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Neurodevelopmental phenotype in 36 new patients with 8p inverted duplication–deletion: Genotype–phenotype correlation for anomalies of the corpus callosum

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Abstract

Inverted duplication deletion 8p [invdupdel(8p)] is a complex and rare chromosomal rearrangement that combines a distal deletion and an inverted interstitial duplication of the short arm of chromosome 8. Carrier patients usually have developmental delay and intellectual disability (ID), associated with various cerebral and extra-cerebral malformations. Invdupdel(8p) is the most common recurrent chromosomal rearrangement in ID patients with anomalies of the corpus callosum (AnCC). Only a minority of invdupdel (8p) cases reported in the literature to date had both brain cerebral imaging and chromosomal microarray (CMA) with precise breakpoints of the rearrangements, making genotype–phenotype correlation studies for AnCC difficult. In this study, we report the clinical, radiological, and molecular data from 36 new invdupdel(8p) cases including three fetuses and five individuals from the same family, with breakpoints characterized by CMA. Among those, 97% ($n = 32/33$) of patients presented with mild to severe developmental delay/ID and 34% had seizures with mean age of onset of 3.9 years (2 months–9 years). Moreover, out of the 24 patients with brain MRI and 3 fetuses with neuropathology analysis, 63% ($n = 17/27$) had AnCC. We review additional data from 99 previously published patients with invdupdel(8p) and compare data of 17 patients from the literature with both CMA analysis and brain imaging to refine genotype–phenotype correlations for AnCC. This led us to refine a region of 5.1 Mb common to duplications of patients with AnCC and discuss potential candidate genes within this region.

KEYWORDS
8p inverted duplication-deletion, AnCC, anomalies of the corpus callosum, candidate genes, intellectual disability (ID), invdupdel(8p)

1 | INTRODUCTION

Interstitial inverted duplication 8p associated with a distal deletion of the short arm of chromosome 8 [invdupdel(8p)] is a complex chromosomal rearrangement with an estimated incidence of 1 in 10 000–30 000 live born infants.[1] The classical chromosomal mechanism leading to invdupdel(8p) rearrangements include a classic recombination with production of a dicentric chromosome, in which a segment including one centromere is then clipped off to produce a monocentric invdupdel(8p).[2] Invdupdel(8p) arises from a maternal paracentric inversion, which is a common polymorphism occurring in around a quarter to a third of European and Japanese populations, respectively.[2,3] Invdupdel(8p) is the most common invdupdel reported rearrangement in humans. This rearrangement has also been reported in mosaic.[4,5]

Since the first description in 1976, about 99 cases of invdupdel (8p) have been reported in the literature, but only few of these rearrangements have been characterized by chromosomal microarray (CMA).[1,2,4–32]

Previous studies demonstrated that invdupdel(8p) is the most common recurrent rearrangements in patients with ID associated with anomalies of the corpus callosum (AnCC).[27,33] As well as the most frequent malformations in invdupdel(8p) patients are AnCC, reported in 81% of cases with cerebral imaging (10/13 in Die-Smulders et al.,[12] 8/10 in Guo et al.,[13] and 4/4 in Feldman et al.[8]). Interestingly, patients with 8p inverted duplication without deletion were also reported with AnCC, pointing toward the duplication as causative for AnCC.[27] The same study defined a large critical interval of 10.7 Mb for AnCC. However, no causal gene has been yet identified which makes it necessary to carry out additional genotype–phenotype correlation studies that would help to refine this region.

To refine the genotype–phenotype correlations of invdupdel (8p) regarding AnCC and refine the clinical phenotype, we report here clinical and molecular data of 36 new invdupdel(8p) cases including three fetuses and five individuals from the same family and review additional data from the 99 previously published patients with invdupdel(8p). We compare clinical and molecular data from our series and published patients to refine genotype–phenotype correlations for AnCC.

