1996). The protein is localized in the nucleoplasm and mitochondria of the cells (Peng et al., 2009) and contains the Jumonji N (JmjN), AT-rich interaction domain (ARID), Jumonji C (JmjC), and zinc finger domains (Cooper et al., 2016; Takeuchi et al., 2006). Unlike in the other Jumonji family proteins, the JmjC domain of JARID2 lacks its histone demethylase activity (Cooper et al., 2016; Takeuchi et al., 2006). Instead, JARID2 interacts with the Polycomb repressive complex 2 (PRC2) that is critical for lineage commitment during embryonic development and maintenance of cell type identity. In the complex, JARID2 contributes to the recruitment of PRC2 to chromatin (Peng et al., 2009) and regulation of histone H3 lysine 27 (H3K27) methylation activity of PRC2 (Son et al., 2013). The

region containing amino acids 119-574, corresponding to exons 4 to 7, appears to mediate these activities (Cooper et al., 2016; Li et al., 2010; Son et al., 2013). Highlighting the crucial role of JARID2, its deletion in mice results in severe abnormalities in multiple organs, neural defects and mid-late gestation lethality (Takeuchi et al., 1995, 2006). During embryogenesis, *JARID2* is predominantly expressed in neurons and is also highly expressed in the adult cerebellum (Bergé-Lefranc et al., 1996; Takeuchi et al., 1995).

In humans, heterozygous deletions containing entire or partial *JARID2* gene have been characterized and associated with several congenital defects (Barøy et al., 2013; Verberne et al., 2021). *JARID2* is located within the 6p22 microdeletion region and two SRO regions (smallest regions of overlap) have been identified. SRO I contains *JARID2* and *DTNBP1* whereas SRO II *GMPR* and *ATXN1* genes. Of those, chromatin modifier genes *JARID2* and *ATXN1* were suggested as likely candidate disease causing genes (Barøy et al., 2013).

Recently, a study including 16 patients from 15 families with different *JARID2* disease-causing variants was published characterizing one whole-gene and 7 intragenic deletions as well as small variant alternations including 2 frameshift, 2 nonsense, one splice-site and 3 missense variants. All variants were predicted to lead to *JARID2* haploinsufficiency due to nonsense-mediated mRNA decay (Verberne et al., 2021). Haploinsufficiency of *JARID2* has been shown to cause a clinically distinct neurodevelopmental phenotype (Barøy et al., 2013; Verberne et al., 2021). The typical features of patients with *JARID2* haploinsufficiency include developmental delay or intellectual disability, autistic features, behavioral abnormalities and mild dysmorphic features such as deep-set eyes and infraorbital dark circles, prominent supraorbital ridges and midface hypoplasia (Barøy et al., 2013; Di Benedetto et al., 2013; Verberne et al., 2021). Duplications and deletions of exon 6 have been identified in patients with intellectual disability as well as in control population and these have been interpreted as benign variation (Tucker et al., 2014; Zahir et al., 2016).

In addition to the present case, DECIPHER database recognizes three other patients with a partial *JARID2* duplication. Two of these have 569 and 576 kb duplications of unknown origin covering only the first exon of *JARID2*. The first-mentioned (ID:260089) has also a second 278 kb microduplication harboring the exons 4-5 of *PTPRD* gene (NM_002839.4). The phenotypic features include intellectual disability, macrocephaly and myoclonus. The latter patient (ID:267637) has also a *de novo* heterozygous missense variant c.902A>G, p.(Tyr301Cys) in *GABRB2*. The phenotypic features include blepharophimosis, broad hallux, frontal bossing, generalized hypotonia, generalized myoclonic and photosensitive tonic-clonic seizures, global developmental delay, kyphosis, large earlobe, macrocephaly and sparse scalp hair. The third patient (ID:255516) has inherited a duplication of *JARID2* exons 1-2 from an unaffected parent. The reported phenotypic features are atrioventricular canal defect, poor speech and short stature.

