CLINICAL REPORT

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A Maternally Inherited 16p13.11-p12.3 Duplication Concomitant with a De Novo *SOX5* Deletion in a Male Patient with Global Developmental Delay, Disruptive and Obsessive Behaviors and Minor Dysmorphic Features

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We detail here the clinical description and the family genetic study of a male patient with global developmental delay, disruptive and obsessive behaviors and minor dysmorphic features and a combination of two rare genetic variants: a maternally inherited 16p13.11-p12.3 duplication and a de novo 12p12.1 deletion affecting *SOX5*. The 16p13.11 microduplication has been implicated in several neurodevelopmental and behavioral disorders and is characterized by variable expressivity and incomplete penetrance. The causes of this variation in phenotypic expression are not fully clear, representing a challenge in genetic diagnosis and counseling. However, several authors have proposed the two-hit model as one of the underlying mechanisms for this phenotypic heterogeneity. Our data could also support this two-hit model in which the 16p13.11-p12.3 duplication might contribute to the phenotype, not only as a single event but also in association with the *SOX5* deletion. The *SOX5* gene plays important roles in various developmental processes and has been associated with several neurodevelopmental disorders, mainly intellectual disability, developmental delay and language and/or speech delay as well as with behavior problems and dysmorphic features. However, many of the physical features and behavioral manifestations as well as language deficiencies present in our patient are consistent with those previously reported for *SOX5* deletions. Patients carrying multiple genomic variants, as the one presented here, illustrate the difficulty in analyzing genotypes when the contribution of each variant results in overlapping phenotypes and/or, alternatively, in the modification of the clinical manifestations defined by the coexisting variant.

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Conflict of interest: none.

Abbreviations: CNV, Copy Number Variant; SNP, Single Nucleotide Polymorphism; IQ, Intelligence Quotient; MRI, Magnetic Resonance Imaging; EEG, Electroencephalogram; ADHD, Attention Deficit Hyperactivity Disorder; CI, Confidence Interval.

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INTRODUCTION

Patients carrying multiple genetic variants are difficult to analyze, but provide interesting information about the relationship between these alterations in the genome. One approach that is resulting particularly useful in the discovery of candidate loci and genes contributing to neurodevelopmental and behavioral disorders consists in genotyping copy number variants (CNVs). Many of the CNVs and genes involved in these phenotypes are characterized by variable expressivity and incomplete penetrance [Malhotra and Sebat, 2012; Rosenfeld et al., 2012; Kirov et al., 2013], making genetic diagnosis and counseling difficult. The underlying causes of this heterogeneity are not clear, but one of the most plausible explanations includes additional genetic factors as potential modifiers of the phenotype [Girirajan et al., 2010].

Here, we present the clinical description of a male patient with two rare genetic variants, a maternally inherited 16p13.11-p12.3 copy number gain and a de novo *SOX5* deletion at 12p12.1, that may act together to define his phenotype, characterized by global developmental delay, disruptive and obsessive behavior and minor dysmorphic features.

MATERIALS AND METHODS

DNA samples from both the patient and his parents were obtained from peripheral blood and genotyped using the Cytogenetics Whole-Genome 2.7 M SNP array and the CytoScan High-Density SNP array (Affymetrix, Santa Clara, CA), respectively. In this family, microarray-based copy number analysis was performed using the Chromosome Analysis Suite software version 1.2.2 (Affymetrix, Santa Clara, CA) and the results were presented on the human genome assembly hg19.

RESULTS

Clinical Report

The patient was evaluated at 7 years of age, referred from his hospital for etiologic study due to his psychomotor developmental delay. He was the first child of healthy and nonconsanguineous parents, and no history of intellectual disability was present in his family. His 12-year-old brother was healthy. During pregnancy oligohydramnios was detected in week 37 and the patient was born after 38 weeks of gestation by vaginal delivery instrumented by forceps. He weighed 2,970 g at birth, his neonatal period was uneventful and metabolic screening was normal. Although he started crawling before the age of one, he failed to walk autonomously before the age of 2 and his movements, both fine and coarse, were very clumsy. However, his family became increasingly alarmed by the slow progress in his language development, so that by the age of 4 only 3–4 disyllabic words were emitted with no functional purpose. The nonverbal compensatory communication resources were inadequate, and only a few months earlier, he had begun to point with his finger with the intention of making a request for something within his immediate vicinity. The parents reported that his comprehensive ability was quite preserved, although they were aware that he did not understand completely what they told him. He had always been a very nervous and restless child; he changed activities very frequently and did not conform to rules within his group of peers. Interactions with his peers often culminated in disruptive behaviors. Although he approached them, he seemed nervous in their company and frequently assaulted them or himself unexpectedly or in response to a setback or frustration. At school, he could not focus on activities and his teacher noted that his pace of learning was slower than that of his schoolmates. The Batelle Developmental Test, performed at the age of 3 years, showed very deficient results, around the 1st centile in all domains explored by the test. In the following years, his learning capacity was improved with speech therapy and specific school support, but he now achieves academic goals with difficulty. However, his behavior is described as inattentive, restless, with aggressive and oppositional reactions. He has very low flexibility and tends to an obsessive behavior. In regards to this, an adherence to a scrupulous order in placing of objects, in keeping doors and drawers always closed and very little variability in his game, which is very repetitive, was identified. This behavioral and cognitive profile prompted the suspicion of an autistic spectrum disorder but final conclusive diagnosis was not established. His language advanced progressively; at the age of 5 years and 10 months, an evaluation of his vocabulary with the Peabody Picture Vocabulary Test showed a standard score of 89 (p22), which corresponded to a chronological age of 5 years and in the assessment of his IQ (Intelligence Quotient) by the Kaufman Brief Intelligence Test, he obtained a score of 96 in his composite IQ (81 in Vocabulary and 116 in Matrices). Instead of intellectual disability, a diagnosis of global developmental delay with moderate language delay—predominantly in expressive language—was established at this point. Moreover, the patient showed strabismus and hypermetropia.

