MECP2 Duplications in Symptomatic Females: Report on 3 Patients Showing the Broad Phenotypic Spectrum

Victoria San Antonio-Arce, MD[1], María Fenollar-Cortés, PhD[2],
Raluca Oancea Ionescu, PhD[2], Teresa DeSantos-Moreno, PhD[1], Jesús Gallego-Merlo[3],
Francisco José Illana Cámara[2], and María Carmen Cotarelo Pérez, MD[2]

Abstract

Xq28 microduplications including the *MECP2* gene constitute a 100% penetrant X-linked syndrome in males caused by over-expression of normal MeCP2 protein. A small number of cases of affected females have been reported. This can be due to the location of the duplicated material into an autosome, but it can also be due to the location of the duplicated material into one of the X chromosomes and random or unfavorable skewed X chromosome inactivation, which is much more likely to occur but may be underdiagnosed because of the resulting broad phenotypic spectrum. In order to contribute to the phenotypic delineation of Xq28 microduplications including *MECP2* in symptomatic females, the authors present clinical and molecular data on 3 patients illustrating the broad phenotypic spectrum. Our finding underlines the importance of quantitative analysis of *MECP2* in females with intellectual disability and raises the question of the indication in females with borderline intellectual performances or learning difficulties.

Background

Xq28 microduplications including the methyl-CpG-binding protein 2 gene (*MECP2*, MIM *300005) constitute a 100% penetrant X-linked syndrome (MIM #300260) associated with a distinct phenotype in affected males characterized by infantile hypotonia, mild dysmorphic features, pervasive developmental/intellectual disability with absent or minimal speech, epilepsy, recurrent infections, progressive leg spasticity, ataxia, autistic features, and, in some cases, developmental regression.[1] The neurological features are thought to be caused by the overexpression of normal MeCP2 protein. In most cases, the duplication is inherited from the carrier mother and located in the X chromosome itself. The female carriers were thought to be unaffected due to the near-100% skewing of X chromosome inactivation (XCI) with preferential silencing of the mutant X chromosome. However, a small number of cases of affected females have been reported. This can be due to the location of the duplicated material into an autosome,[2-7] but it can also be due to the location of the duplicated material into one of the X chromosomes and random or unfavorable skewed X chromosome inactivation, which is much more likely to occur but may be underdiagnosed because of the resulting broad phenotypic spectrum.[7-14]

In order to contribute to the phenotypic delineation of Xq28 microduplications including *MECP2* in symptomatic females, the authors present clinical and molecular data on 3 patients illustrating the broad phenotypic spectrum.

[1] Department of Neuropediatrics, Hospital Clínico Universitario San Carlos, Madrid, Spain
[2] Department of Genetics, Hospital Clínico Universitario San Carlos, Madrid, Spain
[3] Department of Genetics, IIS-Fundación Jiménez Díaz, UAM, Madrid, Spain

