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Clinical report

A three-generation family with terminal microdeletion involving 5p15.33–32 due to a whole-arm 5;15 chromosomal translocation with a steady phenotype of atypical cri du chat syndrome

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ABSTRACT

Cri du chat syndrome is characterized by cat-like cry, facial dysmorphisms, microcephaly, speech delay, intellectual disability and slow growth rate, which are present with variable frequency. The typical cri du chat syndrome, due to 5p15.2 deletion, includes severe intellectual disability, facial dysmorphisms, neonatal hypotonia and pre- and post-natal growth retardation, whereas more distal deletions in 5p15.3 lead to cat-like cry and speech delay and produce the clinical picture of the atypical cri du chat syndrome, with minimal or absent intellectual impairment. In this article we report a three-generation family with an unbalanced whole arm translocation between chromosome 5 and 15 and a microdeletion of 5.5 Mb involving 5p15.33–32. By reporting the smallest terminal deletion of 5p15.3 described so far and by reviewing the literature we discuss the genotype/phenotype correlations of the distal region of the cri du chat syndrome. The previously described critical region for the speech delay may be narrowed down and microcephaly, growth retardation and dysmorphic facial features can be included in the phenotypic expression of the atypical cri du chat syndrome due to 5p15.3 deletions.

1. Introduction

Deletions of variable size of the short arm of chromosome 5 cause the cri du chat syndrome (CdCS, OMIM 123450), a well-defined clinical condition characterized by a cat-like cry in infancy and a variety of physical and psychomotor symptoms such as low birth weight, slow growth rate, facial dysmorphisms, microcephaly, speech delay, intellectual disability (ID) and behavioural disorders, which are present with variable frequency [Cerruti Mainardi, 2006].

Several studies have associated the number of features present in the phenotype with the extent of the genomic deletion, defining that specific characteristics of CdCS, including severe ID, facial dysmorphisms, neonatal hypotonia, pre- and post-natal growth retardation, are due to 5p15.2 deletion, whereas cat-like cry and speech delay have to be ascribed to a more distal deletion in 5p15.3 [Cerruti Mainardi, 2006; Gersh et al., 1995; Overhauser et al., 1994; Wu et al., 2005].

Analysis of the cases published so far shows that CdCS is mainly a sporadic condition, whereas familial cases, due to the transmission of small deletions or unbalancing of parental rearrangements, account for about 10–15% of the total CdCS burden [Cerruti Mainardi et al., 2001].

In the present report we characterize on the clinical and molecular grounds a three-generation family with an unbalanced whole arm translocation between chromosome 5 and 15 resulting in a deletion of 5.5 Mb of 5p15.33–32 and, by reviewing the literature, we discuss the genotype/phenotype correlations of the distal region of the CdCS [Church et al., 1995; Cornish et al., 1999; Gersh et al., 1995; Kondoh et al., 2005; Laczmanska et al., 2006; Rossi et al., 2005; Van Buggenhout et al., 2000; Zhang et al., 2005].

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2. Clinical report

2.1. Patients

The probands are a caucasian male and female twins (III:2 and III:3, Fig. 1) from a second pregnancy of unrelated apparently healthy parents with unremarkable family history for genetic diseases. The mother was 30 years old at birth, the father was 33. After a normal pregnancy induced by FIVET, the twins were born at the 35th week by cesarean section. APGAR score was 5 and 7 at the 1st and 5th minute for the boy and 6 and 8 at the 1st and 5th minute for the girl. Parameters at birth, calculated on twin-specific growth charts [Hall et al., 2006], were the following: length 42 cm (2nd–10th centile), weight 2050 gr (25th–50th centile), head circumference 31 cm (10th–25th centile) for the boy and length 47 cm (75th–90th centile), weight 3000 gr (between the 75th–90th centile), head circumference 31.5 cm (25th–50th centile) for the girl. Scrotal-type hypospadia was diagnosed to the boy, whereas the girl's physical examination was unremarkable. They both presented neonatal hypotonia that fully recovered after the first two months of life (the girl, due to poor sucking and feeding difficulties, was fed by nasogastric tube for the first 2 months of life). At the follow-up visits (3, 6, 12 and 18 months) both children presented growth delay (height, weight and cranial circumference were under the 0.4th centile in all the measurements): at the last assessment at 24 months the boy was 77 cm tall, weighed 8450 gr and had a cranial circumference of 44.5 cm (all under the 0.4th centile); the girl was 78,2 cm tall, weighed 8850 g and had a cranial circumference of 44 cm (all under the 0.4th centile). Clinical history was unremarkable for the girl whereas the boy had presented recurrent respiratory infections and pneumonia during the first year of life. Developmental milestones were the following: at 3 months they developed head control, at 8 months they could sit unsupported, at 16 months they walked, at 21 months they could pronounce a few syllables and at the assessment of the 24 months the girl had a language equivalent to 22 months and the boy to 20 months, according to the Griffiths mental development scales [Huntley, 1996]. At the last follow-up visit at 24 months, the neurological development was found normal for both. Their behaviour is sociable with other children and adults. Common features of the two twins were the presence of a high-pitched cry and facial dysmorphisms: small round face, high arched eyebrows, synophris, epicanthal folds, hypertelorism (interpupillary distance: 5.5 cm, >97th centile), broad nasal bridge, upturned nasal tip, prominent ears, thin upper lip and pointed chin. Moreover, the boy presented left ptosis whereas the girl had a mild strabismus, a flat occiput, a high palate and a single palmar crease.