Physical examination at the age of 7 years showed good general appearance and some abnormal phenotypic features, especially a triangular craniofacial configuration, a short and narrow forehead, a low-set anterior hairline, bilateral telecanthus, deep orbits, strabismus, narrow and slightly downslanting palpebral fissures, mild synophrys, a thin upper lip vermilion, prominent philtral ridges, mild upturned and bulbous nasal tip, an open mouth appearance, gingival hypertrophy and high palate (Fig. 1). He was friendly, emphatic and collaborative. His speech was poor and badly structured, generally following a "question-answer" pattern. Moreover, he was repetitive and with some tangential emissions. His motor coordination was poor, with an ungainly running (torso and arms forward) and a certain general rigidity. The additional neurological and general examinations showed no abnormalities and his somatometric parameters were normal.

Normal results were obtained in the following additional tests: Haemogram test and conventional biochemical profile, thyroid function test, metabolic screening (which included determination of ammonia, organic acids in urine and amino acids in blood and urine), brain MRI, EEG and cardiac examination.

Molecular Analysis

Microarray-based copy number analysis of the patient and his parents allowed to detect a maternally inherited 3.48 Mb copy number gain at 16p13.11-p12.3 (16: 15,286,149–18,771,863; hg19) (Fig. 2) and a de novo heterozygous deletion of 493.94 kb at 12p12.1 (12: 23,769,086–24,262,524; hg19) (Fig. 3). The number of markers

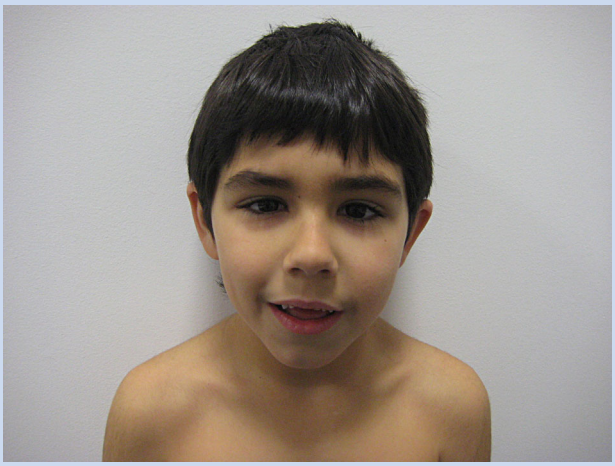

FIG. 1. Craniofacial appearance of the patient. Note a triangular craniofacial configuration, a short and narrow forehead, a low-set anterior hairline, bilateral telecanthus, deep orbits, strabismus, narrow and slightly downslanting palpebral fissures, mild synophrys, a thin upper lip vermilion, prominent philtral ridges, a mild upturned and bulbous nasal tip, an open mouth appearance, gingival hypertrophy and a high palate.

with three copies was 2041 and the median distance between them was 1.71 kb, while the 12p12.1 deletion was covered by 503 markers spaced at 0.98 kb on average. The interval amplified in the 16p13.11-p12.3 chromosomal region affects 20 genes (*MPV17L, C16orf45, KIAA0430, NDE1, MIR484, MYH11, C16orf63, ABCC1, ABCC6, NOMO3, MIR3179-3, MIR3179-2, MIR3179-1, MIR3180-3, MIR3180-1, MIR3180-2, PKD1P1, XYLT1, NOMO2* and *ABCC6P1*), including three OMIM-morbidity genes (*MYH11, ABCC6* and *XYLT1*). The presence of segmental duplications at both sides of the amplification (Fig. 2) suggests that this CNV is caused by non-allelic homologous recombination. On the other hand, the 12p12.1 deletion affects only the gene *SOX5*, specifically nine of its 22 exons (Fig. 3).

DISCUSSION

The range of clinical manifestations reported in patients with 16p13.11 microduplications is broad, including intellectual disability, developmental delay, multiple congenital anomalies and autism [Ullmann et al., 2007; Hannes et al., 2009; Mefford et al., 2009; Nagamani et al., 2010; Girirajan et al., 2011; Ramalingam et al., 2011; Sanders et al., 2011; Girirajan et al., 2012; Tropeano et al., 2013]. Several studies have also examined the role of 16p13.11 duplications in other behavioral and psychiatric disorders, such as attention deficit hyperactivity disorder (ADHD) (with an excess of