2 | PATIENTS AND METHODS

2.1 | Patients

We collected clinical and molecular data of patients with invdupdel (8p) through members of the French Achropuce network (http://www.renapa.univ-montp1.fr/). Clinical data were obtained using a standardized questionnaire filled in by referring clinicians. Thirty-three individuals and three fetuses were recruited. All three fetuses had autopsy including neuropathological examination. Twenty-four patients out of 33 had brain MRI and one patient had transcranial ultrasound (patient 33), but the corpus callosum (CC) of this latter was not described. An expert radiologist (C.G.), with more than 20 years of experience in neuroimaging, ascertained all MRIs with AnCC and classified them into (i) complete agenesis, (ii) partial agenesis of the corpus callosum (ACC), (iii) short and thin CC, (iv) CC hypoplasia (thin but with normal anterior–posterior extent; Figure S1). For patients older than 5, the severity of intellectual disability (ID; mild, moderate, and severe to profound) was clinically determined, in accordance with the DSM-5, using the global psychomotor development and individual's adaptive functioning level across conceptual, social and practical skills, by the referring clinician.

Informed consent to participate in this study and have their data published in a journal article was obtained from all participants (or their parents or legal guardian in the case of children under 18). This project was approved by the local ethics committee (Comité de Protection des Personnes Ile-de-France N°71-10, N° RCB:2010-A00802-37).

2.2 | Chromosomal analyses

All invdupdel(8p) rearrangements were characterized by CMA: SNP-array (Human CytoSNP-12, Illumina, San Diego, CA), or Agilent's SurePrint G3 Human microarray 8 × 60 K or 4 × 180 K, or Agilent's SurePrint HD arrays 2 × 105 K (Agilent Technologies, Santa Clara, CA). Experiments were performed according to the manufacturer's specifications. Rearrangements were confirmed by Fluorescent in Situ Hybridization. Coordinates of the deletions reported in hg18 were converted into hg19/GRCh37 with LiftOver (https://genome.ucsc.edu/cgi-bin/hgLiftOver). Structural variants described are available in the DECIPHER database (https://www.deciphergenomics.org/) and corresponding DECIPHER accession numbers are referenced in the Table S1.

2.3 | Review of the literature

In addition, we performed a review of the literature in PubMed using the terms "inversion duplication deletion chromosome 8p," "inverted duplication chromosome 8p," and "duplication 8p" to retrieve published patients. All articles between 1977 and May 2021 were screened, and we included patients with available breakpoints. As patients with 8p inverted duplication without deletion were also reported with AnCC, we included two patients from the literature with inverted 8p duplication presenting with AnCC.[27]

2.4 | Genotype–phenotype correlation study

To refine the critical region associated with AnCC, we combined the results of CMA in our patients, for which CC structure was known, with patients of the literature whose CMA analysis and brain imaging were available. We used UCSC (https://genome.ucsc.edu/) to align deletions and duplications and defined duplicated regions common to AnCC. We evaluated potential candidate genes involved in AnCC by retrieving known canonical genes from the UCSC, and encoded-protein's functions were assessed from the UniProtKB (https://www.uniprot.org/), associated diseases from OMIM (https://www.omim.org/), and by doing PubMed research.

3 | RESULTS

We collected 36 patients including three fetuses and five individuals from the same family (patients 16, 17, 18, 19, and 20). Our cohort included 23 females (64%) and 13 males (36%). Patients were aged 4 months to 40 years old (mean 8 years and 11 months), and pregnancies were terminated at 30, 27, and 29 weeks of amenorrhea for the fetuses. Two patients were deceased, patient 5 at 4 years old (cause of death undetailed) and patient 33 at 4 months in a context of diaphragmatic hernia.

3.1 | Neurodevelopmental features

Neonatal hypotonia was described in 12/28 patients (data not available for five patients; Table 1). Then, 97% of patients (n = 32/33) developed global development delay including motor delay in 93% (27/29) of patients. Eighty percentage (20/25) of patients older than 3 years and 93% (14/15) of those older than 6 years were able to walk independently. Ninety-six percentage (27/28) of patients had speech delay and 37.5% (9/24) of patients older than 3 years (3–13.8 years) had not acquired language at last evaluation.

Only one patient presented normal psychomotor development, but she was only 18 months old at last clinical evaluation (patient 31). This latter patient carried the smallest duplication (4.9 Mb) of our series.

Patients 16, 17, 18, 19, and 20 were from the same family and included two sibs and their children (Figure 1). All five individuals presented with mild to moderate ID without any major associated malformation. Patient 16 had her first words at 4 years old. Interestingly, they carried one of the smallest 8p duplications of the series (8.4 Mb).