The twins' older sister (III:1, Fig. 1) was born from an uneventful pregnancy induced by FIVET and she had an unremarkable clinical history until the siblings came to our attention (she was 7 years of age). At 7 years of age her height was 113 cm (between the 2nd and the 9th centile), the weight was 20 kg (between the 9th and the 25th centile) and the cranial circumference was 50.5 cm (10th centile); she presented mild strabismus, high-pitched voice and dysmorphic features, including round face, high arched eyebrows, synophris, epicanthal folds, hypertelorism (5.8 cm, >97th centile), broad nasal bridge, upturned nasal tip, thin upper lip, and pointed chin. By questioning the developmental milestones no hypotonia or motor or language delay were reported. She attends the first class of primary school with normal performance.

Data about neonatal and paediatric records of the father (II:1, Fig. 1) are more scanty: he was born at 38 weeks of gestation with a birth weight of 2700 g (10–25th percentile) and had normal psychomotor and language development. At the time of our evaluation he shows short stature (163 cm, 2nd centile),

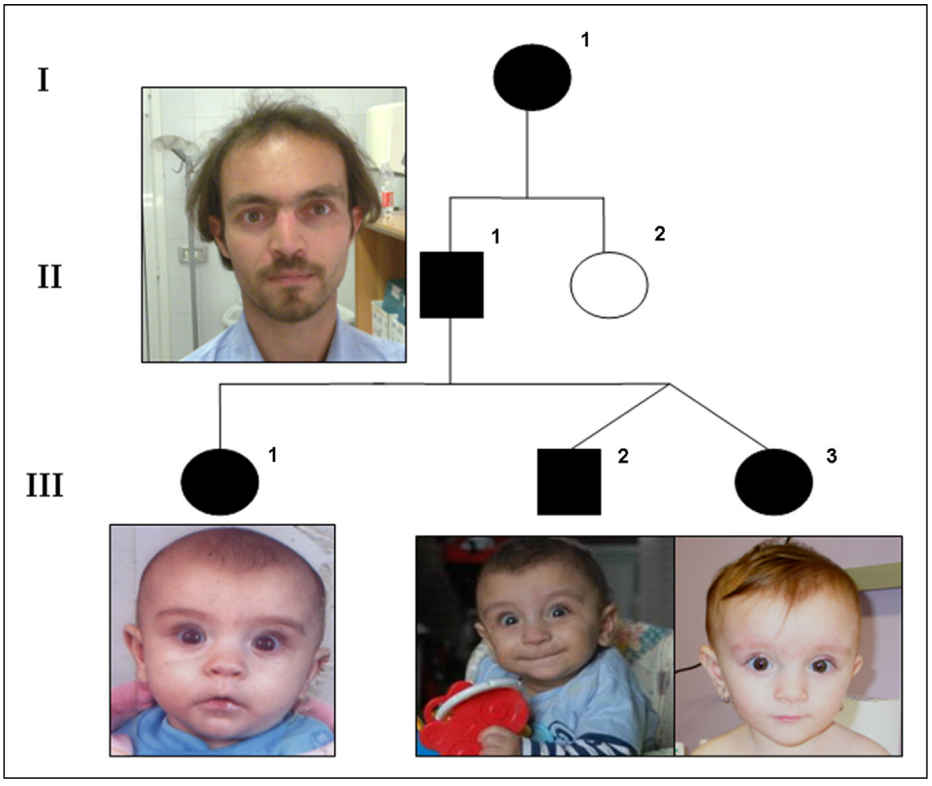

Fig. 1. Pedigree of the three-generation family with der(5)t(5;15)(p15.3;q11.1-2) with microdeletion involving 5p15.33–32; black box indicates affected subject.