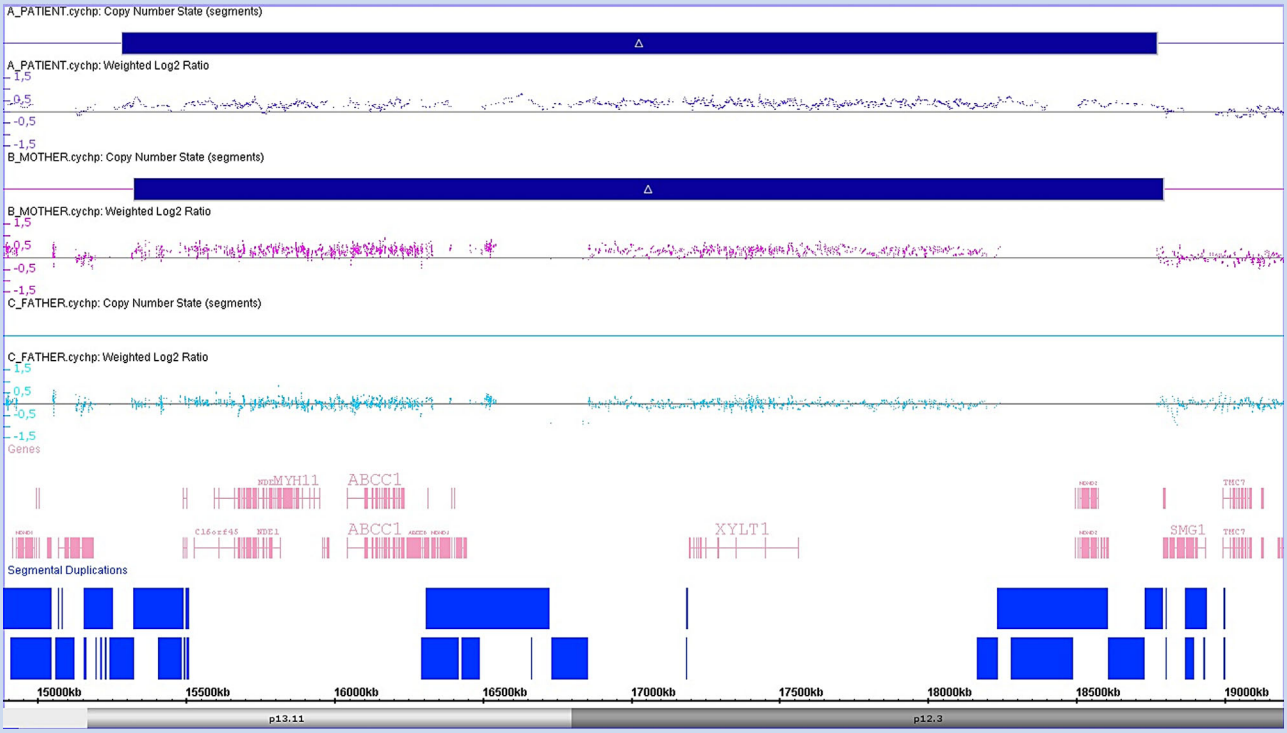

FIG. 2. Family genetic test for the 16p13.11-p12.3 amplification (16:15,286,149–18,771,863; hg19) visualized with the Affymetrix Chromosome Analysis Suite version 1.2.2. A,B: Images of the 16p13.11-p12.3 amplification detected in both the patient (panel A) and his mother (panel B). C: The 16p13.11-p12.3 region presents a normal copy number in the father.

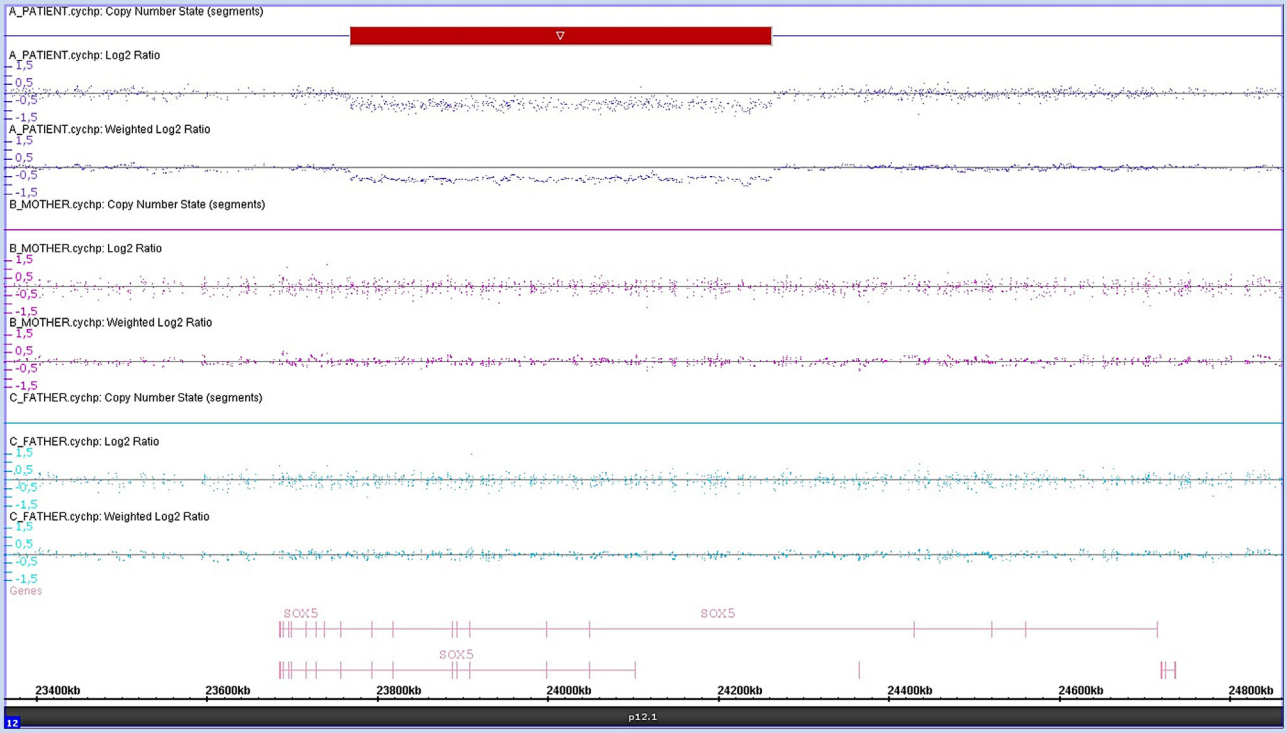

FIG. 3. Family genetic test for the 12p12.1 deletion (12: 23,769,086–24,262,524; hg19) visualized with the Affymetrix Chromosome Analysis Suite version 1.2.2. A–C: Image of the *SOX5* deletion detected in the patient (panel A) but absent in both his mother (panel B) and his father (panel C).

