ARTICLE

Dysmorphic features, simplified gyral pattern and 7q11.23 duplication reciprocal to the Williams-Beuren deletion

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We report a patient with mild pachygyria, ascertained during a screening of subjects with abnormal neuronal migration and/or epilepsy, having a 7q11.23 duplication reciprocal to the Williams-Beuren critical region (WBCR) deletion. He exhibited speech delay and mental retardation together to type II trigonocephaly and other abnormalities. The proband's mother carried the same imbalance, though her phenotype was milder and no abnormal conformation of the cranium was reported. She had suffered a few seizures in infancy, as already described in other duplicated subjects. This genomic imbalance, now described in 17 subjects, including one parent for each of the four probands, is associated with a variable phenotype. Speech impairment is present in most cases; no distinctive facial gestalt is recognizable; seizures have been reported in four subjects and brain magnetic resonance, performed in eight cases, resulted abnormal in six, while detected abnormal neuronal migration in two. Although the clinical description of additional cases is needed to delineate a definite phenotypic core for WBCR duplications, trigonocephaly, also reported in another dup(7)(q11.23) patient, is possibly a trait that, together with speech impairment, may call for clinically oriented specific screening. Abnormal development of the cerebral cortex, reported also in the Williams-Beuren deletion, suggests that at least one gene is present in the critical region whose deletion/duplication impairs neuronal migration.

Introduction

Speech delay of variable severity appears to be the most common phenotypic manifestation in the 15 cases up to

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now reported of 7q11.23 duplication reciprocal of the Williams-Beuren deletion.[1–6] In three instances the duplication was found in either proband's father[2] or mother (cases 5 and 6 in Ber *et al*)[5] who, although briefly described, did not appear to exhibit speech or cognitive impairment, arising the suspicion that the duplication can also be present in seemingly healthy individuals. In an array-CGH screening of 134 patients with cortical malformations and/or epilepsy, we found 2 patients with the 7q11.23 duplication. The first was ascertained for epilepsy[6] whereas

the present case was ascertained because of a cortical malformation. The duplication was also present in his mother who exhibited impaired language processing and expression with defective phonologic and articulation skills. Trigonocephaly, present in the proband and in the patient reported by Kriek *et al*[2] may represent a phenotypic trait that, together with speech impairment, might point to the 7q11.23 duplication.

Clinical report
Proband
The proband, 131/06: case 13 in Table 1 (Figure 1a and b) is the second child of healthy unrelated parents. His sister had normal development. The propositus was born at 40 weeks, after spontaneous delivery, weighing 3060 g (25th percentile), measuring 50 cm (25th percentile) in length and with a cranial circumference (OFC) of 35 cm (50th percentile). Apgar scores were 9 and 10 at 1 and 5 min, respectively. Pilonidal sinus at the very top of the cleft between the buttocks and cryptorchidism were noticed early on. At 6 months of age psychomotor delay was evident: he was not able to roll back to side and front to side and could not wiggle forward on the floor. He was able to hold his head up, to search and play with hands and bring them to mouth; sometimes he had responsive smiling and pronounced extended vowel sounds. Chromosome analysis at 7 months was reported as normal. Clinical examination at 8 months of age revealed mild trigonocephaly, low-set, posteriorly rotated ears, sparse anterior scalp hair, left eye with exotropia, bulbous nasal tip, ogival palate, short philtrum with thin lips, short lingual frenulum, short neck, bilateral pes cavum, severe motor delay and hypotonia. EEG, while awake and during falling asleep, showed unusual rapid beta activity, synchronous over the rolandic and vertex regions. At the age of 14 months the OFC was 47 cm (50th percentile). He was able to roll over, could sit unsupported and stand with support, although axial hypotonia was still evident. Marked drooling of saliva was present. Eye tracking was poor. He was able to produce bisyllabled sounds and to communicate through pointing. Short lingual frenulum had been surgically corrected. Fundus oculi, audiometric investigations, visual and somesthetic evoked potentials and EEG were normal. Griffith's mental development scale gave a global score of 50 (normal range: 85–100) with subscale A (locomotor) score <50, subscale B (personal-social), subscale C (hearing and speech) 56, subscale D (hand and eye coordination) <50. Brain magnetic resonance imaging (Figure 2) showed a simplified gyral pattern, with areas of cortical thickening, slightly open opercular fissures, multiple areas of increased signal in T2 and of reduced signal intensity in T1 in the subcortical white matter, probably corresponding to dilated perivascular spaces, interspersed with radial migration abnormalities. There were, in addition, poorly formed hippocampi and a markedly hypoplastic vermis. A triangular configuration of the skull was present, in association with a prominent metopic suture and with deformity of the sutures of the anterior-basal part of the skull, consistent with type II trigonocephaly.