Corresponding Author:
Victoria San Antonio-Arce, MD, Department of Neuropediatrics, Hospital Clínico Universitario San Carlos, Calle Profesor Martín Lagos s.n., 28040, Madrid, Spain.
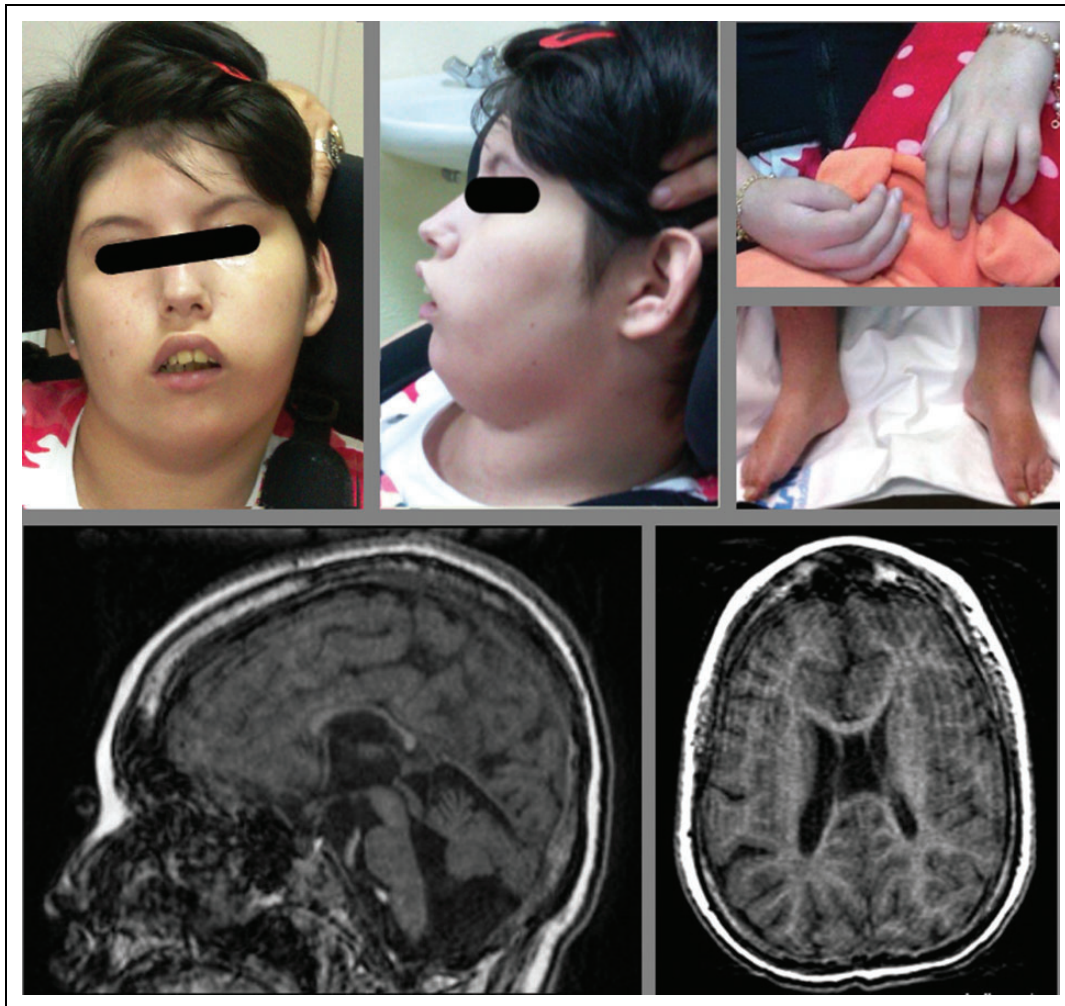Email: victoriasanantonio@gmail.com

Figure 1. Dysmorphic features and brain magnetic resonance imaging showing cerebellar vermis hypoplasia with no enlargement of the fourth ventricle associated with a corpus callosum hypoplasia and probable frontal focal cortical dysplasia (FCD) in patient 1 at age 18 years.

Case Presentation

Patient 1 was second child born to a 33-year-old mother and a 41-year-old father. Parents were healthy and nonconsanguineous. She had a 2-year older healthy brother. There was no history of spontaneous abortions or stillbirths. The family history was unremarkable. Intrauterine growth restriction was diagnosed during pregnancy. The patient was born in the 41st week of gestation; a cesarean section had to be performed for suspected fetal distress; umbilical arterial pH was 7.12; Apgar scores were 3 and 8 at 1 and 5 minutes, respectively; and newborn resuscitation including ventilation with 100% oxygen via endotracheal tube was necessary. She had a birth weight of 2500 g (below the third percentile), a height of 45 cm (below the third percentile), and a cranial perimeter of 33 cm (percentile 10-25). On examination, she showed generalized hypotonia and dysmorphic features: micrognathia, microstomy, short philtrum with inverted V-shaped upper lip, high-arched palate, hypotelorism, low set ears, fusiform fingers, and small feet (Figure 1). Skeletal X-ray survey; cardiac, abdominal, and