16p13.11 duplications noted in the patient group versus controls) [Williams et al., 2010] and schizophrenia (also with an excess in patients versus controls [Ingason et al., 2011], although with very low penetrance values [Kirov et al., 2013]). The detailed evaluation of the clinical manifestations of patients with 16p13.11 duplications shows that the most predominant phenotypes, apart from cognitive defects, are skeletal anomalies, heart and aortic defects and behavior problems [Nagamani et al., 2010; Tropeano et al., 2013]. Our patient presents neither skeletal nor cardiac abnormalities, although he does manifest global developmental delay and behavioral problems (inattentive, restless, aggressive and oppositional reactions, very low flexibility and tendency to obsessive behaviors). Some of these behavioral features (inattentiveness, restlessness, aggressiveness and disruptive temperament) are consistent with previous descriptions [Nagamani et al., 2010; Williams et al., 2010; Ingason et al., 2011; Ramalingam et al., 2011 ; Tropeano et al., 2013], while others (i.e., obsessive behavior) have not been specifically reported in patients carrying 16p13.11 duplications, unless one considers it as a manifestation of an autism spectrum disorder.

Nevertheless, the 16p13.11 chromosomal alterations have also been described in apparently healthy or mildly affected parents [Ullmann et al., 2007; Hannes et al., 2009; Nagamani et al., 2010; Williams et al., 2010; Girirajan et al., 2011; Ramalingam et al., 2011; Girirajan et al., 2012; Tropeano et al., 2013] and in controls [Hannes et al., 2009; Itsara et al., 2009; Williams et al., 2010; Girirajan et al., 2011; Ingason et al., 2011; Girirajan et al., 2012; Kirov et al., 2013 ; Tropeano et al., 2013], so that the clinical interpretation of these genetic variants is a challenge that remains to be addressed. Indeed, the total penetrance of the 16p13.11 microduplication is reduced, estimated in only 10.6% (95% confidence interval [CI] of 7–17), coming from the 8.4% (95% CI of 5.7–13) for intellectual disability/developmental delay, autism spectrum disorders and multiple congenital anomalies and in 2.2% (95% CI of 1.3–3.7) for schizophrenia [Kirov et al., 2013]. Consistent with these data, our patient has inherited the 16p13.11 duplication from his healthy mother. It seems, therefore, that the 16p13.11 microduplications predispose but are not sufficient to cause these phenotypes and their clinical manifestations must be due to additional factors. Possible explanations for this variable expressivity and/or incomplete and reduced penetrance of the 16p13.11 microduplications might include: first, the phenotype could be imperceptible in controls if it is presented clinically attenuated; second, existence of a sex-biased effect of 16p13.11 duplications in these phenotypes. In this sense, our patient is a male who has inherited the duplication from his healthy mother and, even though a single case is not sufficient to establish conclusions, Tropeano et al. [2013] have recently provided evidence for a sex-biased effect, finding a significant enrichment of 16p13.11 CNVs only in male patients, but not in female patients, compared with controls [Tropeano et al., 2013]. Third, phenotypic manifestations may vary depending on the size and location of the 16p13.11 duplication. In relation to this point, it is important to note that, although the size of the most frequent 16p13.11 CNVs is

approximately 1.3–1.6 Mb [Ullmann et al., 2007; Hannes et al., 2009; Nagamani et al., 2010; Ramalingam et al., 2011], there are also atypical larger and shorter rearrangements in this region [Hannes et al., 2009; Nagamani et al., 2010; Ramalingam et al., 2011]. Among these atypical alterations, we might include the 3.48 Mb 16p13.11-p12.3 duplication identified in our patient (Fig 2A). Finally, environmental factors and/or additional genetic alterations (point mutations, indels and/or additional CNVs) could be modulating and/or participating in the phenotype. Several authors have found that the "two-hit" hypothesis, first proposed by Girirajan et al. [2010] for the 16p12.1 microdeletions [Girirajan et al., 2010], could also explain the extreme phenotypic variability associated with the 16p13.11 microduplications [Fullston et al., 2011; Kirov et al., 2013; Tropeano et al., 2013]. The presence of a second-hit CNV in patients with 16p13.11 duplications and developmental delay, autism spectrum disorders and/or congenital malformations has been recently estimated at 8.2% [Kirov et al., 2013]. The possibility of a second-site CNV exists in our patient who, in addition to the maternally inherited 16p13.11-p12.3 duplication, has a heterozygous de novo deletion at 12p12.1 encompassing 9 of the 22 exons of *SOX5*.

The gene *SOX5*, located at the chromosomal region 12p12.1 (12:23,685,230–24,715,382 GRCh37/hg19), consists of 22 exons and belongs, along with *SOX6* and *SOX13*, to the *SOXD* (sex-determining region (SRY)-related HMG-box) family of transcription factors. These genes are involved in diverse developmental functions, including cartilage formation [Lefebvre et al., 1998; Smits et al., 2001; Ikeda et al., 2002; Lefebvre, 2010; Aza-Carmona et al., 2011], neurogenesis [Lefebvre, 2010] and nervous system development [Kwan et al., 2008; Lai et al., 2008; Lefebvre, 2010].

