A complex chromosomal rearrangement in a child with developmental delay, fractious behavior, and craniofacial anomalies, compatible with Smith-Magenis Syndrome


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INTRODUCTION

Smith-Magenis syndrome (SMS) (OMIM No 182290) is a mental retardation syndrome characterised by behavioral abnormalities, including self-injurious behavior, sleep disturbance, and distinct craniofacial and skeletal anomalies. It is usually associated with deletion involving 17p11.2 and is estimated to occur in 1 in 2,500 births. Approximately 90% of cases are leading to protein truncation in retinoic acid-induced gene 1 (RAI1) have been identified in some individuals with phenotypic features consistent with SMS. RAI1 lies within the 17p11.2 locus, but these patients do not have 17p11.2 deletions. Complex chromosome rearrangements (CCRs) are structural chromosome anomalies involving >2 chromosomes or >2 breakpoints. Evaluation of CCRs and their potential phenotypic consequences is a common challenge in the genetics clinic and knowledge about the genotype-phenotype relationships is limited.

METHODS

We report the case of a 14-year-old boy who was referred by SMS, presenting mental developmental delay, fractious behavior, reduced sensitivity to pain, macrocranium, speech delay, and distinctive facial features with macrocephaly, macroretrocollis, and low eye implantation.

The karyotype and fluorescence in situ hybridization (FISH) using WCP specific probes for the chromosomes involved in CCR and the probe D17S258 (17p11.2 probe) for SMS region was performed by standard methods.

Chromosomal Comparative Genomic Hybridization (cCGH) and, lately, microarray studies (array Comparative Genomic Hybridization (aCGH) were performed in order to identify genetic imbalances in the CCR breakpoints.

RESULTS

The cytogenetic analysis revealed a karyotype: 46,XY,del(17)(q11.2→q21.3), −17, +mar(17)(−);the microarray analysis revealed the presence of CCR involving chromosomes 3, 10 and 14 (Figures 1 and 2).

Parental karyotypes were normal, although the father presented a marked cognitive delay.

FISH analyses allowed no deletion in 17p11.2 region and confirmed the cytogenetic results, namely the presence of CCR involving chromosomes 3, 10, and 14 (Figures 3, 4, and 5). FISH also allows to elucidate this involvement of other chromosomes in CCR.

cCGH showed the no existence of gains or losses in CCR breakpoints as well as in other chromosomes. Genomic microarray studies did not reveal any gains/losses of genetic material in the breakpoints regions. The whole genomic array study shows the existence of two losses (2q23.3 and 22q11.21), and one gain in 10p26.3. In the deleted region of chromosome 2 there are no localized genes. In the deleted region of chromosome 22 there is the gene (22q11.23/Tango), not associated to phenotypic alterations. In the duplicated region of chromosome 10 there are localized various genes, with no knowledge of direct association with phenotypic alterations (Figure 6).

DISCUSSION

The diagnosis of SMS is usually based on clinical findings and confirmed by detection of an interstitial microdeletion of 17p11.2 (ranging from 1.5 to 9 Mb, e.g. 5.7-Mb) that is present, in approximately, 95% of SMS cases. In this patient, despite the distinctive clinical features of SMS, deletions or duplications in the SMS critical region were not detected neither by FISH nor by CGH. It has been reported, however, that a small number of SMS present a mutation in the RA1 gene (instead of a 17p11.2 deletion;Figure 7).

In addition, the analysis of the clinical data in SMS corroborates the idea that there are very similar phenotypes among patients with a 17p11.2 deletion and those with a mutation in the RA1 gene.

In the present case, short stature, cardiac and renal anomalies were not observed, which is compatible with the phenotype reported in individuals with a RA1 heterozygous frameshift mutation. However, this could not be confirmed for this patient because sequencing is still to be performed. On the other hand, chronic ear infections, speech delay, and dental anomalies, similar to those observed in our case, are more frequent in cases of del(17p11.2). The patient has been absent of routine clinical reevaluation and treatment. Management of SMS is primarily a multidisciplinary approach and involves treatment for sleep disturbance, speech and occupational therapies, minor medical interventions, and management of behaviors.

On the other hand, a CCR was identified in the present case. It is known that in CCRs de novo, an apparently balanced karyotype may be associated with an abnormal phenotype, including an increased risk of intellectual delay and congenital malformations. These rearrangements can cause disease by physically disrupting genes or altering their regulatory environment. The finding that 23% of the CCRs, although apparently balanced, have been ascertained among individuals with multiple congenital anomalies and/or mental retardation, and that among those with de novo occurrence, more than half have been found in individuals with phenotypic abnormalities, also suggests that imbalances may be a common finding. However, the identified CCR is not a satisfactory explanation for the patient phenotype given that no imbalances were observed by the applied methods.

Additionally, following microarrays analysis, two losses (2q23.3 and 22q11.21) and one gain in 10p26.3 were identified. In the deleted region of chromosome 2 there are no localized genes. In the deleted region of chromosome 22 is present the gene (22q11.23/Tango), not associated to phenotypic alterations. In the duplicate region of chromosome 10 there are localized various genes, with no knowledge of direct association with SMS at the present data.

Flow chart followed for the study case at present data

REFERENCES