renal ultrasound imaging; ophthalmological and ear, nose, and throat examination; and electroencephalography were normal. Brain magnetic resonance imaging showed a cerebellar vermis hypoplasia associated with a corpus callosum hypoplasia. Her karyotype was 46, XX. In the follow-up, she showed a severe global developmental delay: She never walked, had no speech, and showed very poor empathy. However, she showed no developmental regression. No stereotypes were observed. After infancy, she had no feeding difficulties and no infections requiring hospitalization. She developed a microcephaly with cranial perimeter between the 3rd and the 10th percentiles. No postnatal growth retardation was observed. She developed a severe scoliosis. Since the age of 2 years, she had frequent edema related to a hypoproteinemia due to increased enteric protein loss. She had a tendency to constipation. She completed puberty at an average age. Because of ovarian fibrothecoma, she had a bilateral oophorectomy at the age of 17 years and received hormonal replacement therapy. At the age of 16 years, she presented with a difficult-to-control epilepsy, with tonic seizures spontaneous or triggered by feeding and atypical

absences. Brain magnetic resonance imaging at the age of 18 years showed the cerebellar vermis hypoplasia with no enlargement of the fourth ventricle associated with a corpus callosum hypoplasia and a cortical thickening in the interhemispheric portion of the left frontal lobe likely corresponding to a focal cortical dysplasia (Figure 1). Multiplex ligation-dependent probe amplification analysis for the Xq28 region (SALSA P049-B1 and P106 probemix by MRC-Holland, Amsterdam, The Netherlands) showed a de novo duplication including the genes *PNCK, SLC6A8, BCAP31, ABCD1, IDH3G, L1CAM, IRAK1, MECP2, FLNA, GDI1*, and *VAMP7*, confirmed by 400 k array comparative genomic hybridization analysis that showed a 6.14 Mb duplication including 89 genes (Figure 2). Fluorescent in situ hybridization analysis performed on metaphase spreads showed the extra copy of chromosome Xq28 material inserted into one of the chromosomes 21, and microsatellite analysis demonstrated the paternal origin of the duplicated chromosome X. Since the age of 18 years, the patient developed a sinus tachycardia for unknown reason, as well as recurrent respiratory infections requiring hospitalization for antibiotic, fluid, and oxygen therapy, with progressive deterioration in her general clinic state until her death during one of these episodes at the age of 20 years.

Patient 2 is a 10-year-old girl born to a 37-year-old mother and a 39-year-old father. Parents are healthy and nonconsanguineous. The mother had a healthy son 13 years before. She also had a spontaneous abortion. For his part, the father also had a healthy daughter 13 years before. A daughter of a mother's sister has epilepsy, otherwise the family history is unremarkable. The patient was born in the 39th week of gestation with a birth weight of 2620 g (percentile 3-10) and a height of 48 cm (percentile 10-25). The cranial perimeter at birth and the Apgar scores are not known. Early neuromotor development is referred as normal or lightly slow, sitting at 6 to 7 months of age and walking at 16 to 17 months of age. However, a slower development of speech was noted, and first words appeared at 30 months of age. Otherwise her general health is good; she had only frequent upper respiratory tract infections in the first 3 years of life requiring no hospitalization. At the age of 4.5 years, she was first assessed in a neuropediatric setting because of poor attention and hyperactive behavior. A mild neurodevelopmental delay was found. At the age of 6.5 years, she showed difficulties with learning to read. In a neuropsychological assessment at the age of 7 years, she showed intellectual performances at the level of the average and low reading performances for her age, and a specific reading disability was suspected. Moreover, short attention span, increased motor activity, and oppositional and defiant behavior were observed. A specific reading rehabilitation was started. She was newly reassessed at the neuropediatric setting at the age of 9.5 years. She attended regular school with curriculum adaptation; she was not yet able to read appropriately. On examination, her weight was 26.3 kg (percentile 3-10), her height was 130.5 cm (percentile 10-25), and her cranial perimeter was 52 cm (percentile 50). Except a mild clinodactyly of the fifth fingers, she showed no dysmorphic features. She had a high-arched palate. General examination showed no more anomalies. Neurological examination only showed poor motor coordination without ataxia and speech, with poor morphosyntactic skills and some difficulties in pronunciation. Ear, nose, and throat assessment was normal. Electroencephalography and brain magnetic resonance imaging performed at the age of 9.5 years showed no abnormality. Multiplex Ligation-dependent Probe Amplification analysis for the Xq28 region (SALSA P015-E1, P049-B2, and P061-B2 probemix by MRC-Holland) showed a de novo duplication including the gene *MECP2* and a part of the gene *FLNA*. This was confirmed by 400 k array comparative genomic hybridization analysis that showed a 350 kb duplication including 8 MIM genes: *IRAK1* (until exon 13), *MECP2, OPN1LW, TEX28, TKTL1, FLNA, EMD*, and *RPL10* (Figure 2). Due to the small size of the duplication, karyotype was normal. Fluorescent in situ hybridization showed no signal on autosomal chromosomes. Likewise, microsatellite analysis did not report information on the origin of the duplicated chromosome X. A random X chromosome inactivation with a ratio of 45:55 was demonstrated.