As severity of ID was variable (from mild to severe) in invdupdel (8p) patients, we compared severity of ID to the size of the duplication in our series. Using Mann–Whitney test, we observed that severity of ID was significantly correlated to the size of the duplication

TABLE 1 Frequency of clinical features in our cases and the ones from literature

Clinical manifestations	Frequency (present cases)		Details	Literature (99 patients)
US signs during pregnancy[a]	13/34	38%	Fetuses (/3): • AnCC ($n = 3$), IUGR ($n = 1$), nasal bone hypoplasia ($n = 1$) Patients (/31): • IUGR ($n = 5$): isolated ($n = 1$), and associated to: AnCC and gyration anomalies ($n = 2$), VSD ($n = 1$), oligohydramnios ($n = 1$) • TOF ($n = 2$) • Blake's pouch cyst with muscular VSD ($n = 1$) • Transient increased nuchal translucency ($n = 1$) • Pretragal trag (n = 1)	7
Born preterm	5/28	18%		–
Hypotonia	12/28	43%		60
Feeding difficulties	9/28	32%	• Gastroesophageal reflux or swallowing difficulties of variable severity ($n = 9$) • Enteral nutrition required ($n = 2$)	12
Small for gestational age (weight ≤10th percentile)	5/28	18%		
Large for gestational age (weight ≥90th percentile)	6/28	21%		
Global developmental delay	32/33	97%		27
Speech delay	27/28	96%		
Able to speak words	16/28	57%	• First words acquired between 24 months and 6 years old • At last evaluation: 8/11 only spoke words, 2/11 made phrases, and 1 could have a conversation	3
Motor delay	27/29	93%		
Walking achieved	21/29	72%	• Mean age of achievement: 31 months (15 months–9 years)	6
Intellectual disability (patients ≥5 years old)	19/19	100%		38
• Mild ID	5/19	26%		3
• Moderate ID	3/19	16%		9
• Severe ID	11/19	58%		21
Facial dysmorphism[a]	28/32	88%	Common features: • Wide mouth ($n = 9$), broad ($n = 6$) or prominent ($n = 2$) forehead or frontal bossing ($n = 2$), hypertelorism ($n = 5$), sunken eyes ($n = 4$), plagiocephaly ($n = 4$), macrotia ($n = 4$)	62
Cerebral anomalies[a]	21/28	75%	Cerebral anomalies associated in patients with AnCC ($n = 12/17$): • Enlarged subarachnoid space and/or ventricles ($n = 8$), white matter anomalies ($n = 4$), cerebellar hypoplasia ($n = 2$), arachnoid cyst of the posterior fossa ($n = 2$), cortical and subcortical atrophy ($n = 1$), vertebral and basilar artery dysplasia ($n = 1$), thin brainstem ($n = 1$), Dandy–Walker complex ($n = 1$), dilated Blake's pouch cyst ($n = 1$) Cerebral anomalies in patients with normal CC ($n = 4/11$): • Cortical/subcortical atrophy ($n = 2$), enlargement of ventricular system and subarachnoid spaces ($n = 3$), mega-cisterna magna ($n = 2$), simplified frontal gyration with a lipoma of the pituitary stalk ($n = 1$)	53/55 (96%)
• Complete ACC[a]	6/27[b]	22%		28/43 (65%)
• Partial ACC[a]	5/27	19%		8/43 (19%)
• Short and thin CC	4/27	15%		
• CC hypoplasia	2/27	7%		

TABLE 1 (Continued)

Clinical manifestations	Frequency (present cases)		Details	Literature (99 patients)
Congenital heart defects[a]	12/29	41%	• VSD ($n = 3$), TOF ($n = 3$), bicuspid aortic valve ($n = 2$), atrial septal defect ($n = 1$), PFO ($n = 1$), PDA ($n = 1$), bifid cardiac apex with a small left ventricle ($n = 1$), and intermittent aortic valve regurgitation ($n = 1$)	24
Orthopedic anomalies[a]	10/34	29%	• Hypermobility ($n = 5$), scoliosis ($n = 4$), hammertoes ($n = 3$), kyphosis ($n = 2$), pectus excavatum ($n = 1$), narrow thorax ($n = 1$), delayed skeletal maturation ($n = 1$), bilateral polydactyly ($n = 1$), pes planus ($n = 1$), pes valgus ($n = 1$), hyperlordosis ($n = 1$), femoral anteversion ($n = 1$)	37
Seizures	11/32	34%	• Mean age of onset: 3.9 years (2 months–9 years) • Absences ($n = 5$), generalized tonic–clonic ($n = 3$), myoclonic ($n = 2$), focal motor ($n = 2$)	10
Other neurological condition	9/29	31%	• Peripheral spasticity/hypertonia ($n = 6$), hypotonia ($n = 2$), dystonia ($n = 2$), parkinsonism ($n = 1$), difficulties in fine motor skills ($n = 1$)	17
Warning signs of ASD	4/33	12%	• ASD diagnosed ($n = 1$)	7
Other behavioral disorder	8/31	26%	• Bulimia nervosa ($n = 2$), AD/HD ($n = 2$), low frustration tolerance ($n = 2$), auto- and hetero-aggressive behavior ($n = 1$), and hand stereotypies ($n = 1$)	7

