Brief Report: Visual–Spatial Deficit in a 16-year-old Girl with Maternally Derived Duplication of Proximal 15q

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BRIEF REPORT

Brief Report: Visual-Spatial Deficit in a 16-year-old Girl with Maternally Derived Duplication of Proximal 15q

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Abstract Duplications of chromosome 15 may be one of the most common single genetic causes of autism spectrum disorders (ASD), aside from fragile X. Most of the cases are associated with maternally derived interstitial duplication involving 15q11-13. This case report describes a female proband with a maternally derived interstitial duplication of proximal 15q. She did not exhibit any symptoms of ASD apart from some developmental delay. By adolescence, she showed mild dysmorphism, a discrepant profile on the Wechsler Intelligence Scale for Children (Verbal IQ = 87; Performance IQ = 65) and a major deficit in visual-spatial abilities affecting fine motor skills, mathematical reasoning, visual memory and some global reading tasks. This is one of the first reports of a child with a maternal duplication who exhibits a visual-spatial deficit without ASD.

Keywords Chromosome 15 · Prader-Willi/Angelman Syndrome critical region · Maternally derived interstitial duplication · Pervasive developmental disorder · Visual-spatial deficit

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Introduction

According to several authors (e.g. Cook, 2001; Schroer et al., 1998), duplications of chromosome 15 may be one of the most common single genetic causes of autism, aside from Fragile X. It is also the most frequent non-X-linked cause reported in the literature (Lauristen, Mors, Mortensen, & Ewarld, 1999). However, in most genetic abnormalities linked to autism, the autism phenotype or syndrome is not always present and is most likely a secondary phenomenon (Cohen et al., 2005). Duplications of chromosome 15 involved in autistic syndrome are located in the Angelman-Prader-Willi region (15q11-q13). Duplications may result from partial trisomy 15 (presenting an extra marker chromosome visible with conventional cytogenetics, which must be confirmed as 15q11-q13 derivative by Fluorescent in situ hybridization, or FISH), or from

intrachromosomal duplications. In many cases, the duplication is tiny, and only detected when specifically sought using the Prader-Willi locus FISH probe. In practical terms, tiny duplications of 15q11-q13 may be difficult to demonstrate by FISH on metaphasic chromosomes. Examination of interphasic nuclei with 15q11-q13 FISH probes is recommended to increase diagnosis efficiency (Xu & Chen, 2003). Interestingly, an imprinting phenomenon is probably involved, as most of the reported cases with autism exhibited duplications inherited from the mother (Bolton et al., 2001; Browne et al., 1997; Cook et al., 1997; Gurrieri et al., 1999; Mao & Jalal, 2000; Repetto, White, Bader, Johnson, & Knoll, 1998; Thomas et al., 2003; Wandstrat, Leana-Cox, Jenkins & Schwartz, 1998). The molecular genetic aspects were recently reviewed by Sutcliffe and Nurmi (2003).

The typical clinical phenotype of marker chromosome 15 duplication usually includes severe mental retardation, seizures, language disorders and Kanner-type autism (Cohen et al., 2005). Dysmorphic examination is usually normal although downslanting palpebral fissures, broad nasal bridge, epicanthal folds, clino and syndactyly, and short stature have been reported (Bolton et al., 2001; Thomas et al., 2003). Frequently, patients exhibit hypotonia and joint laxity (Bolton et al., 2001; Rineer, Finucane, & Simon, 1998; Wolpert et al., 2000). In a literature review, Wandstrat et al. (1998) reported 17 cases of 15q duplications. Among the nine cases with clinical data, eight exhibited autism. But until the late nineties, the behavioral phenotype was usually poorly described. Thomas et al. (2003) focused on the behavioral phenotype of five patients aged 5–9 years from three different families and exhibiting maternally derived duplication of 15q. Besides symptoms related to autistic spectrum and mental retardation, 4/5 boys had hyperactivity, that improved with methylphenidate, in the most severe cases. However, Bolton et al. (2001) showed that the interstitial duplications of 15q also includes much milder cases with less prominent language delay, impaired social communication and clumsiness than the full syndrome of autism. Boyard et al. (2001) reported a family with a grand-maternally derived interstitial duplication where affected members had limb apraxia, apraxia of speech, phonological awareness deficits, developmental language disorder and dyslexia, but no symptoms of autism or hyperactivity.

