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Case study

Chromosome 17q21.31 duplication syndrome: Description of a new familiar case and further delineation of the clinical spectrum

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ABSTRACT

Introduction: 17q21.31 microduplication syndrome is a recently described condition associated with a broad clinical spectrum, of which psychomotor delay, behavioral disorders and poor social interaction seem to be the most consistent features. Only seven patients have been reported thus far. All have behavioral disorders reminiscent of the autistic spectrum with intellectual skills ranging from normal to mild intellectual deficiency. Other features are variable with no striking common phenotypic features.
Case study: Here we describe the segregation of 17q21.31 duplication in an Italian family.
Discussion: Clinical features and genetic data are reported, and compared with previously reported patients with 17q21.31 microduplication. A comparison of clinical manifestations between deletion and duplication syndromes of the chromosome regione is provided.

1. Introduction

Chromosome 17q21.31 microduplication syndrome was described for the first time in 2007. Kirchhoff et al.[1] reported a 10 year old Moroccan girl with severe psychomotor delay who was found to have a *de novo* 485-kb duplication at chromosome 17q21.31. She presented with facial dysmorphism, short stature, microcephaly, abnormal digits, and hirsutism. Brain imaging was normal. The duplication encompassed the *MAPT* and *CRHR1* genes and was reciprocal to a previously described 17q21.31 microdeletion, associated with a recognizable clinical phenotype.[2] Chromosome 17q21.31 deletion syndrome was subsequently reported to be a single gene disorder, caused by haploinsufficiency of *KANSL1* gene, and

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characterized by moderate-to-severe intellectual disability, hypotonia, friendly behavior and highly distinctive facial features.[3,4]

In 2009 Grisart et al.[5] reported 4 unrelated individuals with different duplications of chromosome 17q21.31 also identified by array-CGH analysis. The patients ranged in age from 6 to 18 years and all had some degree of psychomotor retardation and poor social interaction with communication difficulties reminiscent of autism spectrum disorder. Other phenotypic observations were rather variable. The size of these duplications ranged from 585 to 763 kb. Three patients with complete familial testing available exhibited *de novo* duplications, all of which occurred on the maternal chromosome.

In 2012 Kitsiou-Tzeli et al.[6] reported a sixth case. The patient was an 18 year old girl with a history of delayed psychomotor milestones, behavioral problems and poor speech. She differed from the known reported cases since she had severe obesity, global hirsutism and outbursts of temper. The girl carried a 695 Kb microduplication in the 17q21.31q21.32 chromosomal region, associated with a 413 kb 15q11.2 microdeletion which was paternally inherited. The father has bipolar disorder, while his brother, who has not been tested, has been diagnosed with schizophrenia, further confirming the variable effects of the 17q21.31 microduplication. It should however be noted that neither the father nor his brother exhibits any other phenotypic manifestations.

In 2014 Mc Cormack et al.[7] reported the seventh patient, bearing a 17q21.31 microduplication together with a 7q31.33 microdeletion. No parental studies were performed. The patient is a 7.5 year old girl with microcephaly, developmental delay and mild dysmorphic features.

2. Case study

Our patient is an 8 year old girl, the first of two children of unrelated Italian parents. Her younger brother is healthy.

Family history is positive for behavioral problems and intellectual disability in the mother's branch (Fig. 1). The mother herself [III-4] has an history of mild developmental delay in childhood associated with microcephaly. She attended compulsory education schools with poor performance, and now is a housewife. She is reported by her family to be an anxious person, with poor social interaction. At clinical evaluation occipitofrontal circumference (OFC) was 52.5 cm (3–10th centile), weight was 67 kg (90th centile) and height was 165 cm (75th centile). Moderate signs of a generalized anxiety disorder were detectable, especially regarding unexpected events or social situations, but without any specific phobia, panic attack or compulsive behavior.

The mother's brother [III-5] was reported to have intellectual disability (unspecified degree), behavioral disturbance and irritability with temper outburst. However, conduct problems never required pharmacological treatment since aggressiveness was infrequently reported. His OFC was 55 cm (50th centile), weight 79 kg (90–97th centile) and height 168 cm (10–25th centile). Mild dysmoprhisms were present (i.e. malar flattening, puffy eyelids, donwslanting palpebral fissures, short nose).

No additional intellective evaluation nor psychological questionnaire were possible, since patient's mother and uncle refused any further assessment.

The maternal grandmother [II-13], deceased because of lung cancer at 65 years of age, had, according to reports of family members, behavioral disturbances, irritability and aggressiveness. Her father [I-7], with psychiatric problems, died in a mental hospital.

The father of our proband is in good health, without any remarkable medical history, except for an isolated mild delay in his walking milestones during childhood.

Our proband was born at term (41 weeks), after an uneventful pregnancy. Birth weight was 3530 g (50th centile), length was 48 cm (<10th centile), and OFC was 33 cm (<10th centile). Her growth curves profiles were always at the upper limit both for height and weight for age. At 2 years of age, because of an Achilles tendon retraction, she underwent surgery for tendon lengthening. Her psychomotor development was characterized by trunk control at 6–7 months and independent walking at 2.5 years. First words were reported at 12 months.

The child came to our attention for the first time at the age of 4 years for psychomotor retardation. By the time she was 6, she was overweight (34 kg; >97th centile), with height 124 cm (90–97th centile) and microcephaly (OFC 48,5 cm; <3rd centile). Her general health was good but she exhibited obvious facial dysmorphism, including palpebral fissures slanted

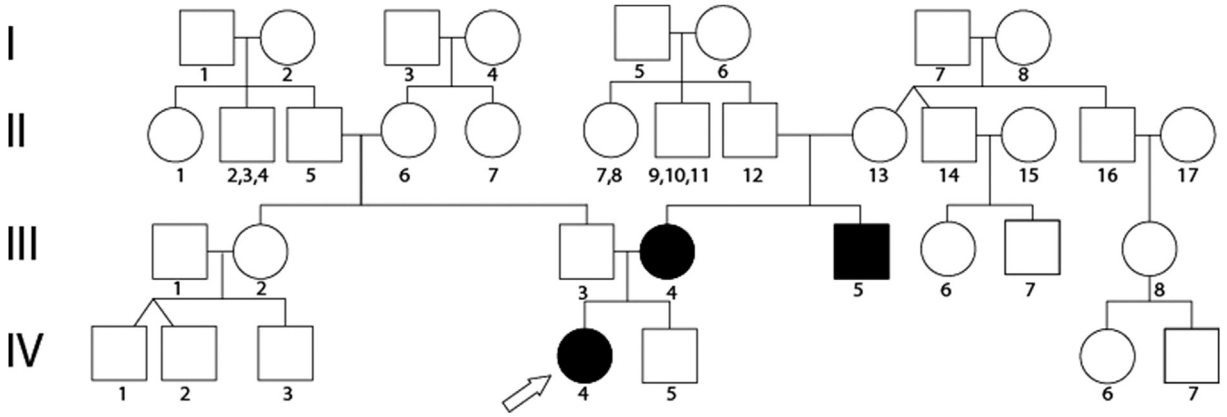

Fig. 1 – Segregation of 17q21.31 microduplication in the family.