The clinical features of our patient are listed in Table IA, which also reviews the literature of *SOX5* alterations, both *SOX5*-only deletions and larger deletions including additional genes, that have been implicated in neurodevelopmental disorders [Rosenfeld et al., 2010; Lamb et al., 2012; Lee et al., 2013; Schanze et al., 2013]. This review reveals that *SOX5* alterations are mainly expressed with intellectual disability/developmental delay (100% of the reported patients), language and/or speech delay (90.91% of patients with *SOX5*-limited deletions and 100% of patients with longer deletions affecting *SOX5* and additional genes) and dysmorphic features (in 72.73% or 80% of patients with *SOX5*-only deletions or with multigenic deletions, respectively). Consistent with these descriptions, our patient has a diagnosis of global developmental delay, with moderate language delay, predominantly in expressive skills. Severe dysmorphic facial features are not part of the presentation of *SOX5* deletions and facial anomalies described so far may be considered minor and probably not distinctive. However, certain features such as strabismus, frontal bossing, upturned bulbous nasal tip, low or depressed nasal bridge, epicanthal folds, prominent philtral ridges, and auricular folding anomalies have proved to be shared in patients described by Lamb et al. [2012] and by Lee et al. [2013]. Patients from Lee et al. [2013] also shared down-slanting palpebral fissures and an open mouth appearance [Lee et al., 2013]. The patient described here shares some of the features noted in early reports, i.e., downslanting palpebral fissures, strabismus, prominent philtral ridges, mild upturned and bulbous nasal tip and an open mouth appearance. However, frontal bossing, depressed or low nasal bridge were not present in our patient who did remarkably present a short and narrow forehead.

Moreover, 54.55% of patients with *SOX5*-limited deletions present behavioral problems (aggressiveness, self-injurious behavior, anxiety, stereotypies, hyperactivity and/or ADHD), while 18.18% have a diagnosis of autism or exhibited autistic features. The behavior of our patient is described as inattentive, restless, with aggressive and oppositional reactions and he has very low flexibility and tendency to obsessive behaviors. This behavior and his cognitive profile pointed to autism spectrum disorder, but no definitive diagnosis was established.

Ophthalmologic abnormalities, found in 63.64% of patients with *SOX5*-only deletions, are among the most frequently reported congenital anomalies associated to *SOX5* alterations. Also consistent with these findings, our patient has hypermetropia and strabismus. Although less frequently reported, brain (42.86%), genital (30%) and skeletal (27.27%) abnormalities have also been found in patients with *SOX5*-restricted deletions. It is noteworthy that the percentages of patients with brain and skeletal abnormalities increased significantly (up to 71.43% and 60%, respectively) in the larger deletions, suggesting that, at least potentially, additional genes within the deletions would be contributing to these manifestations. Our patient, with an intragenic deletion, did not present any of these congenital malformations (Table IA).

The rate of de novo *SOX5*-limited deletions, resulting from the review of previous reports [Lamb et al., 2012; Lee et al., 2013; Schanze et al., 2013] and reflected in Table IB, is estimated to be 80%, while the remaining 20% (2 patients) would have inherited the deletion. However, it is important to note that one of the two reported progenitors carrying *SOX5* deletions was found to be a severely affected mother who also transmitted the deletion to her daughter, also affected [Lamb et al., 2012]. In line with these values and considerations on the de novo rates, the family genetic test of our patient, born to healthy parents, was negative for the *SOX5* deletion (Fig. 3).

Based on the above discussion, we might conclude that many of the physical and behavioral features, including aggressive, oppositional and obsessive behaviors, as well as the deficits in language manifested by our patient are compatible with those found in patients with *SOX5* deletions. However, we cannot exclude that the central phenotype of our patient (global developmental delay, language and speech difficulties and behavioral problems) would result from the concomitant presence of the 16p13.11-p12.3 duplication inherited from his mother and the de novo 12p12.1 deletion affecting *SOX5*. In fact, we cannot ignore the reported sex-bias effect or the influence of the atypical longer 16p13.11-p12.3 rearrangement in this patient. The dissection of the phenotype hardly allows assigning a responsible genomic region for each overlapping feature but could indicate an additive contribution for the 16p duplication to the clinical manifestations of the *SOX5* deletion. The present report illustrates the need for detailed analysis of the phenotype of patients harboring complex genotypes and reflects the difficulty in managing genomic data in the clinical setting, needed and increasingly demanded for genetic counseling.

TABLE I. (A) Summary of the Most Relevant Clinical Features Present in Our Patient and in Previous Reports With *SOX5* Microdeletions. F, Female; M, Male; *n*, Number of Subjects; NA, Not Available; (B) Summary of the Inheritance Pattern in Previously Reported Patients With *SOX5* Microdeletions and Complete Family Genetic Study, Including Our Patient. *n*, Number of Subjects With Complete Family Genetic Study

