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2022-11

Viitasalo , L , Kettunen , K , Kankainen , M , Niemelä , E H & Kiiski , K 2022 , ' A novel partial de novo duplication of JARID2 gene causing a neurodevelopmental phenotype ' , Molecular Genetics and Genomic Medicine , vol. 10 , no. 11 , 2037 . https://doi.org/10.1002/mgg3.2037

http://hdl.handle.net/10138/353530
https://doi.org/10.1002/mgg3.2037

Received: 4 February 2022 | Revised: 3 June 2022 | Accepted: 19 July 2022

DOI: 10.1002/mgg3.2037

Molecular Genetics & Genomic Medicine Open Access WILEY

CLINICAL REPORT

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

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Funding information
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Abstract

Background: 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. Here, we present a previously undescribed partial de novo duplication of the *JARID2* gene in a patient displaying features similar to those of patients with *JARID2* loss-of-function variants.

Case report: The index patient presents with abnormalities in gross motor skills and speech development as well as neuropsychiatric disorders. The patient has markedly dark infraorbital circles and slightly prominent supraorbital ridges. 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 the increased expression of these exons. Expression alterations were also detected in target genes of the PRC2 complex, in which JARID2 acts as an essential member.

Conclusion: Our data add to the variety of different pathogenic variants associated with *JARID2* neurodevelopmental syndrome.

KEYWORDS

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

1 | 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) which 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 the 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 4–7, 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).

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). In humans, heterozygous deletions containing entire or partial *JARID2* gene as well as small variant alternations predicted to lead to *JARID2* haploinsufficiency have been associated with a clinically distinct neurodevelopmental syndrome (Barøy et al., 2013; Verberne et al., 2021). The typical features of these patients 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 the control population and these have been interpreted as benign variations (Tucker et al., 2014; Zahir et al., 2016).

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.

2 | MATERIALS AND METHODS

Various complementing genomic and genetic assays were used. For the entire family trio whole-genome chromosomal microarray and fluorescent in situ hybridization (FISH) were performed. Whole genome sequencing and RNA sequencing were done from the samples of the index patient and the mother; see Figures 1–3, Data S1A–D, and Tables S1–S3. Weight measurements, conventionally expressed as a percentage of the median weight-for-height in Finland, have been transferred to weight-for-age SD values according to Saari et al. (2010).

3 | RESULTS

3.1 | Clinical report

The phenotypic features of the index patient as well as the previously characterized patients (patient no 4 in the study by Barøy et al. and the 16 patients described in the study by Verberne et al.) are presented in Table 1.

The index patient is the second boy 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 4280 g (+1.5 SD), length of 53 cm (+1.0 SD), and occipitofrontal circumference of 36 cm (+0.5 SD). The Apgar scores were 7, 9, and 10 at 1, 5, and 10 min, respectively. He had mild jaundice and slightly elevated bilirubin levels that normalized quickly without treatment. He started walking at the age of 1 year and spoke his first words at 2 years. At three and a half years of age, he was referred to a phoniatrist due to language delay and unclear speech. Submucous cleft palate was observed. Speech therapy helped him reach the age-appropriate level, however, he continued to have unclear articulation. The parents reported persistent coordination problems and clumsiness.

At the age of 6, the patient's cognitive level was estimated to be normal. When starting school, he needed

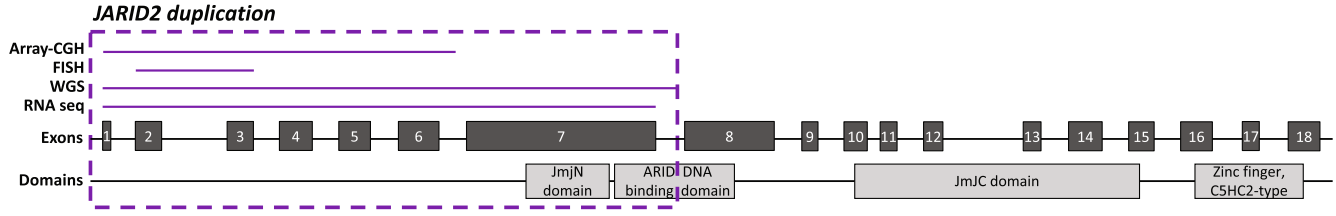

FIGURE 1 A schematic representation of *JARID2* gene and the duplicated region. The partial *JARID2* duplication of the index patient was detected using various methods including whole genome array-CGH (exons 1–6), fluorescence in situ hybridization (exons 2–3), whole genome sequencing (exons 1–7) and 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 Data S1A–D and Table S1.