Here, a comprehensive genetic analysis revealed the presence of a previously uncharacterized partial *de novo* duplication of the *JARID2* gene as the sole finding in a patient displaying a phenotype associated with known *JARID2* loss-of-function variant carriers.

Materials and Methods

See Supplementary Data 1A-D and Supplementary Tables 1-3.

Results

Genetic analyses

Various complementing whole-genome and targeted assays were used to discover and validate the presence of a partial tandem duplication of *JARID2* (Figure 1).

First, a whole genome chromosomal microarray (Figure 1, Supplementary Data 1A, Supplementary Table 1) revealed a partial duplication of the *JARID2* gene, in chromosomal region 6p23p22.3, the size being between 309-346 kb. This duplication GRCh38 chr6:g.(15158120_15181642)_(15490178_15504505)dup encompassed at least exons 1-6 of the 18 exons of *JARID2* (NM_004973.4). The status of exons 7 and 8 remained uninformative. The index patient had no other clinically relevant copy number variants and the parental array-CGH profiles were normal.

A fluorescent *in situ* hybridization (FISH) study (Figure 1, Supplementary Data 1B) targeting the duplicated region was consistent with a tandem duplication. However, the orientation of the duplication remained unelucidated. The parental FISH tests showed normal results, excluding insertional translocation in the parents and corroborating the *de novo* status of the duplication.

Whole genome sequencing (WGS) (Figure 1, Supplementary Data 1C, Supplementary Tables 1-2) defined the breakpoint to intron 7 (NM_004973.4); GRCh38 chr6:g.15160000-15499999dup. Thus, the duplicated exons were 1-7, which contain the JmjN domain and part of the ARID/BRIGHT DNA binding domain. The duplicated allele was of maternal origin. The read pair orientation analysis indicated a tandem duplication, but because of the repetitive nature of the genomic regions around the breakpoints, definitive conclusions could not be established.

RNA sequencing analysis (Figure 1, Supplementary Data 1D, Supplementary Tables 2-3) indicated that the RNA expression levels are elevated for exons 1-7 of *JARID2*, suggesting that the N-terminal fragment is expressed as an isolated transcript. This finding could not be confirmed on protein level due to lack of patient

material. Using a z-score test and 95 percent confidence level, 345 genes (61%) were downregulated and 225 (39%) were upregulated in the patient compared to his mother (Supplementary Table 3). This suggests that the duplication of the N-terminal domain of *JARID2* results in a global transcriptional repression. Many target genes of JARID2 (Peng et al., 2009), showed altered expression in the patient (p-value 0.027). These included genes involved in neuronal development, neuronal function and cellular differentiation, for example *MDGA1*, *SOX6*, *TMTC1*, *ATOH8*, *TSPAN5*, *CACNA1I*, *EGR2*, *KLHL31*, *GATA6*, and *EGR3*.

Clinical report

The study was approved by the Ethical Review Board of Helsinki University hospital (233/13/03/00/11) and was performed in accordance with the Declaration of Helsinki of 1975. The parents gave informed written consent.

The phenotypic features of the index patient as well as the previously characterized patients (Barøy et al., 2013; Verberne et al., 2021) are presented in Table 1.

The index patient is the second child to nonconsanguineous Finnish parents. The pregnancy and delivery were uneventful. He was born at 40 weeks and 5 days of gestation with a birth weight of 4,280 g (+55 percentiles), length 53 cm (+1 SD) and occipitofrontal circumference 36 cm (+0.5 SD). The Apgar scores were 7, 9 and 10 at 1, 5 and 10 minutes, respectively. He had mild jaundice and slightly elevated bilirubin levels that normalized quickly without treatment. He started walking at the age of one year. According to the parents, he had problems with coordination and clumsiness since the first years of life. He spoke his first words at 2 years of age and small sentences (2-3 words) at 2.5 years. He had eartubes inserted at the age of two years because of glue ear. At 3.5 years of age, he was referred to a phoniatrist due to language delay and unclear speech. Submucous cleft palate was observed. Speech therapy was started, which helped him reach the age-appropriate level. However, he continued to have problems with articulation. Ophthalmologist prescribed glasses for strabismus.

