Autism and severe clinical phenotype in a patient with 8p21.2p11.21 deletion: Case report and literature review

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Abstract
Interstitial 8p deletions were previously described, in literature and databases, in approximately 30 patients with neurodevelopmental disorders. We report on a novel patient with a 8p21.2p11.21 deletion presenting a clinical phenotype that includes severe intellectual disability, microcephaly, epilepsy, and autism, the latter having been rarely associated with this genetic defect.

KEYWORDS
genetics, pediatrics and adolescent medicine, psychiatry
1 | INTRODUCTION

Genetic defects of 8p have been associated with a variety of disorders, from neurologic conditions to cancer. Deletions of 8p23.1p11 regions were previously described in approximately 30 patients. A wide variability in deletions size and clinical presentation has been observed, and the proximal 8p interstitial deletion is still poorly defined. Willemsen et al (2009) extensively reviewed 21 patients with deletions overlapping 8p21p12 region and summarized the clinical features in most patients: intellectual disability (ID), postnatal microcephaly, growth retardation, cardiac and ocular anomalies, hypogonadotropic hypogonadism, spherocytosis, and variable facial features.

We report on a patient harboring a de novo 8p21.2p11.21 interstitial deletion with autism as part of a severe neuropsychiatric phenotype. We also briefly review overlapping deletions from literature and databases, detected by chromosomal microarrays, and summarize the clinical features. To our knowledge, autism was rarely reported among the clinical findings of proximal interstitial deletions of 8p; thus, our patient brings new data to support this association.

2 | CASE

The patient, a 10-year-old girl, was referred for genetic evaluation due to severe intellectual disability of unknown cause. She is the first child of healthy nonconsanguineous Caucasian parents, born after an uneventful pregnancy, with a birthweight of 3300 g, birth length 52 cm, and an Apgar score of 7. During the first 3 days after being born, she had breathing and feeding difficulties. Her psychomotor development was delayed: she was able to hold her head up at 9 months, to sit at 12 months, and to walk alone at 30 months. Since infancy, the girl had feeding difficulties and food reflux with failure to thrive. She also contracted frequent respiratory infections, two episodes of febrile convulsions, and epileptic seizures with onset at the age of 9. When she was 3, she was evaluated in the Pediatric Neurology Department for developmental delay; her clinical evaluation revealed speech delay (she said only few syllables) and cognitive delay with a mental age of 10 months. Biological tests, heart ultrasound, and brain magnetic resonance imaging (MRI) were in the normal range. She started a complex program of therapy, including physical therapy, speech therapy, and occupational therapy, with very slow and small progress: she is able to use the toilet, to eat on her own, and to understand few simple orders. She received valproate treatment for the epileptic seizures, with good response.

Her clinical examination at age 10 showed the following: weight 20 kg (−6 SD), height 107 cm (−4 SD), occipitofrontal circumference 47 cm (−4 SD); facial dysmorphism: upslanting, narrow palpebral fissures, synophrys, broad nasal bridge, short nasal philtrum, open mouth with down-turned corners, thin lips, high-arched palate vault; dorsal kyphosis. The neurologic evaluation revealed severe speech delay with the use of only one word (“mama,” but not to identify her mother). The psychiatric evaluation revealed lack of visual and psychic contact, self-injurious behavior, hyperkinesia, and stereotype movements; she was not able to establish social relationships and did not show any evidence of protodeclarative pointing.

Psychological evaluation using the WISC Test (Wechsler Intelligence Scale for Children) revealed severe ID (IQ 30).

Using Diagnostic and Statistical Manual of Mental Disorders (DSM) IV Diagnostic Criteria for Autism, our patient scored 8 out of 12. She showed abnormal functioning in the areas of social interaction, communication, and symbolic or imaginative play, with onset prior to 3 years of age. Assessment using the Autism Diagnostic Interview-Revised (ADI-R) indicated impairments in social interaction, communication, repetitive behaviors, and abnormality of development. Her scores were as follows: 23 (cutoff 10), 10 (cutoff 8), 5 (cutoff 3), and 5 (cutoff 1), respectively.

![FIGURE 1](A, Partial karyotypes and array-CGH profile showing deletion 8p21.2p11.21. B, Schematic representation of 8p depicting the deleted regions of the present patient, the patients reported in literature and those reported in DECIPHER database, with the genomic coordinates from chromosomal microarrays)
**TABLE 1** Summary of genomic and clinical findings reported in patients with neurodevelopmental disorders and 8p interstitial deletions identified by chromosomal microarray

