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Original article

Cytogenetic and molecular characterization of a *de-novo* t(2p;7p) translocation involving *TNS3* and *EXOC6B* genes in a boy with a complex syndromic phenotype

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Abstract

We describe a premature newborn child with left renal agenesis, right low functional kidney, altered chemical-clinical parameters, neutropenia, recurrent pulmonary infections, long bone diaphysis broadening, growth and developmental delay. Postnatal cytogenetic analysis revealed a 46,XY,t(2;7)(p13;p12) *de-novo* karyotype. The chromosome breakpoints were defined by FISH using BAC probes and initially restricted to about 123,000 bp in 2p13 and delimited to 84,600 bp in 7p12. Bioinformatic analysis of these genomic regions showed two genes that are involved in the rearrangement: exocyst C6B (*EXOC6B*) for chromosome 2 breakpoint and tensin3 (*TNS3*) for chromosome 7 breakpoint. A *EXOC6B-TNS3* fusion transcript together with a reciprocal *TNS3-EXOC6B* chimeric RNA have been detected by RT-PCR performed on skin fibroblasts RNA of the proband. These data localize the chromosome 2 breakpoint within the first intron of *EXOC6B*, while the translocation event on chromosome 7 occurred in intron 15 of *TNS3*. We hypothesize that the phenotype observed in the patient results from one or several mechanisms including: haploinsufficiency of *EXOC6B* and *TNS3* genes; a dominant

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negative effect exerted by the chimeric transcripts; a disregulation in the expression of other genes adjacent the breakpoints. Although no clear evidences exist supporting a role of any of the above mentioned mechanisms in the pathogenesis of the complex phenotype, immunofluorescence analysis of tensin1 in the patient's fibroblasts suggests that the *TNS3* gene haploinsufficiency results in a reduced expression of tensin1. These cells may be therefore a model for understanding the role and the organization of the tensin protein family.

Keywords: Balanced chromosomal translocation; *EXOC6B*; Fusion transcripts; Renal agenesis; *Tensin*; *TNS3*

1. Introduction

Chromosomal translocations appear rarely (1:1000) and 50% of the subjects with an apparently balanced *de novo* translocation are phenotypically abnormal [9,14]. The cytogenetic and molecular characterization of balanced chromosomal translocations has facilitated positional cloning of genes that are disrupted or mutated in monogenic diseases such as Duchenne muscular dystrophy, neurofibromatosis-1, neurofibromatosis-2, campomelic dysplasia, and Wilm's tumour/aniridia [26]. In a number of instances an individual carrying a balanced translocation presents a complex phenotype that does not resemble any previously described mendelian disease.

In this study we describe the case of a baby with unilateral renal agenesis, neutropenia, recurrent pulmonary infections, long bone diaphysis broadening, growth and developmental delay. Chromosomal analysis showed that the patient had a *de novo* reciprocal balanced translocation, t(2;7)(p13;p12). One of the peculiar clinical features of the proband is the unilateral renal agenesis (URA). Renal agenesis, or congenital absence of the kidney, is defined as the complete absence of renal tissue resulting from failure of embryonic development of the metanephros [27]. URA is a relatively common congenital urinary malformation. The reported incidence of URA varies from 1 in 500 to 1 in 3200. The discrepancies in the reported incidence may be related to sample sizes, diagnostic methods, selected populations, or ethnic differences. The incidence of URA is higher in males. The male-to-female ratio is reported to vary from 1.2 to 2.3:1. The predominance in males may reflect the earlier differentiation of the Wolffian duct that takes place close to the time of bud formation. The uretral bud is more likely to be influenced by abnormalities of the Wolffian duct than abnormalities of the Mullerian duct, which develops later in fetal maturation. Anomalies outside the renal tract are often associated with URA. Dursun et al. detected non-urological anomalies in 44% of 87 cases of congenital solitary functioning kidneys, with cardiac and gastrointestinal malformations being the most common [7]. A number of multiorgan syndromes with genetic bases associated with URA have been also described in the literature [27] but none recalls the clinical manifestations of the proband in our study.

We report the detailed physical mapping of the translocation breakpoints involving the chromosome 2 gene exocyst *C6B* (*EXOC6B*) and the chromosome 7 gene tensin3 (*TNS3*). Both *TNS3-EXOC6B* and *EXOC6B-TNS3* fusion transcripts were detected as a result of the translocation in the patient.

We hypothesize that the described reciprocal translocation with its molecular consequences is of functional importance for the clinical manifestations in the patient.