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Discovering a familial Xp11.4 microduplication: Does the mother matter?

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ABSTRACT

Interstitial duplications of the short arm of the X chromosome have been rarely described, especially in males. Usually boys present mental retardation, multiple congenital abnormalities and short stature. We describe two sons one with a 2q37.3 deletion and a Xp11.4 duplication and the other with Xp11.4 duplication only, identified by array-CGH. They both presented a phenotype characterized by poor growth, mild facial dysmorphisms, autism and developmental delay. The 2q37.3 identified chromosomal anomaly was inherited from the healthy father and included approximately 8 known genes, while the Xp11.4 duplication resulted inherited from the healthy mother and involved 13 known genes. Of these *TSPAN7* and *CASK*, localized on Xp11.4, genes are of special interest. The alteration on the X chromosome could be more related to the clinical feature presented by the two brothers, while the anomaly on the chromosome 2 is more likely a polymorphism or might influence the phenotype correlated to the Xp11.4 duplication. The healthy phenotype of the mother could be explained by X chromosome inactivation (XCI) phenomenon.

1. Introduction

About 3% of the total population are considered to have intellectual disability (ID), based on IQ test scores. However, if classification is based on the need for support, only about 1% of people are classified as having significant cognitive limitation. Etiology is many-faceted, due to numerous genetic and environmental factors (Raymond, 2006). Mild ID can be attributed to genetic factors in only 5–10% of the cases whereas 22% of severe ID is straightly connected to chromosomal disorders and 21% of severe ID is due to genetic syndromes (Shapiro and Batshaw, 2007). However, the underlying cause remains undetected in 75–80% of mild ID and 20–50% in cases of severe ID (Strømme, 2000).

Interstitial duplications of the short arm of the X chromosome have been rarely described, especially in males. (Monnot et al., 2008). Usually boys present mental retardation, variable multiple congenital abnormalities and short stature, depending on the size and the position of the duplication. (Tzschach et al., 2008). Due to the "X chromosome inactivation (XCI) phenomenon" most female carriers of partial Xp duplications have a normal phenotype, while a few of them exhibit a variable phenotype (Vacca et al., 2016).

Some recent studies showed that several genes, localized on chromosome Xp, are involved in non-syndromic mental retardation such as *TM4SF2/TSPAN7* and *CASK* (Noor et al., 2009; Moog et al., 2015).

We describe two sons of non-consanguineous healthy parents with a 2q37.3 deletion and a Xp11.4 duplication and an intricate phenotype with poor growth, mild facial dysmorphisms, autism and developmental delay.

2. Clinical report

A 20-month-old Italian boy was admitted to the outpatient Endocrine Clinic of the Department of Pediatrics, University of Chieti, Italy, in June 2015 for growth retardation. The boy is the second offspring of unrelated healthy parents; they are both teacher; the father is 46 year-old and the mother is 40 year-old and take care of children with disabilities. Family history is referred negative for genetic diseases. He was born at term (39 weeks). At birth weight was 2600 Kg and length 49 cm. At our first clinical evaluation he showed all the auxological parameters all under the third percentile (height 70 cm, weight 7900 Kg and head circumference 44 cm). The habitus was normal, and he had some facial dysmorphisms,

Abbreviations: XCI, X chromosome inactivation; ID, intellectual disability; GMDS-ER, Griffiths Mental Developmental Scales Extended Revised 0–8 years; ADOS, Autism Diagnostic Observation Schedule; ADI-R, Autism Diagnostic Interview-Revised; FISH, fluorescence in situ hybridization; MICPCH, microcephaly with pontine and cerebellar hypoplasia

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such as mild hypertelorism, retrognathia and metopic suture prominence. The Griffiths Mental Developmental Scales Extended Revised 0–8 years (GMDS-ER) was performed to assess the rate of psychomotor development of the child. He had a mild global developmental delay (general quotient: 68), since he failed to meet expected developmental milestones in several areas of intellectual functioning. He had a non-harmonic developmental profile, performing worse in language skills, eye and hand co-ordination, focused on fine motor skills, manual dexterity and visual monitoring skills, and in performance, focused on the way in which such skills are applied in novel situations.

Laboratory investigations showed normal thyroid function and IGF-1 levels. The caloric food intake was calculated and it resulted appropriate for his age. A cardiac ultrasound resulted negative.

The older brother, was 6-year-old and presented height at 10° centile (108 cm) and weight along the 10–25° centile (18,6 Kg) with mild microcephaly (49,5 cm) and clinical features of autism spectrum disorder associated with intellectual impairment [assessed by The Autism Diagnostic Observation Schedule (ADOS) and the Autism Diagnostic Interview-Revised (ADI-R)], requiring substantial support.

Prenatal and perinatal history was referred negative for both children.

A brain MRI was done and resulted normal for both brothers.

Karyotype analysis resulted normal 46,XY in both children.

On the basis of the presence of multiple congenital anomalies and dysmorphisms we performed an array-CGH analysis using the CytoChip oligo-array ISCA 4X44K resolution (BlueGnome, Cambridge, UK), according to the recommendations of the manufacturer. Data were analyzed using the Blue-Fuse for microarrays software package (BlueGnome). The analysis identified in the first son a microdeletion of 547.6 kb on chromosome 2q37.3, bridging from 242,520,809 bp to 243,068,370 and, in both sons, a microduplication of 4.1 Mb on chromosome Xp11.4, bridging from 37,814,741 bp to 41,964,273 bp, according to the human genome NCBI Build 37 version (Fig. 1a).