Note: In this table, for literature patients, single figures refer to the number of patients for whom the symptom is quoted, which does not imply that the symptom was absent in other patients. Denominators for present cases correspond to cases for which the information was available (exhaustive information is available in the Table S1).

Abbreviations: ACC, agenesis of corpus callosum; AD/HD, attention deficit/hyperactivity disorder; AnCC, anomalies of corpus callosum; ASD, autism spectrum disorder; CC, corpus callosum; IUGR, intrauterine growth retardation; PDA, patent ductus arteriosus; PFO, patent foramen ovale; TOF, tetralogy of Fallot; US, ultrasound; VSD, ventricular septal defect.

[a]Features for which fetuses were taken into account.

[b]The corpus callosum structure wasn't described for patient 33 that only had a cerebral US with reported cerebral malformations.

with a mean duplication size of 10 Mb in patients with mild ID (from 8.4 to 16.5 Mb) and of 21.4 Mb (from 10.4 to 30.3 Mb) for severe ID (Figure 2).

Eight patients (26%) had behavioral disorder (detailed in Table 1), including four patients with additional warning signs of autism spectrum disorder (ASD). One patient had confirmed ASD (Patient 1).

Sixty-three percent of patients presented AnCC ($n = 17/27$). ACC was complete in 35% ($n = 6/17$) of cases and partial in 29% ($n = 5/17$). Twenty-four percentage of patients ($n = 4/17$) had a short and thin CC and 12% ($n = 2/17$) had CC hypoplasia. Other described major cerebral anomalies were cerebellar hypoplasia ($n = 2$), Dandy–Walker complex ($n = 1$), and simplified frontal gyration with a lipoma of the pituitary stalk ($n = 1$).

Thirty-four percent ($n = 11/32$) of patients had epilepsy starting between 2 months and 9 years, characterized by absences ($n = 5$), generalized tonic–clonic ($n = 3$), myoclonic ($n = 2$), and focal motor ($n = 2$) seizures. Other neurological symptoms included spasticity ($n = 6$) and dystonia ($n = 2$).

Among extra-neurological manifestations, 12/29 patients had congenital heart defects (41%) and 10/34 patients had orthopedic anomalies. Other clinical manifestations, including facial dysmorphism, are described within Table 1 and exhaustively listed in Table S1.

3.2 | Chromosomal analyses

All patients carried 8p terminal deletion with recurrent proximal breakpoints ranging from coordinates 5 078 168–7 753 583 (GRCh37; Table S1). Considering the different types of CMA used in our series with their various resolutions, most patients carried a similar deletion. This led us to consider that the 8p deletion only played a minor role in the variability of the observed phenotypes. We thus decided to focus on 8p duplication for genotype–phenotype correlation studies.

8p duplicated sizes were highly variable from one individual to another, ranging from 4.9 to 33.7 Mb. Distal breakpoints were recurrent, from coordinates 12 404 003–12 711 820 in most of the patients ($n = 29/36$). Conversely, proximal 8p duplications breakpoints were not recurrent from one patient to another, leading to different sizes of duplications.