At the age of six, the cognitive level of the patient was estimated to be normal. When starting school, he needed extra support in learning to read. He had problems with attention and behavior and was transferred to a smaller group to help him focus on class. Later, he started in a hospital elementary school with an adjusted curriculum. He had difficulties with tolerating adversities and often threw tantrums. He also had problems with social contacts. At 10 years of age, he was referred to children's neuropsychiatric clinic and was diagnosed with attention deficit hyperactivity disorder (ICD code f90.0), other disorders of psychological development (f88) with specific neurocognitive and Asperger features. Methylfenidate alleviated the

symptoms to some extent. Neuropsychiatric therapy was started and continued for several years. He also received occupational therapy and physiotherapy for posture problems.

When moving to junior high school the patient attended a normal curriculum. At his last evaluation in 2020, he had progressed in many daily activities and improved his social skills but continues to have challenges with attention and interaction. His grades have been on a mediocre level.

The patient has grown approximately on a +2.5 SD curve, the expected height being +0.6 SD. When last measured his weight was +30 percentiles (>2 SD). The patient's facial features include markedly dark infraorbital circles, mild ptosis, slightly prominent supraorbital ridges, mild midface hypoplasia and full earlobes and lips. He has pes planus and syndactyly between II and III toes. Mild balance and coordination problems and slightly low muscle tone were observed in last neurological status.

Discussion

We present a previously undescribed partial *de novo* duplication of the *JARID2* gene in a patient sharing phenotypic features with previously characterized patients with *JARID2* haploinsufficiency. According to our knowledge, this is the first characterized case of *JARID2* duplication with altered expression of the duplicated region exons 1-7. The data suggests that the defective transcripts are not entirely degraded by nonsense-mediated decay, unlike reported for previously described variants (Verberne et al., 2021).

To investigate the effect of the duplication of our index patient on the transcriptional regulatory role of JARID2, we performed to our knowledge the first transcriptomic analysis of *JARID2* variants in human subjects. We discovered that the exons 1-7, present in the partial duplication, were expressed in excess on RNA level. We also noticed that more genes were downregulated in the patient in comparison to his mother, and among these dysregulated genes were several JARID2 target genes identified by ChIP-seq (Peng et al., 2009). These genes are involved in neuronal function and differentiation and the majority of them were downregulated in the patient. The widespread downregulation was unexpected as the patient's phenotype closely resembles that of the previously described *JARID2* haploinsufficiency cases. Loss of PRC2 components typically results in reduced H3K27me3 mark, and consequently, derepression of PRC2 target genes (Azuara et al., 2006; Boyer et al., 2006; Lee et al., 2006; Shen et al., 2008). Previous studies on the function of an isolated N-terminal domain also suggest that the domain enhances the recruitment of PRC2 to chromatin and stimulates its methyltransferase activity (Cooper et al., 2016; Li et al., 2010; Son et al., 2013). On the other hand, full-length *Jarid2* deficiency in mouse ES cells has been shown to reduce the expression of PRC2 target genes via impaired recruitment of PRC1 and RNA polymerase II (Landeira et al., 2010). Given the close resemblance of the patient's phenotype to *JARID2* haploinsufficient patients, our data suggests that the

duplication of exons 1-7 results in loss of function in JARID2 protein and reduced expression of PRC2 target genes.

Compared to the previously reported cases, our index patient showed majority of the most common phenotypic features (Table 1) (Barøy et al., 2013; Verberne et al., 2021). These include developmental delay (speech delay), features of autism spectrum disorder and behavioral problems as well as the notably dark infraorbital circles that were observed in 29% of previous cases, height and weight were >2 SD as in a substantial proportion of previous cases (31% and 25%, respectively). As much as 47%, including the present patient, had perinatal complications, however, majority were rather mild and common findings such as hyperbilirubinemia and thus possibly not related to the *JARID2* variants. He also presented with syndactyly whereas 39% of patients showed hand/foot anomalies. However, these characteristics are also rather frequent and unspecific. In contrast to all the previous cases, the current patient does not present with intellectual disability, and despite continuing challenges, he has attended to normal curriculum.