(A) Clinical features[a]	Lamb et al. [2012] SOX5-limited deletions (9 bp to 466 Kb) *n* = 9 (5 F and 4 M)	Schanze et al. [2013] SOX5-limited deletion (120 Kb) n=1 (1 M)	Lee et al. [2013] SOX5-limited deletion (53 Kb) *n* = 1 (1 M)	Total SOX5-limited deletions % [b]	Lamb et al. [2012] larger deletions (1.41–12.09 Mb; 8-63 genes) *n* = 7 (5 F and 2 M)	Schanze et al. [2013] larger deletions (2.26 and 4.93 Mb; 4 and 23 genes) *n* = 2 (1 F and 1 M)	Lee et al. [2013] larger deletion (3.2 Mb; 4 genes) *n* = 1 (1 F)	Total larger deletions %	Total[b]	Total %[b]	Present patient (493.94 kb; SOX5) *n* = 1 (1 M)
Intellectual disability/ developmental delay	9/9	1/1	1/1	100.00%	7/7	2/2	1/1	100.00%	21/21	100.00%	Yes
Language/speech delay	8/9	1/1	1/1	90.91%	5/5	2/2	1/1	100.00%	18/19	94.74%	Yes
Behavior problems[c]	5/9	1/1	0/1	54.55%	5/5	0/2	0/1	62.50%	11/19	57.89%	Yes
Autism/autistic features/PDD	2/9	0/1	0/1	18.18%	1/5	0/2	0/1	12.50%	3/19	15.79%	No
Hypotonia	4/8	0/1	1/1	50.00%	4/7	1/2	1/1	60.00%	11/20	55.00%	No
Seizures	2/9	0/1	NA	20.00%	1/7	0/2	NA	11.11%	3/19	15.79%	No
Brain abnormalities	2/5	0/1	1/1	42.86%	4/5	1/1	0/1	71.43%	8/14	57.14%	No
Strabismus	6/9	1/1	1/1	72.73%	2/7	1/2	1/1	40.00%	12/21	57.14%	Yes
Ophthalmologic abnormalities	5/9	1/1	1/1	63.64%	3/7	0/2	0/1	30.00%	10/21	47.62%	Yes (hypermetropia)
Dysmorphic features	6/9	1/1	1/1	72.73%	6/7	1/2	1/1	80.00%	16/21	76.19%	Yes
Clinodactyly	1/9	1/1	1/1	27.27%	4/7	0/2	1/1	50.00%	8/21	38.10%	No
Scoliosis	2/9	0/1	NA	20.00%	1/7	0/2	NA	11.11%	3/19	15.79%	No
Other skeletal anomalies	2/9	1/1	0/1	27.27%	4/7	2/2	0/1	60.00%	9/21	42.86%	No
Congenital cardiac defects	1/9	0/1	0/1	9.09%	1/7	0/2	0/1	10.00%	2/21	9.52%	No
Genital abnormalities	2/9	NA	1/1	30.00%	0/7	NA	1/1	12.50%	4/18	22.22%	No
Renal abnormalities	0/9	NA	1/1	10.00%	0/7	NA	1/1	12.50%	2/18	11.11%	No

(B) Inheritance pattern	Present patient (*n* = 1)	Lamb et al. [2012] SOX5-limited deletions (*n* = 7)	Schanze et al. [2012] SOX5-limited deletion (*n* = 1)	Lee et al. [2013] SOX5-limited deletion (*n* = 1)	Total SOX5-limited deletions (%)[d]	Lamb et al. [2012] larger deletions (*n* = 2)	Schanze et al. [2012] larger deletions (*n* = 1)	Lee et al. [2013] larger deletion (*n* = 1)	Total larger deletions (%)[e]
De novo	Yes	5	1	1	80.00%	1	1	1	75.00%
Inherited	No	2[d]	0	0	20.00%	1[e]	0	0	25.00%

Modified from [Lamb et al., 2012; Lee et al., 2013; Schanze et al., 2013].

[a]Not all clinical features could be evaluated in all patients [*n* = 21; Lamb et al. [2012] (*n* = 16) + Schanze et al. [2013] (*n* = 3) + Lee et al. [2013] (*n* = 2)].

[b]Our patient is not included since the 16p13.11-p12.3 microduplication may contribute to his clinical phenotype.

[c]Behavior problems (aggressiveness, self-injurious behavior, anxiety, stereotypies, hyperactivity, ADHD).

[d]One parent is an affected carrier mother, while the other carrier is an apparently normal father.

[e]The carrier parent is an affected father.

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REFERENCES

Aza-Carmona M, Shears DJ, Yuste-Checa P, Barca-Tierno V, Hisado-Oliva A, Belinchon A, Benito-Sanz S, Rodriguez JI, Argente J, Campos-Barros A, Scambler PJ, Heath KE. 2011. *SHOX* interacts with the chondrogenic transcription factors *SOX5* and *SOX6* to activate the aggrecan enhancer. Hum Mol Genet 20:1547–1559.

Fullston T, Gabb B, Callen D, Ullmann R, Woollatt E, Bain S, Ropers HH, Cooper M, Chandler D, Carter K, Jablensky A, Kalaydjieva L, Gecz J. 2011. Inherited balanced translocation t(9;17)(q33.2;q25.3) concomitant with a 16p13.1 duplication in a patient with schizophrenia. Am J Med Genet Part B 156B:204–214.

Girirajan S, Brkanac Z, Coe BP, Baker C, Vives L, Vu TH, Shafer N, Bernier R, Ferrero GB, Silengo M, Warren ST, Moreno CS, Fichera M, Romano C, Raskind WH, Eichler EE. 2011. Relative burden of large CNVs on a range of neurodevelopmental phenotypes. PLoS Genet 7:e1002334.