Here we describe the case of a 16-year-old girl with maternally derived interstitial duplication of chromosome 15q who showed a complex learning impairment related to a visual-spatial deficit and who did not exhibit any symptoms of autism.

Case Report

Family History

There is a family history of depression in J's mother. At least two major depressive episodes occurred and needed specific care. A son of J's maternal grandfather's sister was diagnosed as presenting mental retardation, obesity and delayed language. To our knowledge, he has never been tested for genetic abnormalities.

Early Developmental and Clinical History

J was the second child of unrelated parents. When she was born, her mother was 38 years old, and her father 40 years. J was born at term following an uneventful pregnancy. At birth, J weighed 2.77 kg and measured 49 cm with a 32 cm head perimeter. Early symptoms were limited to hypotonia, slow feeding, external ear malformations and severe strabismus that needed surgery at 6 months. Social abilities were normal although she was described by both parents and teachers as a calm and shy child. She showed discrete delays in the development of motor and language skills. She first sat upright at 7 months, and walked at 16 months but showed an unsteady gait for several months. Later she was described as being clumsy and poorly coordinated. She started to use single words at 18 months with a brief period of echolalia, and short phrases at 3 years old, but she had poor articulation during childhood. She began attending the local Child Development Center at the age of 3, and had regular sessions with a speech therapist and a physical therapist until the age of 6. Although she was able to attend regular school, she needed special education services, a reading specialist for written language acquisition, and a cognitive psychologist for mathematical impairments. She repeated two school years (the 2nd and the 6th grades).[1]

J's medical history was marked by repeated rhinitis and otitis infections and urinary tract infections including one pyelonephritis during childhood, and a rheumatoid purpura. She also had two plastic surgery interventions for her ear malformations. During late infancy, she began to show obesity. At 12 years, she had a weight of 43.5 kg (+0.5 SD), a height of 143 cm (–1.5 DS) a normal head perimeter (53 cm) and a facial dysmorphism. A test for Prader-Willi syndrome was conducted and showed interstitial duplication (see

[1] This is a common practice in France for children who are not making adequate progress.

below). When we first met her, J was a 16-year-old girl, 160 cm tall, and 64 kg. Morphologic examination showed that she had a normal head perimeter (55 cm), facial dysmorphism (thin upper lip, high forehead, epicanthal folds with telecanthus, abnormal ears), and a mammary asymmetry with a limited development of her right breast (4×3 cm^2).

Genetic Analysis

No abnormalities were identified during routine cytogenetic testing that was prescribed during childhood because of the association of dysmorphy, short stature, developmental delay, and malformations. However, given the presence of developmental delay and malformations, further molecular genetic investigations using comparative genomic hybridization (CGH)[2] showed that J carried an interstitial duplication of proximal 15q. We confirmed this duplication by FISH using specific probe (Yac 368H3) for the Prader-Willi critical region. This probe is localized between the centromere of chromosome 15 and SNRPN gene. The distance between our probe and the centromere is 21.18 Mb. We can evaluate the size of this duplication to be less than 3 Mb. Parental origin of the 15q duplication was determined by PCR analysis of microsatellite markers, as follows, from centromere to telomere: D15S101, D15S122, D15S210, PWS-196, AFMa309yg1, GABRB3, and D15S102. Duplication was of maternal origin, involved markers D15S122 to GABRB3, and was flanked by markers D15S101 (15q11) and D15S102 (15q14), which showed normal allelic patterns.

Cognitive and Psychiatric Assessment

J was referred by a private practitioner to an inpatient unit because of (i) increasing intrafamilial oppositional behaviors and refusal to attend school, which was resistant to outpatient and family consultations for 5 months and risperidone (2 mg/day) prescription for one month, and (ii) suspicion of Asperger syndrome, given the genetic duplication. At admission, J was cooperative and was relieved by the separation from the family. She did not show any oppositional behavior during her stay. Communicative and social skills were normal and she did not exhibit stereotyped behavior or limited interests. She appeared to be low in self-confidence and self-esteem, and refusal to attend school was clearly an opposition to both parental pressure and her lack of interest in academics, given her school difficulties and her career ambition to work in animal care. Furthermore, because the discovery of a genetic abnormality was initially seen by J's parents as a confirmation of their belief that J was severely mentally disabled, they had become increasingly protective, enhancing conflicts in adolescence.