3.3 | Review of the literature

We identified 99 patients with invdupdel(8p) from the literature (Table 1). Among those, only 15/99 published patients with invdupdel (8p) have undergone both CMA defining the breakpoints of 8p rearrangements and brain imaging.[1,20,24,26,29,31,32]

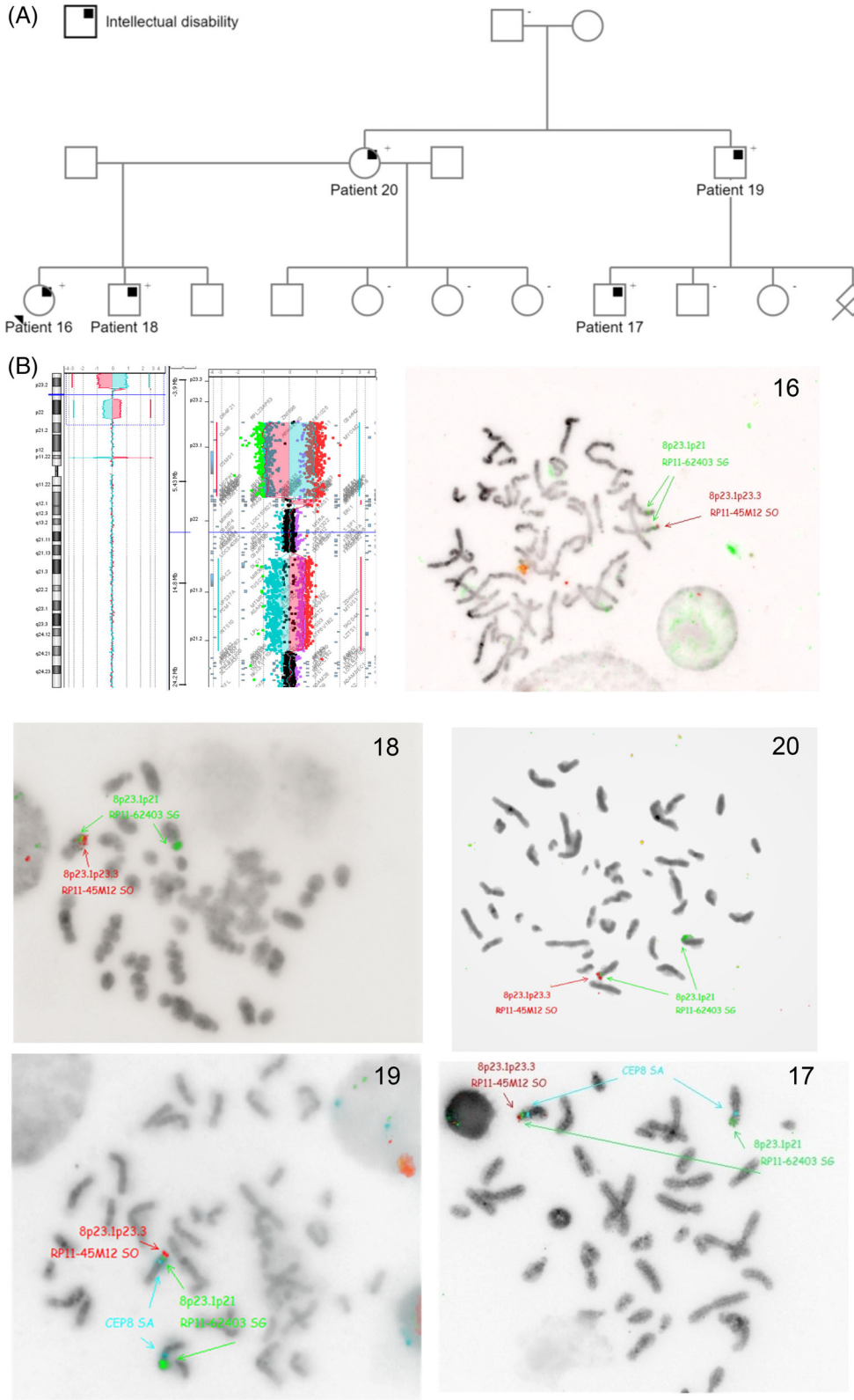

FIGURE 1 Pedigree of a familial transmission of invdupdel (8p) (A) and cytogenetic molecular characterization (B). Proband is indicated by an arrow. Tested individuals are indicated by: +: for carriers of the invdupdel(8p) rearrangement and by: −: for noncarriers; black quarter: individuals with intellectual deficiency. Chromosomal microarray analysis is shown for the proband (Patient 16). FISH images showing chromosome 8 rearrangements are showed for patients 16–20 (number indicated on each panel). The following FISH probes were used: in green the RP11-62403 SG for proximal 8p duplicated region, in red/orange the RP11-45M12 SO for the distal 8p deleted region and for patients 17 and 19: in blue the CEP8 SA for the chromosome 8 centromere [Colour figure can be viewed at wileyonlinelibrary.com]

Reported invdupdel(8p) patients have constant ID, facial characteristic features (97%), hypotonia (66%–96%), orthopedic anomalies (58%), featuring scoliosis (35%–63%), and congenital heart defects (19%–26%).[8,9,12,13] Around 84% of the 43 patients reported for which corpus callosum structure was available (36/43), presented AnCC.