Girirajan S, Rosenfeld JA, Coe BP, Parikh S, Friedman N, Goldstein A, Filipink RA, McConnell JS, Angle B, Meschino WS, Nezarati MM, Asamoah A, Jackson KE, Gowans GC, Martin JA, Carmany EP, Stockton DW, Schnur RE, Penney LS, Martin DM, Raskin S, Leppig K, Thiese H, Smith R, Aberg E, Niyazov DM, Escobar LF, El-Khechen D, Johnson KD, Lebel RR, Siefkas K, Ball S, Shur N, McGuire M, Brasington CK, Spence JE, Martin LS, Clericuzio C, Ballif BC, Shaffer LG, Eichler EE. 2012. Phenotypic heterogeneity of genomic disorders and rare copy-number variants. N Engl J Med 367:1321–1331.

Girirajan S, Rosenfeld JA, Cooper GM, Antonacci F, Siswara P, Itsara A, Vives L, Walsh T, McCarthy SE, Baker C, Mefford HC, Kidd JM, Browning SR, Browning BL, Dickel DE, Levy DL, Ballif BC, Platky K, Farber DM, Gowans GC, Wetherbee JJ, Asamoah A, Weaver DD, Mark PR, Dickerson J, Garg BP, Ellingwood SA, Smith R, Banks VC, Smith W, McDonald MT, Hoo JJ, French BN, Hudson C, Johnson JP, Ozmore JR, Moeschler JB, Surti U, Escobar LF, El-Khechen D, Gorski JL, Kussmann J, Salbert B, Lacassie Y, Biser A, McDonald-McGinn DM, Zackai EH, Deardorff MA, Shaikh TH, Haan E, Friend KL, Fichera M, Romano C, Gecz J, DeLisi LE, Sebat J, King MC, Shaffer LG, Eichler EE. 2010. A recurrent 16p12.1 microdeletion supports a two-hit model for severe developmental delay. Nat Genet 42:203–209.

Hannes FD, Sharp AJ, Mefford HC, de Ravel T, Ruivenkamp CA, Breuning MH, Fryns JP, Devriendt K, Van Buggenhout G, Vogels A, Stewart H, Hennekam RC, Cooper GM, Regan R, Knight SJ, Eichler EE, Vermeesch JR. 2009. Recurrent reciprocal deletions and duplications of 16p13.11: The deletion is a risk factor for MR/MCA while the duplication may be a rare benign variant. J Med Genet 46:223–232.

Ikeda T, Zhang J, Chano T, Mabuchi A, Fukuda A, Kawaguchi H, Nakamura K, Ikegawa S. 2002. Identification and characterization of the human long form of Sox5 (L-SOX5) gene. Gene 298:59–68.

Ingason A, Rujescu D, Cichon S, Sigurdsson E, Sigmundsson T, Pietilainen OP, Buizer-Voskamp JE, Strengman E, Francks C, Muglia P, Gylfason A, Gustafsson O, Olason PI, Steinberg S, Hansen T, Jakobsen KD, Rasmussen HB, Giegling I, Moller HJ, Hartmann A, Crombie C, Fraser G, Walker N, Lonnqvist J, Suvisaari J, Tuulio-Henriksson A, Bramon E, Kiemeney LA, Franke B, Murray R, Vassos E, Toulopoulou T, Muhleisen TW, Tosato S, Ruggeri M, Djurovic S, Andreassen OA, Zhang Z, Werge T, Ophoff RA, Group Investigators, Rietschel M, Nothen MM, Petursson H, Stefansson H, Peltonen L, Collier D, Stefansson K, St Clair DM. 2011. Copy number variations of chromosome 16p13.1 region associated with schizophrenia. Mol Psychiatry 16:17–25.

Itsara A, Cooper GM, Baker C, Girirajan S, Li J, Absher D, Krauss RM, Myers RM, Ridker PM, Chasman DI, Mefford H, Ying P, Nickerson DA, Eichler EE. 2009. Population analysis of large copy number variants and hotspots of human genetic disease. Am J Hum Genet 84:148–161.

Kirov G, Rees E, Walters JT, Escott-Price V, Georgieva L, Richards AL, Chambert KD, Davies G, Legge SE, Moran JL, McCarroll SA, O'Donovan MC, Owen MJ. 2013. The penetrance of copy number variations for schizophrenia and developmental. Delay Biol Psychiatry 75:378–385.

Kwan KY, Lam MM, Krsnik Z, Kawasawa YI, Lefebvre V, Sestan N. 2008. SOX5 postmitotically regulates migration Proc Natl Acad Sci U S A 105:16021–16026.

Lai T, Jabaudon D, Molyneaux BJ, Azim E, Arlotta P, Menezes JR, Macklis JD. 2008. *SOX5* controls the sequential generation of distinct corticofugal neuron subtypes. Neuron 57:232–247.

Lamb AN, Rosenfeld JA, Neill NJ, Talkowski ME, Blumenthal I, Girirajan S, Keelean-Fuller D, Fan Z, Pouncey J, Stevens C, Mackay-Loder L, Terespolsky D, Bader PI, Rosenbaum K, Vallee SE, Moeschler JB, Ladda R, Sell S, Martin J, Ryan S, Jones MC, Moran R, Shealy A, Madan-Khetarpal S, McConnell J, Surti U, Delahaye A, Heron-Longe B, Pipiras E, Benzacken B, Passemard S, Verloes A, Isidor B, Le Caignec C, Glew GM, Opheim KE, Descartes M, Eichler EE, Morton CC, Gusella JF, Schultz RA, Ballif BC, Shaffer LG. 2012. Haploinsufficiency of *SOX5* at 12p12.1 is associated with developmental delays with prominent language delay, behavior problems, and mild dysmorphic features. Hum Mutat 33:728–740.