In order to define the phenotype more precisely and to give proper information to both J and her parents, we conducted a thorough evaluation. Autism Diagnostic Interview-Revised scores (Lord, Rutter, & Le Couteur, 1994) confirmed that the criteria of autistic spectrum disorder were not met in any domain: reciprocal social interaction domain = 3 (threshold = 10); communication domain = 2 (threshold = 8); repetitive and stereotyped behavior domain = 0 (threshold = 3). However, J did score highly in the development domain (score = 4; threshold = 1) reflecting concern about early developmental delay. Details of items scored are given in Table 1.

Psychological and fine motor skill testing is presented in Table 1 and includes investigations of general and specific cognitive abilities, oral and written language, mathematical and fine motor skills. In sum, J exhibited an impaired profile in all tasks involving visual-spatial and constructive abilities. Despite average IQ, she had a lower performance IQ score because she scored lowly on subtests of block design and object assembly. Attention and memory skills were normal except for visual processing. Basic oral and written language was normal except for some syntax tasks and general reading tasks requiring visual memory (long prose) or visual scanning (TV schedule). Similarly all tasks requiring visual-spatial and constructive skills in mathematical tasks (spatial seriating, geometry) and fine motor tasks (motor imitation, visual-motor precision) were impaired. Fig. 1.

Outcome

The investigation helped J and her parents to feel more confident about her potential. We recommended that she entered a vocational program as an intern, and that the family undertook family therapy. Medication was stopped during her stay. At 1-year follow-up, both J and her parents considered the ''crisis'' to be over as J was doing well in her adolescent life and her vocational program. Indeed, when asked for permission to publish J's case, his parents gratefully accepted DNA determination of the parental origin, even though they realized that one of them might experience feelings of guilt.

[2] Comparative genomic hybridization (CGH) is a recent molecular cytogenetic technique that allows comprehensive analysis of the entire genome. This method permits the rapid detection and mapping of DNA sequence copy number differences between a normal and abnormal genome (Lapierre & Tachdjian, 2002.)

Table 1 Summary of psychological test results for a 16-year-old girl with maternally derived q11-q13 interstitial duplication of chromosome 15

Ability and used tests	Score[a]	Comments
WISC III		
Verbal IQ	87	The verbal scores were homogenous whereas performance deficit was only due to very low scores on Block design and Object assembly
Performance IQ	65	
Block design	1 (Normal 8–12)	
Object assembly	2 (Normal 8–12)	
ADI-R		
Social domain	3	Scoring is given according to clinical impairments at 5 years. All symptoms were mild and only the developmental delay reached ADI-R cut off.
Interest in children	1	
Response to other approaches	1	
Group play with peers	1	
Communication domain	2	
Echolalia	1	
Pronominal reversal	1	
[Suspicion of deafness]	2	
Stereotyped behaviour domain	0	
Developmental domain	4	
Age parents first noticed	1	
Age when abnormality first evident	1	
Interviewer's judgment	1	
Age at first phrase	1	
Attention and executive functions		
Attention-Concentration WMS	99	Normal auditory attention, normal concentration but impaired visual attention. Normal executive functions.
Auditory attention NEPSY	>75%	
Visual attention NEPSY	<2% (7.5 years)	
Wisconsin Sorting Card	100%	
Stroop	100%	
La Tour NEPSY	75%	
Knock and tap NEPSY	>75%	
Memory		
Short term auditory memory WMS	90	Memory skills were normal except for long term visual memory
Short term visual memory WMS	96	
Long term auditory memory WMS	96	
Long term visual memory WMS	59 (<–2 SD)	
Oral and written language		
Phonology NEPSY	50% (12.5 years)	Basic oral and written language skills were normal except for complex morpho-syntax comprehension. When global reading tasks required long term visual memory skills (long prose) or visual-spatial scanning (TV schedule), the patient exhibited poor response rates.
Speeded naming NEPSY	>75%	
Oromotor sequences NEPSY	>75%	
Verbal fluency NEPSY	>75%	
Oral morpho-syntax ECOSSE	9 errors (<–2 SD)	
Word identification BELEC	94%	
Basic reading Alouette	1 mn 32s	
Syntax comprehension LMC-R	56% (<–2 SD)	
Short prose comprehension	100%	
Long prose comprehension	42% (<–2 SD)	
Information seeking TVschedule	57%	
Spelling	82%	
Motor skills		
Fingertip Tapping NEPSY	>50%	Several sensory-motor skills were impaired despite normal hand motor co-ordination and sequences. All tests requiring visual-spatial abilities were impaired. A significant dissociation occurred in the left/right orientation test. Body representation was also immature. However, temporal orientation and spatial object representation were within normal ranges.
Manual motor sequences NEPSY	>50%	
Imitation of hand position NEPSY	<25% (8.5 years)	
Visual-motor precision NEPSY	<25% (8.5 years)	
Finger discrimination NEPSY		
– Preferred hand	<2% (5 years)	
– Non-preferred hand	<2% (5 years)	
Design copying NEPSY	2% (7 years)	
Arrows NEPSY	<2% (7 years)	
Route finding NEPSY	>75%	
Block construction NEPSY	<25% (9 years)	
Hand co-ordination LINCOLN-OZERETSKI	Normal	
Static coordination LINCOLN-OZERETSKI	Impaired (10 years)	