Patient 3 is a 3-year-old girl born to a 30-year-old mother and a 36-year-old father. Parents are healthy and nonconsanguineous. They have no more children and no spontaneous abortions. The family history is unremarkable. After an uneventful pregnancy, the patient was born at full term without complications with a birth weight of 4200 g (percentile > 97). The height and the cranial perimeter at birth and the Apgar scores are not known. Newborn hearing screening was normal. Early neuromotor development is referred as normal or lightly slow, walking at 17 months of age. Social interaction is also referred as unremarkable in the first year of life. However, since the age of 2 years a delay in the development of both expressive and receptive language was noted. Otherwise her general health is good; she had only an episode of acute viral bronchiolitis requiring hospitalization for supportive care without further complications at the age of 17 months. At the age of 28 months, she was first assessed in a neuropediatric setting because of the delayed language development. On examination, her weight was at the percentile 97, her height was at the percentile 75 to 90, and her cranial perimeter was at the percentile 90. She showed no dysmorphic features. She had a midline diastema. General examination showed no more anomalies. Neurological examination showed moderate delay in the development of both expressive and receptive language with jargon aphasia, lack of comprehension of verbal commands, and very hyperkinetic behavior with continuous aimless moving and very short attention span. Eye contact was present although very short; she was smiling and tended to imitate motor behaviors. She showed stereotypies in form of hand and arm waving in periods of high excitement; however, she showed no manual stereotypies typical of Rett syndrome. Electroencephalography and a brain magnetic resonance imaging showed no abnormality. A neuropsychological assessment at the age of 37 months showed moderate developmental delay (developmental quotient 60), with no significant discrepancies between verbal and manipulative scales; low task persistence,
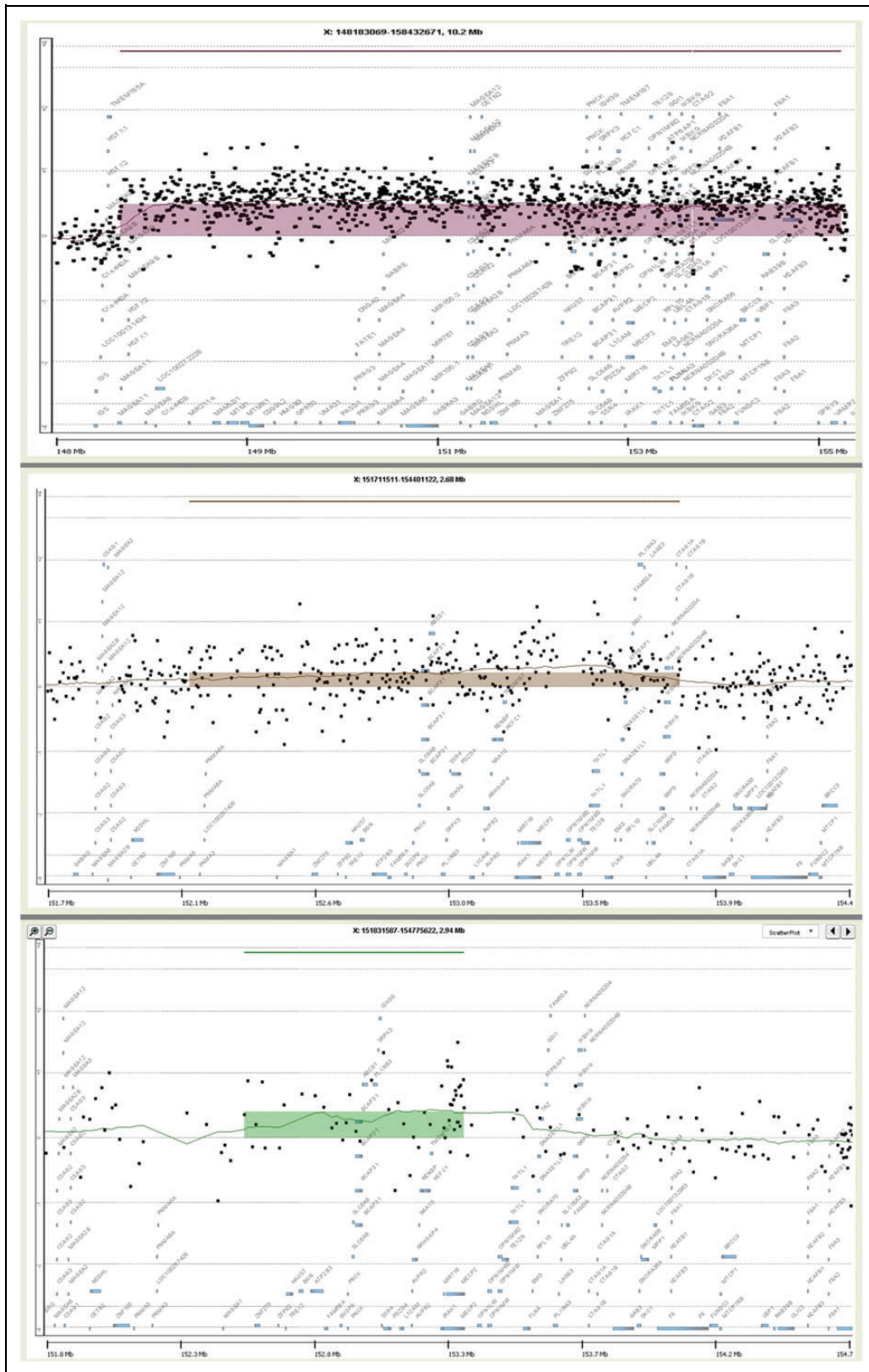
Figure 2. 400 k array comparative genomic hybridization analysis confirming the *MECP2* duplication in, respectively from top to bottom, patients 1 (6.14 Mb), 2 (350 kb), and 3 (80 kb).