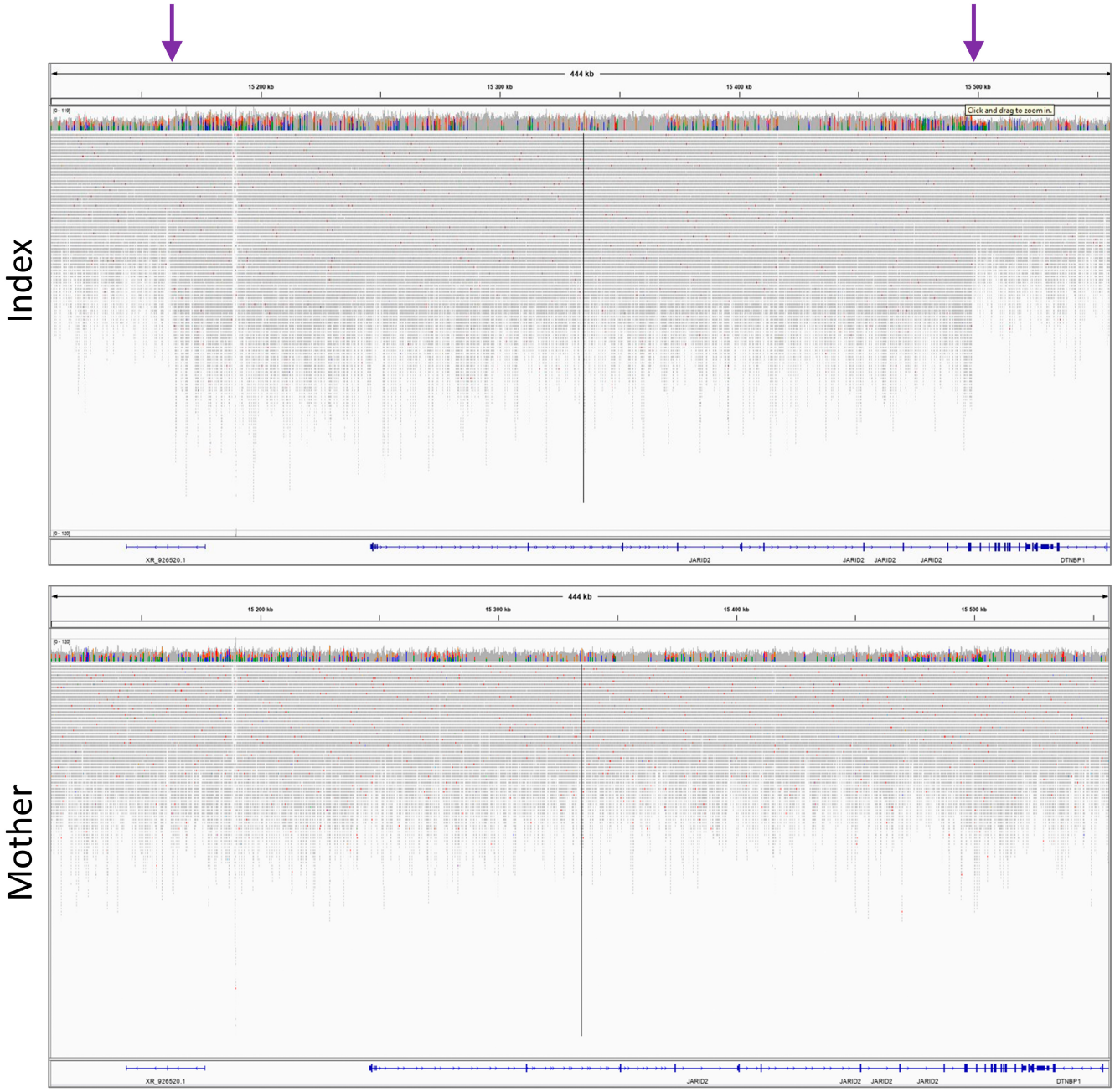

FIGURE 2 IGV alignment view of WGS data of the index patient and mother. The copy-number alteration was visually detectable as double read depth in the index patient compared to the mother, spanning the region chr6:15,164,000–15,497,540. The breakpoints are marked with arrows.

extra support in learning to read and had problems with attention and behavior. He was later transferred to a hospital elementary school with an adjusted curriculum. 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) and Asperger features. When moving to junior high school, the patient attended a normal curriculum. At his last evaluation in 2020, he had progressed in many daily living and social skills. He continued to have challenges with attention and interaction.

The patient has grown approximately on a +2.5 SD curve, the expected height being +0.6 SD. When last measured at the age of 12 his height was +2.6 SD and weight +2.4 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 the last neurological evaluation at the age of 11.