| DECIPHER ID/published patients (ref) | Sex/age | Genetic defect of 8p: cytoband, genomic coordinates (GRCh37/hg19) | Facial dysmorphic features | Develop mental delay | Microcephaly |
|-------------------------------------|---------|---------------------------------------------------------------|---------------------------|---------------------|--------------|
| Present patient F/10 y              |         | 8p21.2 p11.21 (25 278 984-41 469 578)                          | + (upslanting, narrow palpebral fissures, synophrys; broad nasal bridge; short nasal philtrum; open mouth with down-turned corners; thin lips; high-arched palatine vault; dorsal kyphosis) | +                   | +            |
| DECIPHER 267866 M/2 y              |         | 8p22p11.21 (16 850 757-39 899 187)                            | + (abnormality of the pinna, low-set ears, posteriorly rotated ears, downturned corners of mouth, pointed chin, trigonocephaly) | +                   | –            |
| Yu S 1 (2010) M/NA                  |         | 8p22p12 (18 375 250-32 765 636)                               | + (small ears, downslanting palpebral fissures) | NA                  | –            |
| Li T (2016) F/1 y 3 mo              |         | 8p22p11.23 (18 634 986-37 160 315)                            | + (hypertelorism, epicanthal folds, short nose, thin lips, upslant palpebral fissures, high-arched palate) | +                   | +            |
| DECIPHER 323931 F/25 y              |         | 8p21.3p12 (22 938 085-32 022 342)                            | + (upslanting palpebral fissures, hypertelorism, nystagmus, crumpled ear helix, long, and slim fingers) | +                   | +            |
| Zanni G (2011) F/5 y 3 mo           |         | 8p21.3p21.2 (23 117 561-25 349 074)                           | + (dolichocephalic skull, high forehead, sparse hair, low-set and posteriorly rotated ears, bilateral epicanthic folds, a small nose with flat nasal bridge, and a thin upper lip) | +                   | +            |
| Willemsen M 1 (2009) M/1 y 6 mo     |         | 8p21.3p12 (23 207 583-37 245 947)                            | + (upward slanting palpebral fissures, long eye lashes, small arched eyebrows, inverted epicanthal folds, bilateral malformation of the upper helices, a small right auricular pit, a long and smooth philtrum, thin lips and down turned corners of the mouth | +                   | +            |
| DECIPHER 306350 F/7 y               |         | 8p21.2p12 (23 706 968-29 243 144)                            | + (flat face, hypertelorism, flat nasal root, epicanthus, thin palpebral fissures, extroverted upper lip, small mouth) | +                   | +            |
| Willemsen M 2 (2009) F/1 y 10 mo    |         | 8p21.2p12 (24 462 674-31 149 113)                            | + (long eye lashes, narrow palpebral fissures, full hooked nose, broad dental gums and thin upper lip) | +                   | +            |
| Klopacki E (2006) F/2 y 6 mo        |         | 8p21.2p12 (25 095 177-32 909 082)                            | + (thin upper lip, microphthalmia particularly of the left eye, nystagmus, strabismus convergens, and bifid uvula) | +                   | +            |
| Congenital heart defect | Autistic features | Other behavioral problems | Abnormalities of erythrocytes (congenital spherocytosis, other) | Miscellaneous |
|------------------------|------------------|--------------------------|---------------------------------------------------------------|---------------|
| −                      | +                | + (self-injurious behavior, hyperkinesia) | −                                                             | Growth delay feeding difficulties and food reflux with failure to thrive, frequent respiratory infections, epileptic seizures |
| −                      | −                | −                        | −                                                             | Feeding difficulties in infancy, congenital nystagmus, optic disk hypoplasia, cryptorchidism, hydronephrosis, micropenis, short stature, muscular hypotonia growth delay (short stature) |
| + (ventricular septal defect, patent ductus arteriosus, pulmonary valve atresia) | NA               | NA                       | −                                                             | Hypospadias, Hirschprung disease, growth delay |
| + (atrial septal defect—surgery corrected) | NA               | NA                       | −                                                             | Ocular abnormality, simian creases, malformed hands and feet, calcium deficiency, periventricular leukomalacia growth delay |
| + (tetralogy of Fallot—surgery corrected) | −                | −                        | −                                                             | Mild hypoacusia |
| −                      | −                | −                        | + (anemia)                                                     | Gastroesophageal reflux and frequent gastrointestinal and respiratory infections, growth delay, hypothyroidism, generalized hypotonia and joint hyperlaxity, café-au-lait spots, and lentigines on the lower extremities, epilepsy, cerebellar vermis hypoplasia, classical Dandy-Walker malformation |
| + (perimembranous ventricle septum defect—surgery corrected) | NA               | NA                       | −                                                             | Feeding difficulties, hypoplasia of the corpus callosum and hypomyelination, prominent metopic suture without craniosynostosis, astigmatism, severe bilateral sensorineural hearing loss, hypospadias, growth delay |
| −                      | −                | −                        | −                                                             | Growth delay and relative overweight, astigmatism, single umbilical artery |
| NA                    | NA               | NA                       | −                                                             | Neonatal hypotony, neonatal gastroesophageal reflux, little eye contact and a high hypermetropia without structural eye abnormalities (after the age of 4 mo), growth delay |
| −                      | −                | + (reduced sense of pain and sleep disturbances) | −                                                             | Feeding difficulties, short stature, generalized muscular hypotonia, no Achilles reflex, hypoplastic optic nerve papillae, peripheral neuropathy with dysmyelination, dilatation of the inner ventricles and a small corpus callosum, growth delay |