Mother
The mother (1333/06: case 14 in Table 1), 31 years old, was born as the second child of healthy unrelated parents. Her brother was healthy. She had had normal developmental milestones. At 1 year and 2 years 6 months (Figure 1c) she had two epileptic seizures, after which she was given phenobarbital for 3 years. Her EEG was reported as normal. At primary school (Figure 1d), she learned to write and read but was not able to understand simple and logic concepts of mathematics and exhibited memory difficulties. She stopped her studies after the first 8 years of compulsory school. Presently, her stature was 163 cm (50th percentile), weight 64 kg (75th percentile). Her expressive language skills were very poor, with simple sentences, phonology deficits and defective articulation of speech sounds. Although not formally tested, comprehension appeared to be limited.

Materials and methods
Molecular karyotyping was performed through array comparative genomic hybridization (array-CGH) with the Agilent kit (Human Genome CGH Microarray, Agilent Technologies, Santa Clara, CA). The array-CGH platform is a 60-mer oligonucleotide-based microarray that allows a genome-wide survey and molecular profiling of genomic aberrations with a resolution of ∼100 kb (kit 44B). To better define the breakpoints of the duplication and to increase the resolution of experiments, a customized array (constituted by 44000 oligomeres) was designed using all possible probes mapped in duplicated region and present in the Agilent catalog (https://earray.chem.agilent.com/ earray/) and adding a bigger number of control probes than those duplicated. In this way, we obtained a resolution of 1 kb in single copy region. DNA, for all experiments, was extracted from peripheral blood of patients with QIAamp DNA Blood Mini Kit (Qiagen) according to the manufacturer's protocol. The array-CGH experiments have been done according to De Gregori *et al* (2007).[7] The array was analyzed through the Agilent scanner and the Feature Extraction software (v9.1). Graphical overview was obtained using the CGH analytics software (v3.4.27) according to hg 17 (genome building 35 of May 2004). Genotyping of polymorphic loci on DNAs of proband, mother and paternal and maternal grandparents was performed by amplification with primers labeled with fluorescent probes (ABI 6-Fam and 8-Hex) followed by analysis on an ABI 3100 Genetic Analyzer (Applied Biosystems). The primers for polymorphic loci were chosen

