Reduced cajal body number in a patient haploinsufficient for COIL

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Introduction
In this study we present a child and his mother who are both carriers of an apparently balanced translocation t(11;17) and with similar clinical symptoms including developmental delay, long face and bulbous nose, proximal symphalangism, bilateral cutaneous syndactyly of 2nd and 3rd toes and mild scoliosis. At the chromosome 17 breakpoint we revealed presence of a microdeletion, which includes among others COIL, NOG and MS2 genes. COIL encodes for p80 coilin, the molecular marker of the Cajal Bodies (CBs), which are subnuclear domains that contain a wide variety of components, including factors involved in splicing, pre-rNA processing, histone pre mRNA 3’ maturation as well as transcription factors (1). CBs have recently been implicated in the assembly and/or modification of the RNA-processing machinery (2). NOG encodes for noggin and is essential for cartilage morphogenesis and joint formation (3). MS2 (musashi 2) encodes an RNA binding protein that regulates the expression of target mRNAs at the translation level and is thought to play a role in the proliferation and maintenance of stem cells in the central nervous system (4).

Results
Cytogenetic analysis of the mother and the child revealed an apparently balanced translocation t(11;17)(p15.5;q23.2). We mapped both chromosome breakpoints with FISH using BAC clones and revealed a -296 deletion at 17q23.2 (Fig.1). This microdeletion spans 16 known genes, including COIL, NOG, and MS2 (Fig.2).
We investigated the Cajal body number of the transformed lymphoblastoid cells, and the patient CBs were present in only ~2.5% of the cells, as opposed to ~34% in the control cell-line (Fig.3). These results suggest that haploinsufficiency of COIL gene leads to reduced number of Cajal bodies.

Discussion and Conclusion
The phenotypes of the patients may be explained by haploinsufficiency of the genes deleted at 17q23.2. One of the genes deleted from this region is COIL. Deletion of exon 2-7 of COIL led to reduced viability in homozogous mice (5). The mouse knockout model has shown that full-length coilin is essential for proper formation and maintenance of CBs and recruitment of snRNP and SMN complex proteins to CBs (5). If Cajal Bodies, key organelles involved in RNA processing in general, are in significantly lower numbers, main molecules necessary for RNA processing may be absent or reduced, resulting in alterations in RNA-splipping and transcription. The reduction of CBs in the patients suggests that haploinsufficiency of COIL could have phenotypic consequences. The limb defects (symphalangism, syndactyly) are consistent with the deletion of NOG, mutations of which are associated with symphalangism (3). Similarly, mental retardation may be caused by any of the unknown genes including MS2, which is expressed during CNS development of in mice (4).

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