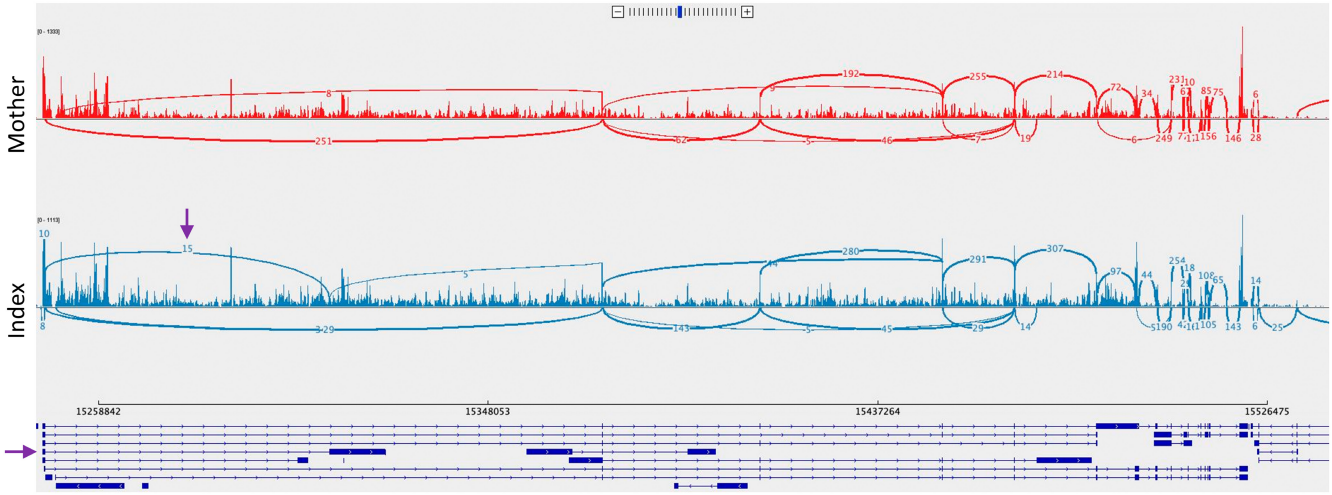

FIGURE 3 Sashimi plot for *JARID2* gene in the index (blue) and mother (red). The RNA sequencing data revealed expression from an atypical exon in the index supported by 15 junction reads. Only junctions covered by five or more reads were included. At bottom, transcript reconstructions of the index revealed an atypical transcript in the index spanning from 15,245,989 to 15,324,347 on chromosome 6 (GRCh38).

3.2 | 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, Data S1A, and Table S1) 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, Data S1B) 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; Figures 1 and 2, Data S1C, and Tables S1 and S2) defined the breakpoint within 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. WGS was performed for the index and his mother, with low coverage, to determine the exact breakpoints of the duplication. Therefore, a complete WGS analysis to rule out other possible causes for the index patients' disorder was not performed. However, the data was analyzed in a duo setting, but no other candidate gene variants were detected.

RNA sequencing analysis (Figures 1 and 3, Data S1D, and Tables S2 and S3) indicated that the RNA expression levels were 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 (Table S3). 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*.

4 | DISCUSSION

We present a partial de novo duplication of the *JARID2* gene in a patient sharing phenotypic features with 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 suggest that the defective transcripts are not entirely degraded by nonsense-mediated decay, unlike those 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

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

1 = Barøy et al. (2013), patient 4 2 = Verberne et al. (2021)	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	Current 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	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	−	+	−	+	+	−	−	+	−	+	+	−	+	−	+	+	−	+	56
Behavioral abnormalities	−	−	+	−	−	−	−	+	−	+	+	+	−	−	+	+	−	+	44
Abnormal MRI	−	na	na	na	−	−	na	−	−	+	na	−	+	+	+	na	na	na	40
Hypotonia	+	−	−	−	+	−	−	+	−	−	+	−	+	+	−	−	−	−	33
Eye/vision abnormalities	+	−	−	+	−	−	−	−	−	−	+	−	−	−	+	+	−	+	33

(Continues)

TABLE 1 (Continued)

1 = Barøy et al. (2013), patient 4																		Proportion of positive findings (%)
2 = Verberne et al. (2021)	1	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	Current patient	
ASD diagnosis	–	–	–	–	–	–	–	+	–	–	–	+	+	–	–	–	–	17
Epilepsy	–	–	–	–	–	+	+	–	–	+	–	–	–	–	–	–	–	17
Gait disturbance	+	–	–	–	–	–	–	–	–	–	+	–	–	–	–	–	–	11
Other																		
Perinatal complications	–	–	–	+	+	–	+	+	–	na	+	–	+	–	+	–	+	47
Hand/foot anomalies	+	+	–	+	–	+	–	–	–	–	–	–	–	+	–	–	+	39
Dental anomalies	–	–	–	–	–	+	–	–	+	–	–	–	–	–	–	–	+	17

Abbreviations: –, no; +, yes; ASD, autism spectrum disorder; dn, de novo; F, female; f, frameshift; M, male; ms, missense; na, not available; ns, nonsense; p, paternal; ss, splice site.