Table 1 Clinical features of subjects with 7q11.23 duplication

Reference	Somerville, 2005 (8 years 10 months old)	Kriek, 2006 (Case 1; 1 year old)	Torniero, 2007 (12 years 9 months old)	Kirkhhoff, 2007 (23 years old)	Depienne, 2007 (12 years 5 months old)	Berg, 2007 (Case 1; 3 years and 6 months old)	Berg, 2007 (Case 2; 11 years and 9 months old)	Berg, 2007 (Case 3; 4 years and 6 months old)	Berg, 2007 (Case 4; 3 years old)	Berg, 2007 (Case 5; 7 years old)	Berg, 2007 (Ccase 6; 6 years old)	Berg, 2007 (Case 7; 19 years old)	Present case (26 months old)	Present case (Mother, 31 years old)
Case Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Ascertainment	Severe expressive-language delay	Neurodevelopmental delay	Epilepsy	Mental retardation	Autism	Global developmental delay	Global developmental delay and behavioral problems	Delayed motor milestones, pervasive developmental disorder, speech delay	Speech delay and possible ASD	Speech delay and dysmorphic features	Global developmental delay and severe language delay	Mental retardation, seizure disorder, and submucous cleft palate	Abnormal neuronal migration in association with neurodevelopmental delay	Mother of case 13
Language impairment	Severe	Moderate	Severe	Severe	Severe	Severe	Severe	Moderate	Severe	Moderate	Severe	?	Severe	Moderate
Visuo-spatial skills	Good	NA	Poor	NA	Poor	?	Spared	Spared	Spared	NA	NA	NA	NA	NA
Mental retardation	Mild	NA	Moderate	NA	Severe	Mild	Mild	Mild	Mild	Mild	Moderate	Moderate	–	NA
Developmental delay	+	+ (mild)	+	+	+	+	+	+	+	+	+	+	+	+
Dismorphic features	Mild: retrognathia; short philtrum; dolichocephaly; high and narrow forehead; high and broad nose; high-arched palate dental malocclusion; facial asymmetry	Trigonocephalic synostosis of the ridge, no dysmorphic features	Mild: low-set ears with mild posterior rotation; round face; short philtrum; thin lips; asymmetric opening of the mouth; stocky short neck	Mild: low and broad forehead; narrow palperal fissures; protruding right ear with dysplastic lobe	Mild: retrognathia; incomplete folding of the helix of both ears	Prominent forehead, midface hypoplasia, high/broad nose, anteversed nares, mild helical overfolding, low/rotated ears, short philtrum, thin lips and generalized hypotonia, cleft lip and palate	Mild malar hypoplasia, prominent forehead, low-set ears, high/broad nose, low/rotated ears, short philtrum, thin lips and mildly decreased muscle tone	Mild: slightly elongated columella, short philtrum, thin lips, mild cubitus valgus, fifth finger clinodactyly, joint laxity, and slight hypotonia	Mild: prominent forehead, high/broad nose, abnoraml helices, thin lips	Hypertelorism, shawl scrotum, neutropenia, astigmatism	Cafè-au-lait macules, thin fingers	Small and simple ears, a somewhat tubular nose, a high-arched palate and dental crowding, and a grade II/VI cardiac murmur, submucous cleft palate	Trigonocephalic synostosis of the metopic ridge; occipital plagiocephaly; temporal indentation; micrognathia; low set ears; bulbous nasal tip; ogival palate; short lingual frenulum; almost absent neck; cryptorchidism	Mild: high forehead, posteriorly rotated ears
Neurological examination	Mild dysmetria and mild difficulty with tandem gait	NA	Mild dysmetria with tandem gait and unipedal stance	NA	Normal but walks awkwardly	Generalized hypotonia	Decreased muscle tone	Hypotonia, oromotor apraxia,	No abnormality reported	Stereotypical movements	No abnormality reported	Delayed developmental milestones, dysarthric speech	Motor awkwardness; sialorrhea; sporadic eye contact	NA
Brain MRI	No significative abnormalities	NA	Cortical dysplasia of the left temporal lobe	NA	Mild dilatation of the left temporal horn	Mild cerebral atrophy	?	?	Mild prominence of the lateral and third ventricles, but no dilatation or hydrocephalus	Nonspecific prominence of the ventricles and subarachnoid spaces and nonspecific white matter T2 signal abnormality, possibly representing gliosis	Normal	?	Pachygyria (cortical thickening and simplified gyral pattern); radial migration abnormality, hypoplastic cerebellar vermis	NA

Table 1 (Continued)

Reference	Somerville, 2005	Kriek, 2006	Torniero, 2007	Kirkhhoff, 2007	Depienne, 2007	Berg, 2007	Berg, 2007	Berg, 2007	Berg, 2007	Berg, 2007	Berg, 2007	Berg, 2007	Present case	Present case
	(8 years 10 months old)	(Case 1; 1 year old)	(12 years 9 months old)	(23 years old)	(12 years 5 months old)	(Case 1; 3 years and 6 months old)	(Case 2; 11 years and 9 months old)	(Case 3; 4 years and 6 months old)	(Case 4; 3 years old)	(Case 5; 7 years old)	(Case 6; 6 years old)	(Case 7; 19 years old)	(26 months old)	(Mother, 31 years old)
Case Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Epilepsy	−	−	+	−	−	+	−	−	−	−	−	+	−	+
EEG findings	NA	NA	Abnormal EEG (sharp waves on the left temporal region)	NA		?	?	?	?	?	?		At 8 months unusual monomorphic rapid beta activity, synchronous over the rolandic and vertex region; normal at following EEGs	NA
Origin of the 7q11.23 duplication	De novo (maternal origin)	Inherited from the father	De novo (maternal origin)	Absent in the mother, father unavailable	De novo (paternal origin)	?	?	De novo	De novo; the duplication was larger than the classical one (3.5 Mb)	Inherited from the mother	Inherited from the mother	?	Inherited from the mother	De novo (maternal origin)

+, presence.
?, unknown.