Lee RW, Bodurtha J, Cohen J, Fatemi A, Batista D. 2013. Deletion 12p12 involving *SOX5* in two children with developmental delay and dysmorphic features. Pediatr Neurol 48:317–320.

Lefebvre V. 2010. The SoxD transcription factors–Sox5, Sox6, and Sox13–are key cell fate modulators. Int J Biochem Cell Biol 42:429–432.

Lefebvre V, Li P, de Crombrugghe B. 1998. A new long form of Sox5 (L-Sox5), Sox6 and Sox9 are coexpressed in chondrogenesis and cooperatively activate the type II collagen gene. EMBO J 17:5718–5733.

Malhotra D, Sebat J. 2012. CNVs: Harbingers of a rare variant revolution in psychiatric genetics. Cell 148:1223–1241.

Mefford HC, Cooper GM, Zerr T, Smith JD, Baker C, Shafer N, Thorland EC, Skinner C, Schwartz CE, Nickerson DA, Eichler EE. 2009. A method for rapid, targeted CNV genotyping identifies rare variants associated with neurocognitive disease. Genome Res 19:1579–1585.

Nagamani SC, Erez A, Bader P, Lalani SR, Scott DA, Scaglia F, Plon SE, Tsai CH, Reimschisel T, Roeder E, Malphrus AD, Eng PA, Hixson PM, Kang SH, Stankiewicz P, Patel A, Cheung SW. 2010. Phenotypic manifestations of copy number variation in chromosome 16p13.11. Eur J Hum Genet 19:280–286.

Ramalingam A, Zhou XG, Fiedler SD, Brawner SJ, Joyce JM, Liu HY, Yu S. 2011. 16p13.11 duplication is a risk factor for a wide spectrum of neuropsychiatric disorders. J Hum Genet 56:541–544.

Rosenfeld JA, Ballif BC, Torchia BS, Sahoo T, Ravnan JB, Schultz R, Lamb A, Bejjani BA, Shaffer LG. 2010. Copy number variations associated with autism spectrum disorders contribute to a spectrum of neurodevelopmental disorders. Genet Med 12:694–702.

Rosenfeld JA, Coe BP, Eichler EE, Cuckle H, Shaffer LG. 2012. Estimates of penetrance for recurrent pathogenic copy-number variations. Genet Med 15:478–481.

Sanders SJ, Ercan-Sencicek AG, Hus V, Luo R, Murtha MT, Moreno-De-Luca D, Chu SH, Moreau MP, Gupta AR, Thomson SA, Mason CE, Bilguvar K, Celestino-Soper PB, Choi M, Crawford EL, Davis L, Wright NR, Dhodapkar RM, DiCola M, DiLullo NM, Fernandez TV, Fielding-Singh V, Fishman DO, Frahm S, Garagaloyan R, Goh GS, Kammela S, Klei L, Lowe JK, Lund SC, McGrew AD, Meyer KA, Moffat WJ, Murdoch JD, O'Roak BJ, Ober GT, Pottenger RS, Raubeson MJ, Song Y, Wang Q, Yaspan BL, Yu TW, Yurkiewicz IR, Beaudet AL, Cantor RM, Curland M,

Grice DE, Gunel M, Lifton RP, Mane SM, Martin DM, Shaw CA, Sheldon M, Tischfield JA, Walsh CA, Morrow EM, Ledbetter DH, Fombonne E, Lord C, Martin CL, Brooks AI, Sutcliffe JS, Cook EH, Jr, Geschwind D, Roeder K, Devlin B, State MW. 2011. Multiple recurrent *de novo* CNVs, including duplications of the 7q11.23 Williams syndrome region, are strongly associated with autism. Neuron 70:863–885.

Schanze I, Schanze D, Bacino CA, Douzgou S, Kerr B, Zenker M. 2013. Haploinsufficiency of SOX5, a member of the SOX (SRY-related HMG-box) family of transcription factors is a cause of intellectual disability. Eur J Med Genet 56:108–113.

Smits P, Li P, Mandel J, Zhang Z, Deng JM, Behringer RR, de Crombrugghe B, Lefebvre V. 2001. The transcription factors L-Sox5 and Sox6 are essential for cartilage formation. Dev Cell 1:277–290.

Tropeano M, Ahn JW, Dobson RJ, Breen G, Rucker J, Dixit A, Pal DK, McGuffin P, Farmer A, White PS, Andrieux J, Vassos E, Ogilvie CM, Curran S, Collier DA. 2013. Male-biased autosomal effect of 16p13.11 copy number variation in neurodevelopmental disorders. PLoS One 8: e61365.

Ullmann R, Turner G, Kirchhoff M, Chen W, Tonge B, Rosenberg C, Field M, Vianna-Morgante AM, Christie L, Krepischi-Santos AC, Banna L, Brereton AV, Hill A, Bisgaard AM, Muller I, Hultschig C, Erdogan F, Wieczorek G, Ropers HH. 2007. Array CGH identifies reciprocal 16p13.1 duplications and deletions that predispose to autism and/or mental retardation. Hum Mutat 28:674–682.

Williams NM, Zaharieva I, Martin A, Langley K, Mantripragada K, Fossdal R, Stefansson H, Stefansson K, Magnusson P, Gudmundsson OO, Gustafsson O, Holmans P, Owen MJ, O'Donovan M, Thapar A. 2010. Rare chromosomal deletions and duplications in attention-deficit hyperactivity disorder: A genome-wide analysis. Lancet 376:1401–1408.