(Continues)
Array-based comparative genomic hybridization (array-CGH) was performed on peripheral blood genomic DNA according to manufacturer's protocol, using a 44K Microarray kit (Agilent Technologies). GTG-banded karyotype analysis was performed on chromosomes obtained from peripheral blood cultures stimulated with phytohemagglutinin according to standard methods. The genomic profile generated by array-CGH showed an interstitial 8p21.2p11.21 deletion, spanning approximately 16.2 Mb. No other CNVs were detected in our patient genomic profile, with the 44k microarray kit. The GTG-banded karyotype of the proband confirmed the deletion (Figure 1A); parents karyotypes were normal. Our patient karyotype is therefore:

\[ 46,XX,\text{del}(8)(p11.2p21).\text{arr}[\text{GRCh37}] \]

\[ 8p21.2p11.21(25278984_41469578)x1\text{dn}. \]

The patient was included in a cognitive stimulation program, including Applied Behavior Analysis therapy, in a special center for children with autism spectrum disorders (ASDs). She continued the therapy with valproate for epilepsy, with periodic reevaluation by neurologic examination, biological tests, and electroencephalograms (EEG).

The study was approved by the Ethics Committee of Victor Babes National Institute of Pathology. Written informed consent for research and data publication was obtained from the parents, prior to inclusion in this study.

### 3 | DISCUSSION

The short arm of chromosome 8 is known as a “hub” for neuropsychiatric disorders. Interstitial 8p deletions, proximal to 8p23.1, are rare events, previously reported in approximately 30 patients presenting with developmental disorders, 13 of them being molecularly characterized by chromosomal microarray (Table 1, Figure 1B). The clinical features described in the majority of patients included the following: ID, postnatal microcephaly, growth retardation, cardiac and ocular anomalies, hypogonadism, spherocytosis, and dysmorphic facial features (upslanting palpebral fissures, ogival palate, malocclusion, microteletelia, long limbs and fingers, hypoplasia distal phalanges, bilateral simian line, big toes, clinodactyly of the fifth finger with overlapping fingers).

| DECIPHER ID/published patients (ref) | Sex/age | Genetic defect of 8p: cytoband, genomic coordinates (GRCh37/hg19) | Facial dysmorphic features | Develop mental delay | Microcephaly |
|--------------------------------------|---------|---------------------------------------------------------------|-----------------------------|---------------------|--------------|
| DECIPHER 281733                      | F/9 y   | 8p21.2p12 (25 594 263-35 377 574)                             | + (down slanting palpebral fissures, ears low plant with auricular simplified structures, ogival palate, malocclusion, microteletelia, long limbs and fingers, hypoplasia distal phalanges, bilateral simian line, big toes, clinodactyly of the fifth finger with overlapping fingers) | +                   | +            |

| Walker S (2013)                     | NA      | 8p12 (32 111 587-32 175 992)                                  | NA                          | NA                  | NA           |
|-------------------------------------|---------|---------------------------------------------------------------|-----------------------------|---------------------|--------------|
| Yu S 2 (2010)                       | M/NA    | 8p12 (32 189 595-35 280 851)pat                               | + (epicanthal folds, sparse eye brows, mild hypertelorism) | +                   | –            |
| Miya K (2012)                       | F/1 y 7 mo | 8p11.22p11.1 (39 678 598-43 333 638)                         | + (hypertelorism, epicanthus, a depressed nasal bridge, and arched eyebrows) | +                   | –            |

The present patient, as well as the patients reported in literature and those from the DECIPHER database (https://decipher.sanger.ac.uk/), except for two with no available data, showed developmental delay/ID. Growth delay and microcephaly were observed in 11 and 9, respectively (Table 1). Hypotonia (6 patients) and feeding difficulties in infancy (6 patients) were also frequently observed features. Four patients had brain malformations (hypoplasia of the corpus callosum in 3 patients and cerebellar vermis hypoplasia in one patient). Epileptic seizures were noted only in two patients, but this may be explained by an older onset age onset of epilepsy; one patient had febrile seizures. The facial dysmorphism is very heterogeneous among the reviewed patients; the most prevalent features, overlapping with the facial gestalt of our patient, were thin upper lip (5 patients), upslanting palpebral...
fissures, narrow palpebral fissures, and flat nasal root (3 patients). Downturned corners of the mouth and high-arched palate were observed only in two patients. Other common facial features not observed in our patient are epicanthic folds (in 6 patients out of 12), hypertelorism, and low-set ears (3 patients).

