CLINICAL REPORT

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Mosaic Partial Trisomy 19p12-q13.11 Due to a Small Supernumerary Marker Chromosome: A Locus Associated With Asperger Syndrome?

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In the neurodevelopmentally impaired population the frequency of small supernumerary marker chromosomes (sSMC) is about 0.3%. To find the origin of a sSMC in a 4-year-old boy with Asperger syndrome (AS) a microarray-based comparative genomic hybridization (aCGH), using a 135K-feature whole-genome microarray, and Metaphase FISH analysis, was performed. The sSMC was characterized as being composed of 18.4 Mb from 19p12q13.11. Based on the size and genic content, it is expected that the partial trisomy detected is responsible for the characteristics observed in the patient. In that case it could be an indication of a novel locus associated with AS.

Key words: asperger syndrome; chromosome 19p12q13.11; sSMC; CGH array; FISH

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INTRODUCTION

Small supernumerary marker chromosomes (sSMC) are structurally abnormal chromosomes that are found in 0.75/1,000 of unselected prenatal and 0.44/1,000 of unselected postnatal cases, being much more frequent among the neurodevelopmentally impaired (2.88/1,000) [Liehr and Weise, 2007]. When found de novo prenatally, there is a ~26% risk of phenotypic abnormalities [Graf et al., 2006]. Molecular cytogenetic techniques characterize the size and gene content of sSMCs, which allows for a more informed interpretation of their potential phenotypic impact.

Here we report on a 4-year-old boy with Asperger syndrome (AS) and sSMC leading to mosaic partial trisomy 19p12q13.11.

MATERIALS AND METHODS

Conventional Cytogenetic

Twenty cells from the patient and both parents were analyzed using G-banded metaphase chromosomes, which was obtained from blood.

Oligonucleotide-Based aCGH

Microarray-based comparative genomic hybridization (aCGH) was performed (in the patient only) using a 135K-feature whole-genome microarray (SignatureChip Oligo Solution™, custom-designed by Signature Genomic Laboratories, made by Roche NimbleGen, Madison, WI), according to previously described methods [Duker et al., 2010].

Fluorescence In Situ Hybridization (FISH) Analysis

Metaphase FISH analysis was performed using BAC clones RP11-587H3 from 19p12 and RP11-96A7 from 19q12 to visualize the abnormalities, according to previously described methods [Traylor et al., 2009].

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CLINICAL REPORT

The patient is a male infant, the first child of a healthy 39-year-old mother and 54-year-old father. The pregnancy was complicated in the last month by oligohydramnios. The mother had no history of medication or drug use. There was no family history of any malformation or mental retardation. The child was born by cesarean at 39.5 weeks gestation with a birth weight of 2,605 g (3rd–10th centile) and length of 46.5 cm (3rd–10th centile). The Apgar scores were 8 and 9. The neonatal period was complicated by lack of breast suction and mild hypotonia. Moderate to severe gastroesophageal reflux disease was diagnosed in the first month and was treated with medication until 8 months.

His developmental milestones were delayed as follows: he walked at 16 months of age, spoke a few words at 24 months and was toilet trained at 3–4 years old. Now at 4 years and 10 months of age he attends preschool and is reported to have a short attention span. He shows behavioral and social features of autism spectrum disorder: marked solitariness, poor ability to relate to others, stereotypic motor mannerisms and obsessive-compulsive behavior. At the age of 4 years, and following the DSM-IV behavioral criteria, neurological, and psychological evaluation showed he met criteria for the diagnosis of AS. He loves music and does not show any aggressive behavior.

At 4 years and 10 months physical examination showed a height of 110 cm (50th–75th centile), weight of 23.5 kg (90th centile) and head circumference of 50 cm (50th centile). His inner canthal distance was 2.8 cm (50th centile), and outer canthal distance was 8.2 cm (50th centile). He had a long face with a high nasal bridge and thin upper lip. No other dysmorphic features were noted. Neurological examination revealed diffuse mild hypotonia with normal deep tendon reflexes. Magnetic resonance imaging of the brain and ophthalmological examination were normal. An auditory brainstem response showed unilateral mild sensorineural hearing loss.

RESULTS

Conventional cytogenetic studies showed a sSMC in approximately 60% of cells, and aCGH (using a 135K-feature whole-genome microarray) showed partial trisomy of 18.4 Mb from 19p12q13.11, including approximately 10 Mb of non-centromeric material containing at least 55 genes (chr19:19,804,957-38,213,484, UCSC hg18 assembly; Fig. 1). No other significant copy number changes were detected by aCGH. FISH confirmed the trisomic material to be present on a sSMC in 43% (13/30) of metaphase cells.