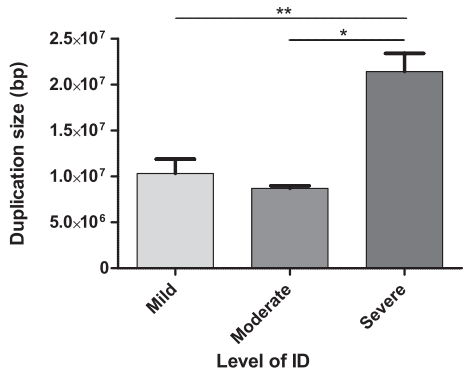

FIGURE 2 Mean duplication size according to the severity of intellectual disability (ID). Mann–Whitney test: $^{**}p$-value = 0.0045, $^{*}p$-value = 0.0126. Bar errors represent standard error mean (*SEM*). bp, base pair

3.4 | Genotype–phenotype correlation in AnCC

To refine the critical region associated with AnCC, we combined the results of CMA in our 27 patients, for which CC structure was known, with 15 patients of the literature whose CMA analysis and brain imaging were available (Figure 3).[1,20,24,26,27,29,31,32] We also included two patients with duplication (without deletion) previously reported by Sajan et al.[27] We thus defined a region of 5.1 Mb duplicated region common to all patients with AnCC, reducing the 10.7 Mb region previously proposed by Sajan et al. This region (located chr8:22553631-27672961) contained 51 canonical genes with 37 OMIM genes including four genes linked with a neurological phenotype: *RHOBTB2* (#607352), *NEFL* (#162280), *CHRNA2* (#118502), *GNRH1* (#152760). This region also included two genes, without known OMIM phenotype, coding for proteins that may be involved in neuronal growth, development, and/or migration: *NEFM* and *DPYSL2*.

4 | DISCUSSION

In this study, we report a series of 36 novel patients with invdupdel (8p) characterized by CMA, including five individuals from a same family, along with a review of published patients.

We confirm that invdupdel(8p) is associated with a neurodevelopmental disorder characterized by mild to severe global developmental delay, predominating on language acquisition. While most patients could walk (96% of patients older than 6 years), a minority had acquired a complex level of language and 37% of patients older than 3 years had not yet acquired language. As previously suggested,[1,25] patients with the smallest duplications of the series tended to have a less severe neurodevelopmental phenotype. We confirm that the level of ID correlates with the size of the duplication. As a support for this hypothesis, the only patient of our cohort without developmental delay in our series, although being young (18 months), carried the smallest duplication of the whole cohort. We also report here the first observation of invdupdel(8p) transmission in several members of a same family, across two generations and up to third degree relatives (patients 16–20, Figure 1). All five individuals had mild to moderate ID. This family demonstrates that patients carrying an invdupdel(8p) rearrangement do not necessarily have fertility impacted and that the rearrangement can be transmitted throughout the descendance. As this is the first description of invdupdel (8p) transmission, the risk of recurrence in the following generations can hardly be estimated, but patients should be informed of this risk during genetic counseling.

As previously noted in different series, epilepsy and progressive spasticity are common neurological complications in invdupdel (8p) patients that are important to detect since both can impair motor and cognitive skills of these individuals.[12,13,18]

As expected, AnCC were the most frequent brain malformation in invdupdel(8p) patients and gathered different types and shapes of corpus callosum (complete or partial agenesis, short and/or hypoplastic).

This study confirms that most patients carried similar 8p terminal deletions suggesting that the deletion could not explain phenotypical variability in invdupdel(8p) patients. Conversely, duplicate sizes were highly variable pointing toward the role of duplication in the phenotype. Sajan et al. previously suggested the role of the 8p duplication in AnCC, confirmed by the description of two cases of pure 8p duplications (without deletion) associated with AnCC. Furthermore different chromosome 8 imbalances with 8p21-pter trisomy, such as mosaic trisomies, 8p tetrasomies, and duplications of different portions of 8p, had been associated with AnCC.[34]

The terminal deletion takes away a maximum of 73 known canonical genes that include only three genes associated with disorders in OMIM: *CLN8* (ceroid lipofuscinosis), *ARHGEF10* (slowed nerve conduction velocity), and *MCPH1* (microcephaly 1). Thinning of the CC has been described in three patients with pathogenic variants (not detailed) in *CLN8*,[35] but no other AnCC has been reported associated with these three genes.