poor planning capacity, lacking trial and error strategies, no verbal self-regulation in manipulative tasks, and presence of jargon aphasia during free play were also observed. She has been newly reassessed at the neuropediatric setting at the age of 38 months. She attends regular infant school with educational psychology and speech and language therapy, she has shown modest progress, she is able to use 20 to 30 single words and interacts better with her peers. Multiplex Ligation-dependent Probe Amplification analysis for the Xq28 region (SALSA P245-B1, P015-E1, P049-B2, and P061-B2 probemix by MRC-Holland) showed a de novo 80 kb duplication confirmed by 400 k array comparative genomic hybridization analysis including a part of the gene *MECP2* (exons 2 to 4) and a part of the gene *IRAK1* (exons 1 to 11; Figure 2). Due to the small size of the duplication, karyotype was normal, and fluorescent in situ hybridization showed no signal on autosomal chromosomes. Likewise, microsatellite analysis did not report information on the origin of the duplicated chromosome X. A random X chromosome inactivation with a ratio of 45:55 was demonstrated.

Conclusions

Our 3 patients illustrate the broad phenotypic spectrum of Xq28 microduplications including *MECP2* in symptomatic females.

Patient 1 is, to our knowledge, the ninth female reported in the literature affected because of the location of the duplicated material into an autosome. These cases occur mostly de novo, and the clinical picture is quite homogeneous and as severe as in males. Almost all patients present with dysmorphic features, major hypotonia, and moderate-to-severe developmental/intellectual disability. Intrauterine growth retardation, like in our patient 1, has been previously reported in 2 other female patients.[2,3] Postnatal growth failure and microcephaly are nearly constant features. Feeding difficulties, recurrent infections, and constipation are present in more than half of the patients; however, our patient 1 presented with feeding difficulties and recurrent respiratory infections only after the epilepsy onset at age of 16 years. Epilepsy, present in a third of patients, has indeed onset in late childhood or in adolescence, so it might be that it presents later on in the younger patients reported. Our patient 1 showed in addition a brain malformation with cerebellar vermis hypoplasia associated with a corpus callosum hypoplasia, which to our knowledge has only been previously reported in one affected female.[7] The severity of these cases is thought to be due to the fact that the duplicated material is located on an autosome entailing a functional disomy of the *MECP2* gene. The presence of a second associated cytogenetic alteration with loss or gain of material in the autosome where the duplicated material is inserted is reported in more than half of cases and surely plays a role in the clinical expression. So does the size of the duplication and the contained genes. Our patient 1 had a 6.14 Mb duplication including 89 genes; some of them may be responsible for other associated and not previously reported symptoms, such as the protein loss enteropathy; and beyond *MECP2*, at least one of them, *GDI1*