Three other patients with a partial *JARID2* duplication in the DECIPHER database (ID:s 260089, 267637 and 255516) share some of the clinical features with our index case and the patients described in the literature, such as developmental delay, intellectual disability, macrocephaly and frontal bossing. The characterized patients present with a rather wide spectrum of features, making it difficult to evaluate the genotype-phenotype correlation. In addition, two of these DECIPHER patients have a second genetic variant, which further complicates the evaluation. The only previously characterized patient with *JARID2* partial duplication as the sole finding, had a smaller duplication, spanning only the first two exons of *JARID2*. As opposed to the majority of previously described patients with *de novo* variants, this patient had inherited the duplication from an unaffected parent, which increases the uncertainty of the effect of this particular duplication (Table 1). Many factors, such as the location and exact breakpoints of the duplications, are likely to affect their pathogenicity and thus more data would be required to evaluate the significance of the duplications reported in DECIPHER.

In conclusion, we present a *de novo JARID2* duplication in a patient whose clinical presentation significantly overlaps with formerly characterized patients with *JARID2* haploinsufficiency. Our findings suggest, that in addition to haploinsufficiency, other molecular mechanisms might lead to JARID2-associated condition. Since the neurocognitive capacity of the current patient is higher than in patients with whole gene deletions and *JARID2* variants predicted to undergo nonsense-mediated decay, partial duplications might be associated with somewhat milder phenotype. However, functional studies are needed to demonstrate the molecular mechanisms and the associated phenotypes of different *JARID2* variants.

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Table 1. A review of the molecular genetic and clinical findings of index patient and presently published patients with *JARID2* variants.

1= Baroy et al. 2013 2= Verbene et al. 2020	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	Index patient	Proportion of positive findings (%)
Gender	M	F	F	M	M	F	M	M	M	M	M	M	M	M	M	M	F	M	
Age at last follow-up (y)	6.5	17	19	9	3.5	7	38	4	10	12.5	7.3	23	4	3.2	8	39	10.8	12	
Genetic variant																			
Variant type	del	del	del	del	del	del	del	del	del	fs	ns	fs	ns	ss	ms	ms	ms	dup	
Size (kb)	189	30	90	100	120	140	140	205	320									309	
Exons		2	2-3	2	2-3	2-5	2-5	1-2	1-18	13	8	16	16	11	4	8	7	1-7	
Inheritance	dn	dn	dn	dn	dn	p	na	na	dn	dn	na	dn	dn	dn	dn	dn	dn		
Growth																			
Height > 2 SD	-	-	+	-	-	+	na	+	-	+	-	-	-	-	+	-	-	+	35
Weight > 2 SD	-	-	-	+	-	-	na	+	-	-	-	-	-	-	+	-	+	+	29
Head circumference > 2 SD	-	-	na	na	-	-	na	+	-	-	-	na	-	-	+	-	-	-	14
Facial features																			
Deep set eyes	+	+	+	-	-	+	+	-	-	-	-	-	+	+	-	-	-	+	44
Full lips	+	+	-	-	+	-	-	-	-	+	+	+	-	-	-	-	-	+	39
High anterior hairline	na	+	+	-	+	+	+	-	-	+	-	-	-	-	-	-	-	-	35
Infraorbital dark circles	+	+	-	+	-	+	+	-	-	-	-	-	-	-	-	-	-	+	33
Prominent supraorbital ridges	+	-	-	-	-	+	+	-	-	-	-	+	-	-	-	-	-	+	28
Deep set nasal root	+	+	-	-	+	+	+	-	-	-	-	-	-	-	-	-	-	-	28
Midface hypoplasia	+	-	+	-	-	+	+	-	-	-	-	-	-	-	-	-	-	+	28
Bulbous nasal tip	+	+	-	-	-	+	+	+	-	-	-	-	-	-	-	-	-	-	28
Short philtrum	+	+	+	-	-	-	-	-	-	+	-	-	-	-	-	-	-	-	22
Broad forehead	-	-	-	+	-	+	+	-	-	-	-	-	-	+	-	-	-	-	22
Neurology																			
Developmental delay	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	100
Intellectual disability	-	+	-	+	-	+	+	+	-	+	+	+	+	na	+	-	+	-	65
ASD features	-	+	-	+	+	-	-	+	-	+	+	-	+	-	+	+	-	+	55
Behavioral abnormalities	-	-	+	-	-	-	-	+	-	+	+	+	-	-	+	+	-	+	44
Abnormal MRI	-	na	na	na	-	-	na	-	-	+	na	-	+	+	+	na	na	na	40
Hypotonia	+	-	-	-	+	-	-	+	-	-	+	-	+	+	-	-	-	-	33
Eye/vision abnormalities	+	-	-	+	-	-	-	-	-	-	+	-	-	-	+	+	-	+	33
ASD diagnosis	-	-	-	-	-	-	-	-	-	+	-	-	-	-	+	+	-	-	17
Epilepsy	-	-	-	-	-	-	+	+	-	-	-	+	-	-	-	-	-	-	17
Gait disturbance	+	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	11
Other																			
Perinatal complications	-	-	-	+	+	-	+	-	-	+	na	-	+	-	+	+	-	+	47
Hand/foot anomalies	+	+	-	+	-	+	-	+	-	-	-	-	-	-	-	+	-	+	39
Dental anomalies	-	-	-	-	-	+	-	-	+	-	-	-	-	-	-	-	-	+	17