In this study, we refine the minimal 8p duplicated region proposed by Sajan for AnCC from 10.7 to 5.1 Mb containing 51 genes. Among those, four OMIM genes are associated with a neurological phenotype: *RHOBTB2* (Developmental and epileptic encephalopathy 64, dominant), *NEFL* (Charcot–Marie–Tooth disease), *CHRNA2* (Epilepsy, nocturnal frontal lobe, type 4), *GNRH1* (Hypogonadotropic hypogonadism 12 with or without anosmia).

Among those, only *RHOBTB2* variants have been reported with AnCC in developmental and epileptic encephalopathy 64 (DEE64) with patients with a thin CC. In 10 unrelated patients with DEE64[36] 5 different de novo heterozygous missense pathogenic variants were identified in the *RHOBTB2* gene. RHOBTB2 is a small Rho GTPase that interacts with the cullin-3 protein, an ubiquitin E3 ligase necessary for mitotic cell division. All the variants affected either the first or second BTB domains, at positions important for stabilizing interactions within the domain or for dimer formation. Straub et al.[36] suggested that pathogenic variants in *RHOBTB2* resulted in altered protein function rather than haploinsufficiency or a loss of function. This was in line with neuronal overexpression of the single RhoBTB ortholog in Drosophila that resulted in increased seizure susceptibility as well as severe locomotor defects.[36] The