(MIM*300104), is related to brain development and its mutation is responsible of an X-linked mental retardation syndrome (#300849). A duplication of *GDI1* was present in a male with a brain malformation similar to our patient 1[15]; however, *GDI1* was not included in the duplication of the other reported female wearing this malformation,[7] so its responsibility remains undemonstrated.

Unlike the other reported cases, a case of a female with *MECP2* duplication due to an unbalanced X-autosome translocation presenting with a milder phenotype has been reported[6]; she presented with moderate developmental/intellectual disability with walking and speech development, without growth failure, microcephaly, or dysmorphic features. The small size (129 Kb) of the duplication and the absence of a second cytogenetic alteration could be related to the mildness in this case.

Contrarily, affected females with intrachromosomal microduplications of Xq28 including *MECP2* present with a broad phenotypic spectrum. The authors assume that our patients 2 and 3 belong to this group because of the absence of the typical severe clinical picture observed in affected females with the duplicated material into an autosome although, due to the small size of the duplication, karyotype and fluorescent in situ hybridization analysis failed to demonstrate this point. Table 1 shows the genetic and clinical data observed in our patients and in those previously reported in the literature. Only 14 affected female patients with intrachromosomal duplications of Xq28 including *MECP2* have been reported previously, even when this kind of duplication is much more likely to occur. At least half of patients show autistic features. Six patients present with a more severe phenotype with moderate-to-severe intellectual disability with poor or absent speech, with or without associated epilepsy; other 6 patients have only mild-to-moderate developmental/intellectual disability with preserved speech; and the other 2 have borderline or normal intellectual performances. In half of patients, the duplication was inherited from an asymptomatic mother. The lack of symptoms in unaffected females is thought to be due to complete or extreme (at least 75:25) skewing of X chromosome inactivation with the abnormal X chromosome preferentially inactivated.[7-9] It has been postulated that mutations in other genes in chromosome X could be responsible for random X chromosome inactivation or unfavorable skewed X chromosome inactivation with the normal X chromosome preferentially inactivated. The coduplication of the neighboring genes *ARD1A* or *HCFC1* has been postulated to be responsible for complete skewing X chromosome inactivation with inactivation of the duplication-bearing X, so smaller deletions not including these genes would result in random inactivation and thus in the appearance of symptoms. This point has not been proved, since affected females carrying the same duplication as their unaffected mother have been further described.[9] Also, mutations in *ATRX* have been associated with extreme skewing in female carriers.[13,16] But in fact, the factors influencing the presence and the severity of clinical features in women are not well understood. On one hand, like in other X-linked recessive disorders, the degree of activation of the duplication-bearing X chromosome has been

Table 1. Genetic and Clinical Data in Reported Symptomatic Females With Intrachromosomal Xq28 Duplication Including *MECP2*.