among those known and present in the site of UCSC Genome Browser (http://genome.ucsc.edu/). Additional primers were designed by searching dinucleotide repeats, with the highest number of copies within the duplicated 7q11.23 region, using the database tool Tandem Repeats Finder (http://tandem.bu.edu/trf/trf.intermediate.submit.html). The primers for these unlisted polymorphic dinucleotides were designed using Primer 3 Input (http://frodo.wi.mit.edu/cgi-bin/primer3/primer3_www.cgi). FISH was performed on metaphase and interphase cells from the patient, his mother and maternal grandmother to investigate if the duplication was direct or inverted and if it was mediated by a paracentric inversion.[8] To this purpose, we used the following BAC clones: RP11-815K13 proximal to the critical region, CTA-208H19 and RP5- 1186P10, both within the critical duplicated region. DNA extraction, labeling, hybridization and detection and FISH experiments were undertaken, as described previously.[9] We also performed analysis of the breakpoints with self-chain and segmental duplications repeats tools from UCSC Genome Bioinformatics (http://genome.ucsc.edu/).

Results

Whole genome array-CGH with a resolution of about 100 kb revealed a duplication in the proband of at least 1.718 Mb ranging from 71.865 to 73.583 Mb, flanked by oligomeres at 71.846 and 73.926 Mb that were not duplicated (Figures 3a and b). Actually, the abnormal segment included part of the segmental duplications (SDs) flanking the WBS region, whose copy number status is difficult to determine through array-CGH experiments. After exclusion of probes falling into those SDs, the duplication ranged from 72.295 to 73.583Mb (1.288 Mb). Array-CGH experiment performed on the proband's mother demonstrated that she had the same duplicated region, while her parents did not (cases 1878/06 and 1879/06). Several known CNVs were present in proband's and mother's array profiles (4 and 6, respectively); they were all reported in the database of the genomic variants (http://projects.tcag.ca/variation/) and, obviously, could not be attributed to the proband or the reference DNA (pool of 10 males for the proband and of 10 females for his mother). To better characterize the breakpoints of the duplicated region, a customized-array platform, with specific oligomeres for 7q11.23 region and control oligomeres localized in different chromosomes, was drawn allowing a resolution of about 1 kb in single copy regions. Excluding the SDs blocks flanking the duplication, the array-CGH experiment revealed that the duplicated region ranged from 72.276 to 73.586 Mb (Figure 3c) and it was of at least 1.31 Mb. Microsatellite analysis performed on proband, parents and maternal grandparents showed the rearrangement to have occurred at the grandmother's meiosis. In fact, the

Figure 1 (**a**, **b**) The proband at 26 months of age showing the prominence of the metopic suture and narrowing of bitemporal distance; the mother at 2 (**c**) and 7 (**d**) years of age.

Figure 2 Magnetic resonance imaging of the brain. (**a**) T2 weighted axial image. Note the prominence in the frontal midline, corresponding to the metopic suture. Areas of increased signal of the white matter are visible near the occipital horns. (**b**) T1 weighted coronal image. Note thickening of the cerebral cortex in the parietal lobes, especially on the right, with an overlying simplified gyral pattern. The caliper on the right side of the image measures 1 cm; cortical thickness at the level of the parietal lobes and insular cortex is above 1.5 cm, while thickness of he normal cortex is around 0.4 cm. Some cystic areas are visible in the subcortical white matter just beneath the left parietal lobe. (**c**) T1 weighted coronal image, taken more caudally with respect to (**b**). Radially disposed cystic areas span from the lateral ventricular walls to the subcortex in the white matter. They most likely represent columns of radial migration abnormality.