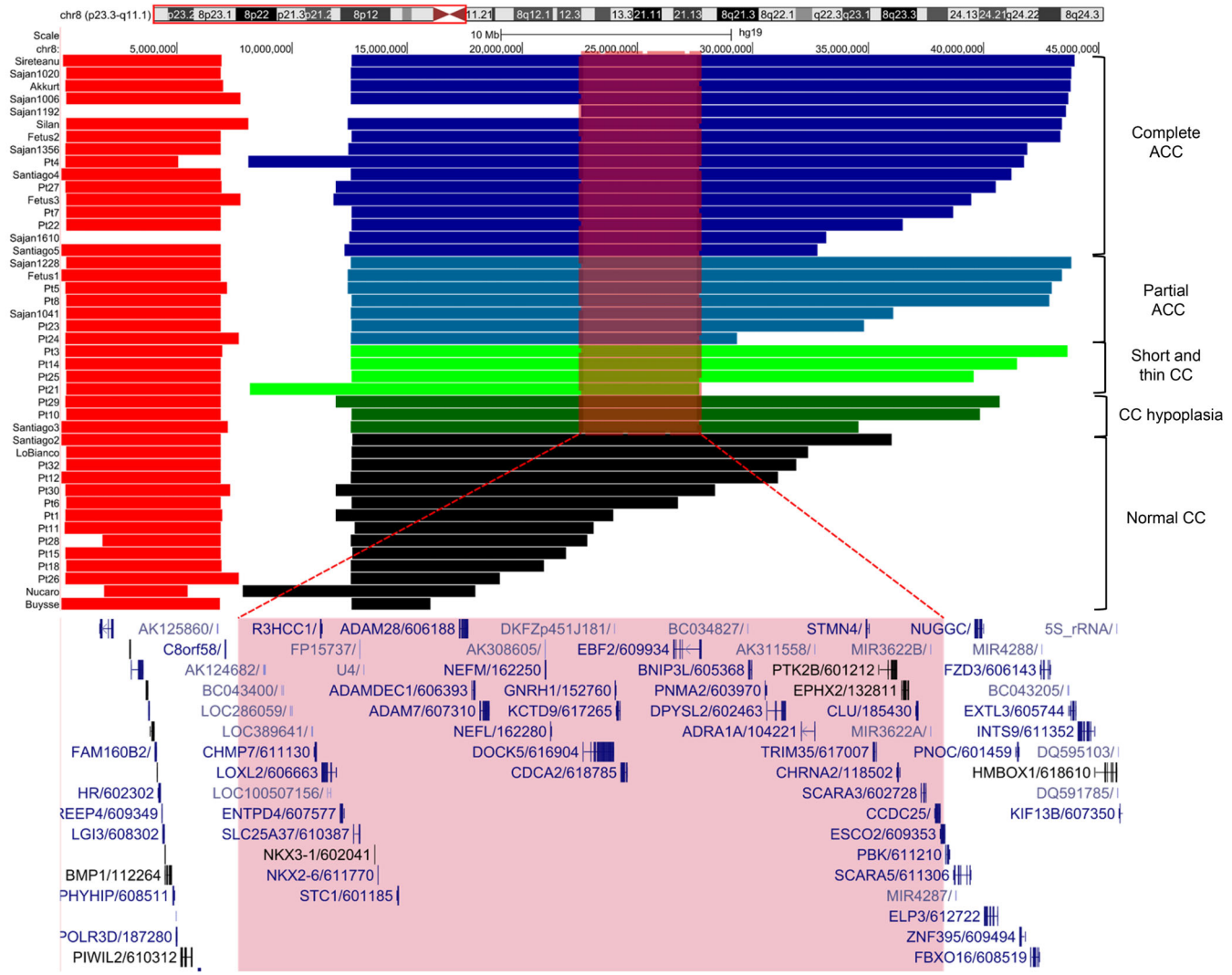

FIGURE 3 Mapping of deletions and inverted duplications of 27 of our cases and 17 from literature[1,20,24,26,27,29,32] (15 inverted duplications with deletion, and 2 cases with only the duplication) on chromosome 8. Deletions are in red, duplications are in blue: dark blue for patients with complete agenesis of corpus callosum (ACC), lighter blue for partial ACC, light green for patients with short and thin corpus callosum (CC), dark green for patients with CC hypoplasia and black for normal CC. The 5.1 Mb duplicated region common to all AnCC (dotted red rectangle), is defined by the beginning of Sajan 1192's duplication and the end of Pt21's duplication, corresponding to the following coordinates: chr8: 22553621-27672961. UCSC genes, with their corresponding OMIM accession number, comprised within the 5.1 Mb duplicated region, are represented in the highlighted red panel below. Pt, patient [Colour figure can be viewed at wileyonlinelibrary.com]

overexpression of RHOBTB2 related to 8p duplication could therefore be a good hypothesis to explain AnCC in invdupdel (8p) patients. Nevertheless, duplications of this gene are reported in the Database of Genomic Variants, which is not in favor of its involvement.

Considering another candidate gene, without a known OMIM phenotype, *DPYSL2* encodes a cytosolic phosphoprotein that is a member of the collapsin response mediator protein family. Collapsin response mediator proteins form homo- and hetero-tetramers and has been demonstrated to play a role in neuronal development and polarity, and in axonal growth and guidance.[37–39] DPYSL2 regulates signaling by class 3 semaphorins including the guidance factor semaphorin 3C that is expressed by CC neurons and acts to orient axons crossing through the CC; transient neurons work together with their glial partners in guiding callosal axons.[40] However, no AnCC have been reported associated with *DPYSL2* variants so far.

NEFM and *NEFL* encode two proteins of neurofilaments subunits that forms type IV intermediate filament heteropolymers, which are major components of the neuronal cytoskeleton and functionally maintain neuronal caliber.[41] They may also play a role in intracellular transport to axons and dendrites. While *NEFM* variants are not associated with any known disease, the protein is used as a biomarker of neuronal damage[42] and *NEFL* pathogenic variants are associated with Charcot–Marie–Tooth disease (type 1E, 1F).

5 | CONCLUSION

Considering all the genes included into the minimal duplicated region, no obvious causative gene really stands out to explain AnCC in invdupdel(8p) patients. Other pathogenic mechanisms should thus be considered like chromatin interaction disorder. Recent studies have shown that structural variants can disrupt the complex three-dimensional architecture of the genome, causing position effects and thereby contributing to developmental disorders.[43,44] The development of high-throughput chromosome conformation capture revealed that chromatin interactions are organized into topologically associating domains (TADs) which build a framework for contacts of regulatory elements and genes. Structural variants can lead to TADs disruption, abnormal chromatin interactions, and subsequent misregulation of gene expression, emerging as largely unexplored mechanisms involved in genetic disorders.[45,46]

Additional studies are needed including high-throughput chromosome conformation capture (Hi-C) analyses in invdupdel(8p) patients.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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