Patient ID	Reardon et al[8] Patient III-4 in family I	Mayo et al[9] Patient III:7	Grasshoff et al[10] Patient 1	Grasshoff Patient 2	Bijlsma et al[7] Patient 4	Bijlsma Patient 5	Shimada et al[11] Patient 4	Scott Schwoerer et al[12] Proposita	Scott Proposita's twin sister	Fieremans et al[13] Patient 1	Fieremans Patient 2	Novara et al[14] Patient 1	Novara Patient 2	Novara Patient 3	This Study Patient 2	This Study Patient 3
Size of the dupl.	0.7 Mb	300 kb	266 kb	478 kb	700 kb	107.5 Kb	660 kb	290 kb	290 kb	0.44 Mb	1.46 Mb	167 kb	621 kb	390 kb	350 kb	80 kb
Inheritance	Inherited	dn	dn	dn	Inherited	dn	Inherited	Inherited	Inherited	dn	dn	Inherited	Inherited	dn	dn	dn
Parental origin	Maternal	Paternal	Paternal	Paternal	Maternal	–	Maternal	Maternal	Maternal	Paternal	Maternal	Maternal	Maternal	Paternal	–	–
Second cytogenetic alteration (origin)	–	dupl 2q37.3 (dn)	dupl 2q37.3 (dn)	–	–	dupl 2q (paternal)	–	–	–	–	dupl Xq28 (paternal)	–	–	–	–	–
X Chromosome inactivation	Random 70:30	Skewed 75:25	Random 61:39	Random 71:29	Random 63:37	Skewed 84:16	Skewed 12:88	Inconcl	Inconcl	Skewed 100:0	Skewed 100:0	Random in blood 3.1 and in saliva 2.7	Skewed in blood 100:0, random in saliva 0.39	Skewed in blood 14.7 and in saliva 11.7	Random 55:65	Random 55:65
Age at last examination	12 years	7 years	7 years 6 months	20 years	26 years	7 years	6 years	25 years	26 years	13 years	12 years	14 years	21 years	19 years	10 years	3 easy 2 months
Intrauterine growth retardation	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Postnatal growth failure	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Microcephaly	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Dysmorphic feat	+	+	–	–	–	–	+	+	+	+	+	+	+	–	–	–
Brain malform	–	–	–	–	–	–	–	–	–	–	+	–	–	+	–	–
Hypotonia	+	+	–	–	–	+	+	+	+	+	+	+	+	+	+	–
Devlp delay	+	+ (mi-mo)	+ mi	+ (mi-mo)	–	+ (mod)	+ (mo-se)	+ (mo-se)	+ (se)	–	+ (mo-se)	+ (mi-mo)	+ (mi-mo)	+ (mi-mo)	+ (mi)	+ (mo)
Intellectual disability	?	+ (se)	+ (mi)	+ (mi-mo)	– (bl)	+ (mi-mo)	+ (mo-se)	+ (se)	+ (se)	+ (mi)	+ (mo-se)	+ (mo-se)	– (bl)	+ (mi)	+ (mi)	?
Poor/absent speech	–	+	–	–	–	–	+	+	+	–	+	–	–	–	+	–
Lack/loss of ambul	–	–	–	–	–	–	+	+	+	–	+	–	–	–	–	–
Learning diffic	+	–	+	+	+	–	–	–	–	–	+	–	–	–	–	–
Autistic feat	–	+	+	+	–	?	–	?	+	+	+	+	+	+	+	?
Hand stereotypies	–	+	–	–	–	–	+	+	+	+	–	–	–	–	–	–
Breath stereotypies	–	–	–	–	–	–	–	+	+	–	–	–	–	–	–	–
Epilepsy	–	+	–	–	–	–	–	+	+	–	–	–	–	–	–	–
Late-on spasticity	–	+	–	+	–	–	–	+	+	–	–	–	–	–	–	–
Scoliosis	–	–	–	+	–	–	–	+	+	–	–	–	–	–	–	–
Ataxia	–	–	–	–	–	–	–	+ (mild)	+	–	–	–	–	–	–	–
Devlp regression	–	–	–	–	–	–	+	?	?	+	–	–	–	+	–	–
Feeding diffic	–	–	–	–	–	–	+	?	?	+	+	–	–	+	–	–
Recurrent infect	–	–	?	–	–	+	+	–	–	+	–	–	–	–	?	–
Constipation	–	+	+	–	+	+	–	–	–	–	+	–	–	–	–	–
Premature death	–	–	–	–	+	+	–	–	–	–	–	–	–	–	–	–

Abbreviations: Ambul, ambulation; bl, borderline; devlp, developmental; diffic, difficulties; dn, de novo; dupl, duplication; exam, examination; feat, features; inconcl, inconclusive; infect, infections; late-on, late onset; malform, malformation; mi, mild; mo, moderate; se, severe.