DISCUSSION

We report on a 4-year-old boy with a mosaic sSMC derived from 19p12q13.11, diagnosed with AS, representing an apparently novel association between AS and this cytogenetic locus. Smaller 19q12 and 19q13.11 duplications have been reported in individuals with autism spectrum disorders, though the causative natures of these duplications have not been established [Szatmari et al., 2007; Christian et al., 2008]. There are five reports of well-characterized sSMCs derived from material within the 19p13.11q13.1 region in individuals without phenotypic abnormalities [Liehr 2010]. This overlaps with the sSMC found in our patient, though it is possible that our patient's sSMC contains additional 19q13.11 material that was not present in the one report of a benign sSMC containing this band [Tonnies et al., 2007]. Additionally, several individuals have been reported with similar sSMCs (derived from 19p12q12, 19p12q13.1, and 19p11q13.1) and phenotypic abnormalities [Liehr et al., 2006; Baldwin et al., 2008; Liehr, 2010]. While no patient has been reported to have an autism spectrum disorder, developmental delay was present in all of these individuals, including significant speech delays, and reported behavioral abnormalities include anxiety, impulsivity, and hyperexcitability [Liehr 2010].

The sSMC is likely causing the patient's features, given its size and genic content. While no genes on the sSMC can be directly related to AS, 30 of the genes involved encode zinc finger transcription factor proteins containing the Krüppel-associated box domain (KRAB). Members of this family are related to embryonic development, cell differentiation, cell proliferation, apoptosis, neoplastic transformation and cell cycle regulation, and are also quite conserved throughout evolution [Tian et al., 2006]. One of these genes, ZFP536, was reported as one of the two transcription factors which

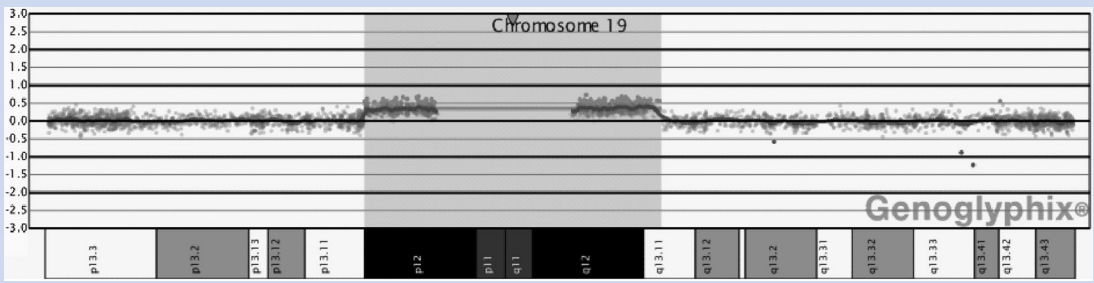

FIG. 1. Microarray and FISH characterization of a mosaic supernumerary chromosome derived from 19p12q13.11. Microarray plot showing a mosaic gain of 940 oligonucleotide probes from the pericentromeric region of chromosome 19 at 19p12q13.11 (chr19:19,804,957-38,213,484, UCSC March 2006 hg 18 assembly), approximately 18.4 Mb in size. Probes are ordered on the *X*-axis according to physical mapping positions, with the most distal p-arm probes to the left and the most distal q-arm probes to the right. Results are visualized using Genoglyphix software (Signature Genomic Laboratories, Spokane, WA).

are strongly regulated during the later phase of terminal oligodendrocytes differentiation in vitro, what makes ZFP536 an interesting candidate to have its relevance determined in AS [Dugas et al., 2006].

Many authors have attempted to correlate specific loci with AS, but no recurrent loci have been found [Chodirker and Chudley, 2008]. Possible explanations are that chromosomal abnormalities reported in patients with AS (including in this work) are more coincidental than causative, that different loci exist for different endophenotypes in AS, or that these different loci are related through a heretofore unrecognized pathway. Further replication of partial trisomy 19p12q13.11 in association with AS in other populations is needed to clarify the syndrome's etiology.

ETHICAL STANDARDS

Written informed consent was obtained from all participants, and the study was approved by the PUCPR Ethical Committee.

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