Interestingly, the autistic features were rarely reported both in the patients summarized here (Table 1—present patient and one reported by Walker et al, 2013), as well as in the literature dating before the microarray era. The rare occurrence of autism among the clinical spectrum of interstitial 8p deletions can be assigned to various factors. Many of the reported patients may have been too young for an ASD diagnosis to be made; also, some of the reports are dated several decades ago, when autism was a rare diagnosis.

Among the genes found to be deleted in the 8p21.2p11.21 region in our patient, the neuregulin 1 (NRG1) gene has been previously associated with psychiatric diseases like schizophrenia and bipolar disorder, mostly in genome wide association studies (GWAS).13-17 NRG1 is important for both normal nervous system development (central and peripheral) and the maintenance of the normal functioning of mature nervous system,15 being involved in neurodevelopment, neurotransmission and synaptic plasticity.18 NRG1 abnormalities in ASD patients are rare occurrences. Walker et al (2013) reported a de novo 8p12 deletion, encompassing NRG1 in a patient with ASD. In other four patients, deletions of the same cytoband (8p12) were inherited from a healthy parent, raising the possibility of an incomplete or variable penetrance of autistic features.9 In our patient, the NRG1 loss occurred de novo, as part of a large copy number variant (CNV) involving many other neighboring genes (over 100 RefSeq genes).

Another gene deleted in our patient, the cholinergic receptor nicotinic alpha 2 subunit (CHRNA2), encodes for neuronal receptors involved in fast synaptic transmission (nicotinic receptors for acetylcholine); the alpha subunit encoded by the CHRNA2 gene is expressed in the brain, and mutations in this gene have been associated with autosomal dominant nocturnal frontal lobe epilepsy, type 4 (OMIM# 610 353).19 Several other genes in the region have been associated with ID syndromes, however mostly when affected by homozygous mutations (EXTL3, TTI2, and MAK16).

Further evidence supporting the role of 8p chromosome in psychiatric disorders comes from GWAS. A meta-analysis of GWAS comprising over 16 000 subjects with schizophrenia and ASD showed new loci overlapping both conditions, including chr8:38014429-38316849 (containing BAG4, FGFR1, LETM2, LSM1, WHSC1L1) and chr8:27276705-27557405 (containing CHRNA2, CLU, EPHX2, MIR6842, MIR6843, PTK2B, SCARA3) (Build GRCh37/hg19), both sets of genes deleted in our patient.20

Several study limitations have to be mentioned, such as the paucity of clinical data from the patients published in large studies or databases and the limited data regarding the deletion size and genomic location for cases published prior to routine microarray investigations. Also, due to the large gene content of the deleted region, genotype-phenotype correlations are difficult to draw. The cumulative effect of haploinsufficiency of many genes within the deleted region is the most probable mechanism that leads to the phenotype of our patient. Another challenging aspect is the diagnosis of ASD in a patient with severe ID. However, this diagnosis can be established in the presence of limited social responsiveness and of stereotyped behavior, often associated

### Table 1 (Continued)

| Congenital heart defect | Autistic features | Other behavioral problems | Abnormalities of erythrocytes (congenital spherocytosis, other) | Miscellaneous |
|-------------------------|------------------|--------------------------|-------------------------------------------------------------|---------------|
| + (aneurysm of the interatrial septum) | – | – | – | Microsomia, corpus callosum hypoplasia, severe scoliosis, growth delay |
| NA | + | NA | NA | NA |
| NA | NA | NA | – | Hypotonia |
| NA | NA | NA | + (anemia) | Intrauterine and postnatal growth delay, febrile seizures |
with other behavior problems (inattention, hyperkinesia, aggressivity).

4  CONCLUSIONS

Our patient supports the association between proximal 8p interstitial deletion and a clinical phenotype including autism, severe ID and speech delay, epilepsy, and dysmorphic features. To our knowledge, autism has rarely been reported among the clinical findings. This is why our case contributes to accurate description of proximal 8p deletions phenotype.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

All authors have made substantial contributions to all of the following: AA and MB substantially contributed to conception and design; AA, SMP, ACTC, AE, SL, SG, LC, MG, CP, LB, and AN: contributed to acquisition, analysis, or interpretation of data. AA, SMP, ACTC, and MB: drafted the manuscript. AA, SL, SG, LC, MG, CP, LB, AN, and MB: critically revised the manuscript for important intellectual content. All authors approved the final version for submission.

ETHICAL APPROVAL

The study was approved by the Ethics Committee of Victor Babes National Institute of Pathology and complies with the Declaration of Helsinki. Written informed consent for research and data publication was obtained from the parents, prior to inclusion in this study.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable for this article as the data were not submitted to a public repository.

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