JARID2, we performed an exploratory transcriptome analysis from the RNA sequencing data from the patient and his mother as a reference. We discovered that the exons 1–7 of *JARID2* 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). However, other factors, such as age, may have also contributed to the gene expression differences between the two individuals, which could not be ruled out. JARID2 target 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 suggest that the duplication of exons 1–7 might result in loss of function in JARID2 protein and reduced expression of PRC2 target genes. Interestingly, it has been suggested that certain genes might be bidirectionally dosage sensitive as both haploinsufficiency and triplosensitivity interfere with normal protein function (Collins et al., 2021).

Our index patient shares a majority of the most common phenotypic features of the previously reported patients (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. The patient's height and weight were >2 SD that were reported in 31% and 25% of the other patients, respectively. A majority of the formerly reported patients (11/16, 69%) had mild to moderate intellectual disability, and the rest had a milder developmental delay (Barøy et al., 2013; Verberne et al., 2021). The current patient was diagnosed with speech delay and he needed extra support at school but was eventually able to attend a normal curriculum, implicating a somewhat milder presentation than in most of the previously reported patients.

As much as 47%, including the present patient, had perinatal complications, however, the majority were rather mild and common findings such as hyperbilirubinemia and thus probably not related to the *JARID2* variants. He also presented with syndactyly whereas 39% of other patients showed hand/foot anomalies. However, these characteristics are also rather frequent and unspecific.

The DECIPHER database recognizes three other patients with a partial *JARID2* duplication (IDs: 260089, 267637, and 255516) in addition to the present case. These patients share clinical features with our index patient and the patients described in the literature, such as developmental delay, intellectual disability, hypotonia, seizures, and macrocephaly. The DECIPHER patients also have features not associated with the published patients with *JARID2* alternations, including sparse scalp hair, blepharophimosis, broad hallux, kyphosis, and myoclonus. In addition to a partial *JARID2* duplication, the DECIPHER patient 260089 has a second 278 kb microduplication harboring the exons 4–5 of *PTPRD* gene (NM_002839.4), and the patient 267637 has a de novo heterozygous missense variant c.902A>G, p.(Tyr301Cys) in *GABRB2*, complicating the evaluation of the clinical significance of the *JARID2* variants. As opposed to the previously described patients with de novo variants and one variant inherited from an affected parent, the DECIPHER patient no 255516 had inherited the duplication from an unaffected parent, which increases the uncertainty of the effect of this particular duplication. 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 a *JARID2*-associated disorder. The neurocognitive capacity of the current patient seems higher than most of the patients with whole gene deletions or *JARID2* variants predicted to undergo nonsense-mediated decay (Barøy et al., 2013; Verberne et al., 2021). Thus, 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.

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.

AUTHOR CONTRIBUTIONS

Conceptualization: all authors. Geneticanalyses: K. Kiiski, K. Kettunen, E.H. Niemelä, M. Kankainen. Clinical evaluation: L. Viitasalo. Manuscript preparation: L. Viitasalo, K. Kiiski. Writing, reviewing & editing: all authors. Project administration: L. Viitasalo, K.Kiiski.

ACKNOWLEDGMENTS

We would like to thank the family for taking part in this research. The authors thank Hanna Tammio for excellent technical assistance and MD PhD Kristiina Avela and MD PhD Sonja Strang-Karlsson for great support in clinical evaluations. We also thank the Core facility Sequencing Unit at FIMM Technology Centre supported by University of Helsinki and Biocenter Finland.

FUNDING INFORMATION

Special Funding for University Level Health Research (Kiiski, Viitasalo, Kettunen, Kankainen).

CONFLICT OF INTEREST

The authors have no conflict of interest to report.

ETHICAL APPROVAL

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

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Viitasalo, L., Kettunen, K., Kankainen, M., Niemelä, E. H., & Kiiski, K. (2022). A novel partial de novo duplication of *JARID2* gene causing a neurodevelopmental phenotype. *Molecular Genetics & Genomic Medicine*, *10*, e2037. https://doi.org/10.1002/mgg3.2037