ASD= autism spectrum disorder, dn= *de novo*, F= female, fs= frameshift, M= male, ms= missense, na= not available, ns= nonsense, p= paternal, ss= splice site, + yes, - no.

Figures

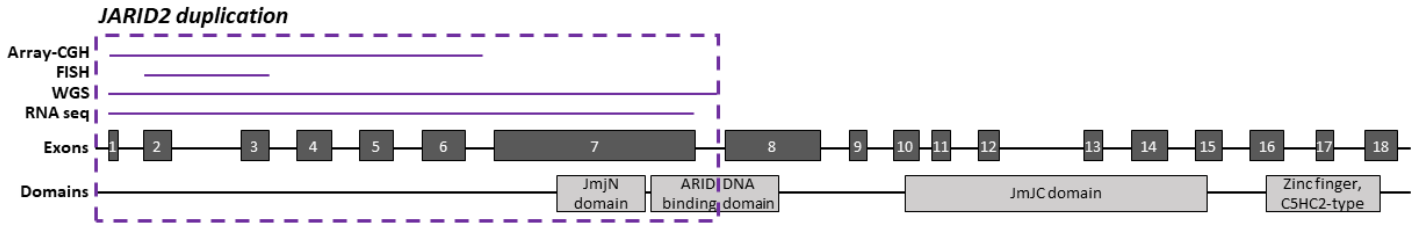

Figure 1

Figure 1. A schematic representation of *JARID2* gene and the duplicated region. The partial *JARID2* duplication of the index patient was detected using various methods including whole genome array-CGH (exons 1-6), fluorescence *in situ* hybridization (exons 2-3), whole genome sequencing (exons 1-7) and RNA sequencing (exons 1-7). The duplication covers the JmjN domain and part of the ARID/BRIGHT DNA binding domain. The figure is not in scale due to large introns. Detailed results of each method are presented in the Supplementary Data 1A-D and Supplementary Tables 1-3.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryData1.pdf
- SupplementaryTable1CNVresults.xlsx
- SupplementaryTable2QualityMetrics.xlsx
- SupplementaryTable3RNAseq.xlsx