Table 1 continued

Ability and used tests	Score[a]	Comments
Kinetic coordination LINCOLN-OZERETSKI	Impaired (11 years)	
Syncinesia LINCOLN-OZERETSKI	Impaired (6 years)	
Laterality	Right (7/10)	
Left/right knowledge Piaget-Head	16/20	
Left/right orientation Piaget-Head		
Verbal instruction	15/15	
Imitation	11/30 (< 9 years)	
Human body drawing Goudenough	24/51 (9 years)	
Mathematical abilities		
Dot enumeration (1–3 dots) Unicog	100% (+137 ms)	Despite normal accuracy on arithmetic tacks, the patient exhibited prolonged reaction times (RTs) for enumeration (especially for groups of 4–8 dots), numerical comparison (symbolic and non-symbolic), and subtraction. RTs are compared to an age and gender matched control. Spatial seriation and all geometric tests were impaired.
Dot enumeration (4–8 dots) Unicog	98% (+ 627 ms)	
Numerical comparison (digits) Unicog	100% (+294 ms)	
Numerical comparison (dots) Unicog	100% (+323 ms)	
Addition of 1 digit numbers Unicog	100% (–226 ms)	
Subtraction of 1 digit numbers Unicog	100% (+185 ms)	
Multiplication Unicog	97% (–61 ms)	
Logical categorical thinking UDN-II	Not acquired (< 7 years)	
Spatial seriation UDN-II	Not acquired(< 10 years)	
Numerical seriation UDN-II	Acquired (>11 years)	
Inclusion UDN-II	18/36 (< –2 SD)	
Geometry REY FIGURE		

[a] Indications are given where scores were below normal depending on the norms for that test (if available). E.g. (7 years) means that the score corresponds to an age of development of 7 years; (< –2 SD) means that the score is below 2 standard deviations from the mean of a same age normative sample; Not acquired (< 10 years) means that the dimension tested is not acquired, whereas it should have been acquired by the age of 10 years

WISC-R: Wechsler Intelligence Scale for Children; CMS: Children Memory Scale (Cohen, 1997); BELEC: Batterie d'évaluation du langage écrit [*written language evaluation battery*] (Mousty, Leybaert, Alegria, Content, & Morais, 1994); NEPSY: Bilan neuropsychologique de l'enfant [*neuropsychological test for children*] (Korkman, Kirk, & Kemp, 2003); LMC-R: Epreuve de la competence en lecture [*reading proficiency test*] (Khomsi, 1999); ECOSSE: Epreuve de compréhension morphosyntaxique [*Test of morphosyntactic comprehension*] (Lecocq, 1996); UDN-II: Construction et utilisation du nombre [*construction and utilisation of number*] (Meldjac & Lemel, 1980); UNICOG: Computerized numerical cognition battery (as described in Wilson, Revkin, Cohen, Cohen, & Dehaene, 2006)

Discussion

There have been very few reports of 15q11-13 duplication involving the maternally inherited chromosome describing detailed cognitive assessment in subjects without ASD. Bolton et al. (2001) described several subjects with much milder symptoms than the full syndrome of autism. However, in most affected individuals of Bolton's series, ADI-R social domain and language scores were notably impaired and associated with