The chromosomal abnormalities were confirmed by fluorescence in situ hybridization (FISH) analysis using a Cytocell® subtelomeric 2q commercially available probe (Cytocell Ltd., Cambridge, UK) and a BlueFish RP11-330L22 probe (Xp11.4) (Bluegnome-Cambridge UK), according to the manufacturer's instructions.

The 2q37.3 identified chromosomal anomaly was inherited from the father and included approximately 8 known genes, while the Xp11.4 duplication resulted inherited from the mother and involved 13 known genes (Fig. 1b).

XCI was evaluated based on promoter methylation and CAG-repeat polymorphism in the human androgen receptor (AR) gene at Xq11.2. The Peak Scanner software v2.0 (Thermo Fisher Scientific) was used to analyze the raw data and to calculate the area under the curve (AUC) for each allele. XCI ratios equal to or less than 80:20 were considered "random" patterns while ratios greater than 80:20 were considered "skewed" patterns, accordingly to previously published criteria (Allen et al., 1992; Amos-Landgraf et al., 2006; Giorda et al., 2009; Busque et al., 2009).

The mother, who has the same duplication of the 2 affected boys, has a random inactivation (65%) on blood.

3. Discussion

In this study we report the description of two brothers who both presented a duplication of the Xp11.4 inherited from the healthy mother. The alteration on the X chromosome, involving 13 genes, could be more related to the clinical feature presented by the two brothers. The healthy phenotype of the mother could be explained by X chromosome inactivation (XCI) phenomenon. That is a mechanism by which mammals compensate for dosage of X-linked genes in females (XX) versus males (XY). XCI patterns can be random or show extreme skewing, and can modify the mode of inheritance of X-driven phenotypes, which contributes to the variability of human pathologies (Vacca et al., 2016). This is the reason why the mother apparently has a normal phenotype and neuropsychiatric development. Unfortunately, the XCI study doesn't give us a really complete demonstration of the clinical relevance of the duplication on Xp, because the mother of the 2 brothers, has a random inactivation (65%) on blood.

The younger brother presented even a deletion of the 2q37.3 chromosome. This deletion includes almost 8 OMIM genes (THAP4, ATG4B, DTYMK, ING5, D2HGDH, GAL3ST2, NEU4, PDCD1). Some of these (GAL3ST2 and NEU4) are expressed in the brain but their function

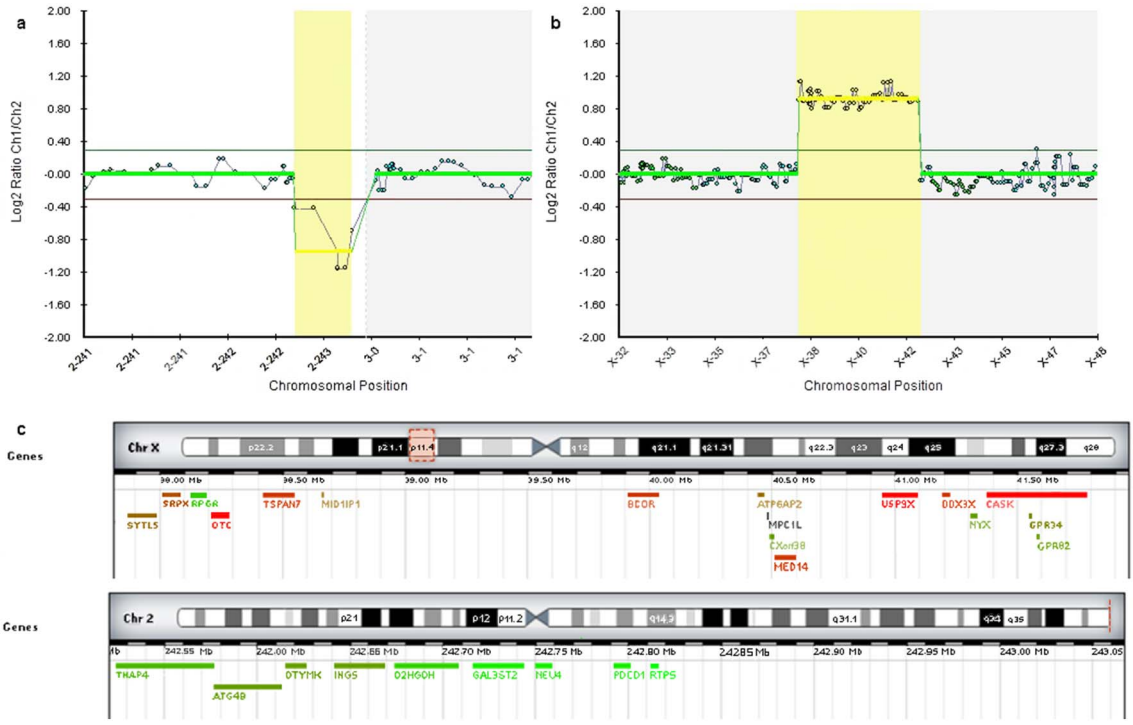

Fig. 1. a. Array-CGH analysis: microdeletion of 547.6 kb on chromosome 2q37.3, bridging from 242,520,809 bp to 243,068,370 bp; b. Array-CGH analysis: microduplication of 4.1 Mb on chromosome Xp11.4, bridging from 37,814,741 bp to 41,964,273 bp; c. Chromosome 2q37.3 and Xp11.4 and the genes contained.