proband's mother had three alleles, two maternal and one paternal at D7S2476 (Figure 3d) and STS3_dup7q. Array-CGH has also been performed in grandparents' DNAs confirming the absence of 7q11.23 duplication. FISH analysis, in both the proband and in his mother, demonstrated that the duplication was in tandem (Figure 3e).
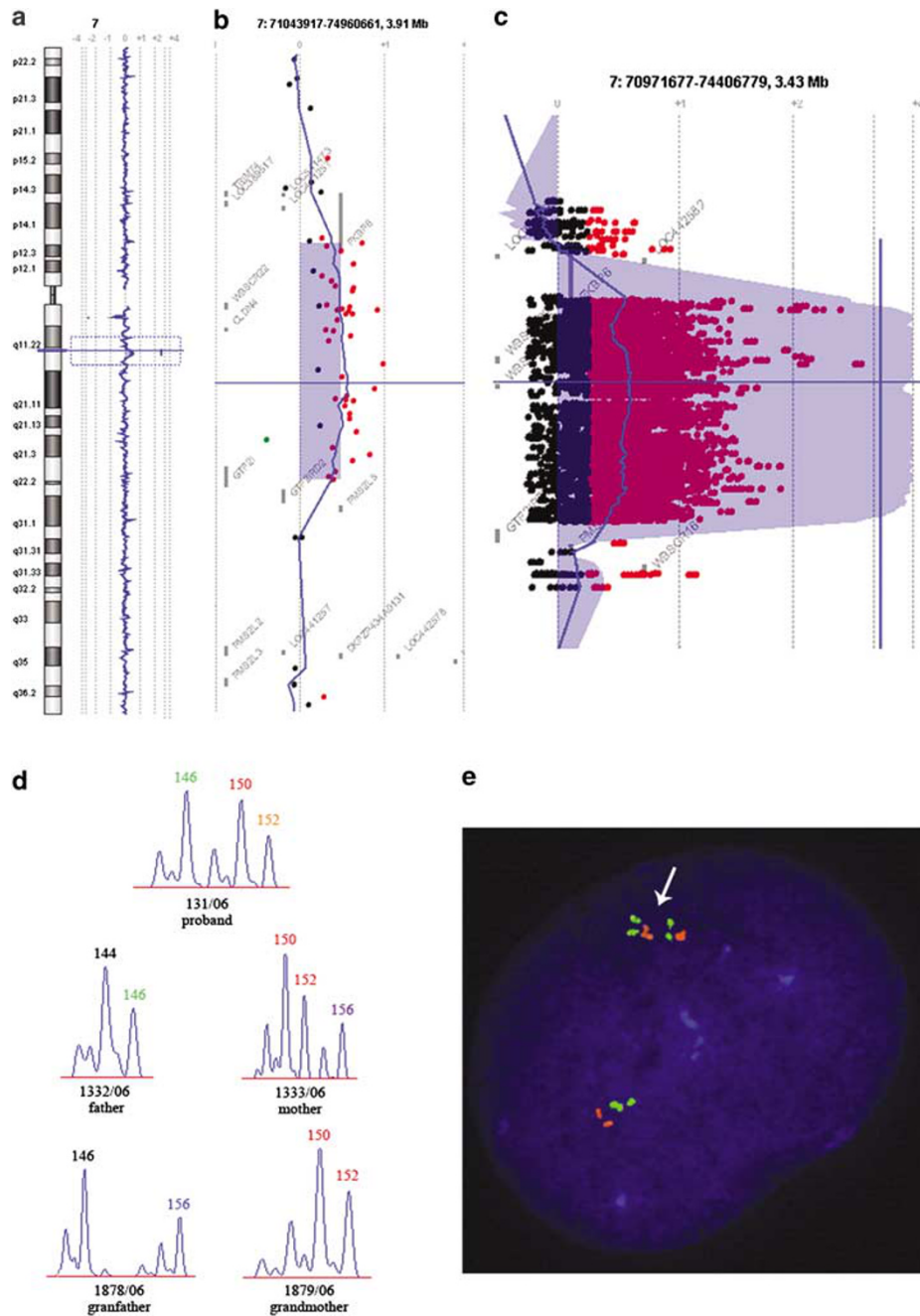
Figure 3 (a) Chromosome 7 profile of the 44 k array (about 100 kb resolution) and its enlargement (b) showing the 7q11.23 duplication (red spots) found in the proband and his mother; in gray are listed some of the genes included in the shown region (from 71.043 to 74.960 Mb); (c) profile of the customized array at the final resolution of 1 kb in single copy regions showing that the dup (7)(q11.23) covers the Williams-Beuren classical deletion of about 1.3 Mb; (d) D7S2476 microsatellite analysis of DNAs from the proband, his parents and maternal grandparents showing the grandmaternal origin of duplication; (e) interphase FISH in proband's lymphocytes with CTA-208H19 and RP5-1186P10, both within Williams-Beuren critical region (red and green, respectively) showing that the duplication (white arrow) is direct.