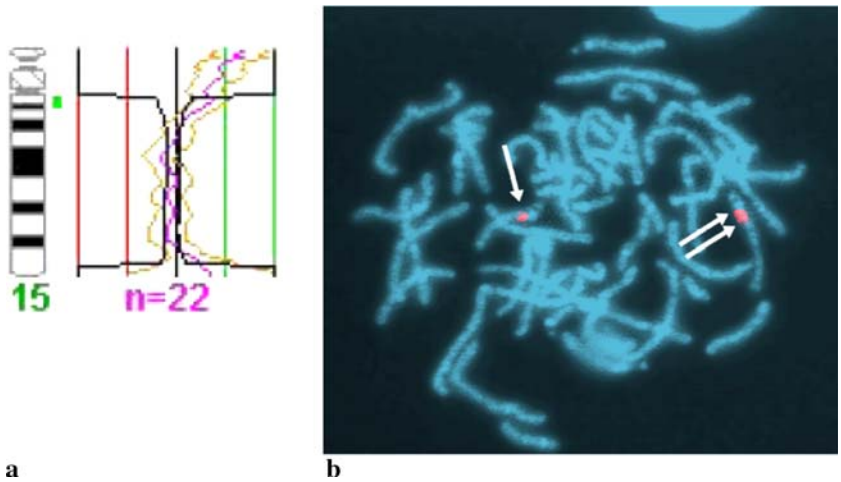

Fig. 1 **a.** High resolution comparative genomic hybridization (HR-CGH) showed a duplication of 15q11, de novo. The vertical wide green bar on the right of the chromosomal ideogram indicates the size and the mapping position of the gain. **b.** The duplication 15q11 was confirmed by fluorescent in situ hybridization (FISH)

mental retardation and clumsiness whereas repetitive and stereotyped behavior scores were low. Also, Boyard et al. (2001) reported a family with a grand-maternally derived interstitial duplication where affected members had limb dyspraxia, dyspraxia of speech, phonological awareness deficits, developmental language disorder and dyslexia, and no symptom of autism. Similarly, the present case report did not show symptoms of autism despite some developmental delay. By adolescence, the girl showed mild dysmorphism, a discrepant profile on the Wechsler Intelligence Scale for Children and a major deficit in visual-spatial abilities affecting fine motor skills, mathematical reasoning, visual memory and some global reading tasks. This profile is clearly in the spectrum of maternally derived proximal duplications of chromosome 15, as apraxia, developmental delay, hypotonia, clumsiness have been described in the syndrome (Bolton et al., 2001). However, the detailed cognitive evaluation of the case showed that learning difficulties may be linked to a visual-spatial deficit. Therefore, it appears that besides developmental delay, impairments in social and communication skills belonging to the autistic spectrum, and clumsiness, the phenotypic manifestations of proximal 15q duplications may also involve visual-spatial disabilities.

On the contrary to maternally derived duplications, paternally derived duplication is assumed not to be associated with ASD (Bolton et al., 2001; Cook et al., 1997; Gurrieri et al., 1999; Mao & Jalal, 2000; Repetto et al., 1998; Thomas et al., 2003; Wandstrat et al., 1998). However, Veltman et al. (2005) recently reported a family study of paternally inherited duplication of proximal 15q in which one of the three carriers exhibited a clear autism syndrome. Interestingly, the other carriers of the family exhibited difficulties in mathematics and fine motor skills. Therefore, although the imprinting phenomenon is highly probable given the frequent opposite expression of maternally versus paternally derived duplication phenotypes, the existence of atypical genotype/phenotype expression (current case; Bolton et al., 2001; Boyard et al., 2001; Veltman et al., 2005) suggests that other factors might be involved. Some biases in assessing the phenotype/genotype relationship of proximal 15q duplications should be kept in mind: (1) cases that come to attention tend to be those which are most severe; (2) detailed cognitive assessments are not usually conducted in subjects not presenting major psychopathology; (3) a descriptive study based on a sample recruited in the general population is as of yet not available.

Finally, in terms of clinical practice, this case highlights that detailed cognitive evaluation of patients exhibiting a complex phenotype may help in managing adolescent oppositional behaviors. By sharing a common basis of knowledge with us (the current testing results), J's parents were able to link their overprotective behaviors not to the presumption of a severe mental deficiency, but to the stresses that occurred during J's development. In doing so, they enabled J to work through her adolescent worries, engage her professional wishes and continue with her life. From our side, we were able to use the evaluation results to make J realistic proposals in terms of a vocational program, which allowed her to avoid further unsuccessful experiences in school and their negative impact on her self-esteem.

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