Note. ? means doubtful or not reported/not known.

thought to be the most important factor influencing the clinical expression in females with intrachromosomal duplications of Xq28 including *MECP2*. However, in reported cases, similar rates of inactivation have been found in patients with different degrees of severity; even 100% skewing of X chromosome inactivation with the normal X chromosome completely inactivated has been reported in 2 patients both with a less severe clinical picture than those observed in males and with different degree of severity between them: one with moderate-to-severe developmental delay and mental retardation with poor speech and the other one with mild mental retardation with normal speech.[13] Also, similar X chromosome inactivation patterns have been found in affected patients and their respective unaffected mothers,[14] and random X chromosome inactivation has been found in asymptomatic females.[11] Thus, our patients 2 and 3 have random X chromosome inactivation and a very mild clinical presentation. The different rates of X chromosome inactivation observed in different samples within the same patient could explain the lack of correspondence with the clinical severity, as most assessments are made in peripheral blood or in saliva and not in target tissue, in this case brain. Moreover, it has been proposed that de novo occurrence of the duplication might have an effect on the X chromosome inactivation by preventing a protective ''mutation-induced'' skewed X chromosome inactivation by a yet unrecognized mechanism; this would mean that here could be a different trigger for the methylation process from an inherited duplication than from the one that occurred de novo.[10] Most of the de novo Xq28 duplications seem to occur in the X chromosome of paternal origin because of the X chromosome vulnerability at male meiosis.[17] This fact, together with the X chromosome inactivation pattern, could play a role in the phenotypic variability in females with intrachromosomal duplications of Xq28, since the existence of imprinting effects of the X chromosome influencing early brain development has been suggested.[18] However, this point has not been proven in affected females with Xq28 duplication reported so far. Nor the size of the duplication, provided that the critical region containing *MECP2* is included,[7,10] seems to influence the clinical severity in male patients[1,19]; although duplications of *IRAK1* have been hypothesized to be responsible for the occurrence of recurrent respiratory infections,[20] this point has not been proven in females. From our patients, all 3 have *IRAK1* completely or partially included in the duplication; patient 1 presented with respiratory infections only in late years, after the epilepsy onset and the resulting feeding difficulties; patient 2 had only frequent mild upper respiratory tract infections in the first years of life; and patient 3 reported no recurrent infections at all. On the other hand, the copy number does seem to correlate with the severity of clinical features in affected males,[15] and it could also explain the severity of the phenotype in the female patient reported by Mayo et al,[9] with a complex segmental rearrangement with duplication and triplication of Xq28. The disturbance of other genes in the point of insertion of the duplicated material can also play a role in the clinical expression.

During the previous years, large cohorts of patients of both sexes with intellectual disability have been investigated with high-resolution arrays for submicroscopic genomic imbalances through different array technologies, and only a few affected females—2 cases of 1000 unselected patients with intellectual disability[10] and 1 case of 108 fetuses with congenital structural abnormalities[21]—have been reported, thus authors conclude that duplication of *MECP2* is a rare cause of intellectual disability in females. However, the clinical picture in patients with intrachromosomal duplications may be, as in our patient 2, quite mild. These cases are usually not included in these cohorts and no genetic tests are performed. This could make that these cases were underdiagnosed, which could have implications as these patients could have severely affected sons.

Our finding underlines the importance of quantitative analysis of *MECP2* in females with intellectual disability even in the absence of Rett features and raises the question of the indication of genetic testing in females with borderline intellectual performances or learning difficulties. The presence of some autistic features or the predominant involvement of language development may be key signs in these cases.

Authors Contributions

VSA-A contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; and agreed to be accountable for all aspects of work ensuring integrity and accuracy. MF-C contributed to acquisition, analysis, and interpretation; drafted the manuscript; critically revised the manuscript; and gave final approval. ROI contributed to acquisition; drafted the manuscript; critically revised the manuscript; and gave final approval. TDM contributed to acquisition; drafted the manuscript; and gave final approval. JG-M contributed to acquisition. FJIC contributed to acquisition. MCCP contributed to acquisition, analysis, and interpretation; critically revised the manuscript; and gave final approval.

Author's Note

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the editor of this journal.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

Patients' parents or guardians gave written informed consent for publication.

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