Discussion

To our knowledge 15 cases of 7q11.23 duplication, reciprocal to the Williams-Beuren deletion syndrome, have been published. Based on available descriptions, no clearly defined phenotype can be attributed to WBCR duplication,

making clinically oriented specific screening unreliable. Amongst the previous descriptions, ascertainment had been prompted for different reasons (Table 1) ranging from developmental and language delay to autism. Both our cases (cases 3 and 13) belong to a cohort of individuals

analyzed by array-CGH because of anomalous cerebral cortex development and/or epilepsy. In 11 of the reported cases, parents were also analyzed for the presence/absence of the rearrangement. The finding that four of the parents (cases 2, 10, 11 and 13) had the same duplication present in their offspring but a relatively normal phenotype points to phenotypic variability. Retrospectively, the mother of the patient reported herein (case 14) had in fact poor language skills whereas no details were reported about the cognitive status of the father of case 2 and the mother of case 10. The mother of case 11 exhibited no developmental delay and was able to complete high school in a regular classroom setting. This observation recalls what can be observed in the 22q11 deletion syndrome for which different definitions have been used, such as DiGeorge syndrome, velocardiofacial syndrome, conotruncal anomaly face, Cayler syndrome and Opitz GBB syndrome and different diagnoses have at times been made, even in different members of the same family segregating the same deletion.[10]

Mild trigonocephaly was a phenotypic feature of our patient. Trigonocephalic synostosis of the metopic ridge had been described in only 1 out of 17 reported patients with the same duplication (case 2). In addition, plagiocephaly was reported in one out of three cases with supernumerary ring chromosomes, all mosaic, including the WBS region.[11,12] Trigonocephaly might be either coincidental with the WBCR duplication or resulted from a duplicated dosage-sensitive gene within the critical region, whose effects act with low penetrance. Since trigonocephaly is exceedingly rare (1:10 000–15 000),[13] and assuming that the frequency of WBCR duplication is the same of the deletion (1/20 000) or even lower,[14] the probability for the two events to co-occur is about 1:200 000 000. Clinical variability between family members carrying the same mutation for one of the known genes that have been associated with trigonocephaly represents a major challenge for genetic counseling.[15]

Although the clinical risk for trigonocephaly associated with WBCR duplication is likely to be relatively low, in our opinion, association of this phenotypic trait with poor speech development should prompt a search of the 7q11.23 duplication. Magnetic resonance imaging of the brain, performed in the case reported by Torniero et al[6] and in the child described in this report, revealed abnormal development of the cerebral cortex, which is likely to contribute to cognitive and language impairment. In particular, Torniero's case exhibited cortical thickening and an abnormal gyral pattern in the left sylvian and temporal cortex. In the patient described here, similar abnormalities were more widely distributed, bilaterally involving the parieto-occipital cortex. Additional abnormalities were also noted, including multiple cystic areas within the subcortical white matter in the parieto-occipital cortex, interspersed with radial white matter fibers,

consistent with radial migration abnormality. Cortical abnormalities consisting in mild cerebral atrophy were also reported in case 6, although atrophy is an aspecific term and not clearly related to prenatal or postnatal events. Gyral pattern abnormalities in individuals with Williams syndrome have been reported possibly contributing to the distinct cognitive and behavioral profile accompanying the disorder.[16–19] These findings point to the presence in the critical region of at least a gene whose deletion/duplication impairs neuronal migration, to an extent that may be detected or not using MRI.

Conclusion

The two patients we are reporting in this paper confirm the phenotypic variability associated with the 7q duplication reciprocal to the Williams-Beuren deletion. We found two such cases (cases 3 and 13 in Table 1) among 134 patients analyzed for abnormal neuronal migration and/or epilepsy. These series of patients represent, in turn, a subset of 510 individuals we analyzed for idiopathic mental retardation with or without associated dysmorphisms or congenital malformations. Thus, the frequency of the WBCR duplication is 0.39% of the whole sample we examined and is four times higher in the sample with abnormal neuronal migration and/or epilepsy. This figure is strikingly similar to that of WBS deletion estimated from Stevenson et al[20] in a large cohort of patients with mental retardation, corresponding to 0.31%. However, the presence of the duplication in four healthy or nearly healthy parents of 13 probands suggests that its frequency is even higher and that the duplication might go undetected in some individuals. In fact, in the mother of our proband no cytogenetic abnormality had been suspected in childhood, in spite of her exhibiting an association of seizures and poor school achievement. These findings point to enlarge whole genome investigations not only to individuals with the classical chromosomal phenotype (mental retardation, facial dysmorphisms and/or congenital anomalies) but also to those exhibiting mild cognitive impairment, with or without epilepsy.

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