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Uniparental disomy of chromosome 16 as a cause of primary ciliary dyskinesia

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INTRODUCTION

Primary Ciliary Dyskinesia (PCD) is a rare genetic condition affecting cilia structure and function[1]. Patients manifest chronic respiratory infections beginning in early childhood, with or without abnormally positioned internal organs and infertility. About 50 genes have been described, almost all with an autosomal recessive inheritance[2]. We present a patient with neonatal respiratory distress, *situs inversus*, cough and mucus production.

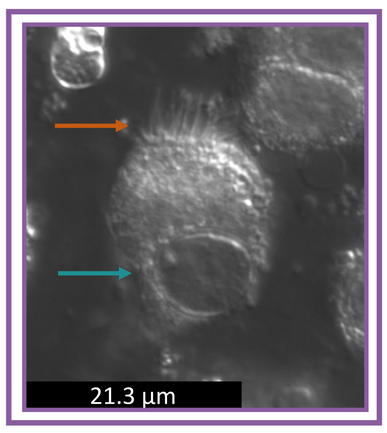

Figure 1. Epithelial nasal cell under x60 magnification. Cilia are pointed with an orange arrow and the nucleus with a blue.

METHODS

Ciliary beat pattern and ultrastructure were studied on samples of nasal curettage using a high-speed camera accoupled to an inverted microscope and electronic microscopy (EM) respectively. Clinical Exome (CE) was sequenced from blood samples and detected variants were classified according to the ACMG guidelines[3]. Segregation analysis of the candidate variant was assessed with Sanger sequencing. Finally, CytoScan HD trio array (Affymetrix) was carried out to seek copy number variants and runs of homozygosity (ROH).

Keywords:

Ciliary epithelial cells | Respiratory disease | Nasal biopsy | *DNAAF1* | Uniparental disomy

RESULTS

Beat pattern study revealed immobile cilia while EM showed outer dynein arm absence. CE detected the c.1300_1322del;(p.(Gly434Profs*4)) pathogenic variant in the autosomal recessive *DNAAF1* gene in homozygous state. This gene is linked to PCD type 13 (OMIM #613193), with an autosomal inheritance fashion. Segregation analysis failed at detecting this variant in the father (Fig. 2), but paternity was genetically confirmed. Finally, the SNP-array revealed two ROH of 38.73Mb and 6.68Mb at 16p11.2-16q22.1 and 16q23.3-16qter respectively (Fig. 3). The *DNAAF1* gene is located at 16q24.1, thus explaining the homozygous state of the detected variant as a result of a segmental maternal uniparental isodisomy (UPiD(16)).

Figure 2. Electropherogram showing Sanger sequencing results. Yellow background shows the homozygous frameshift in the index case. In the mother the double peak indicates the heterozygous deletion. No deletion was found in the father's sample.

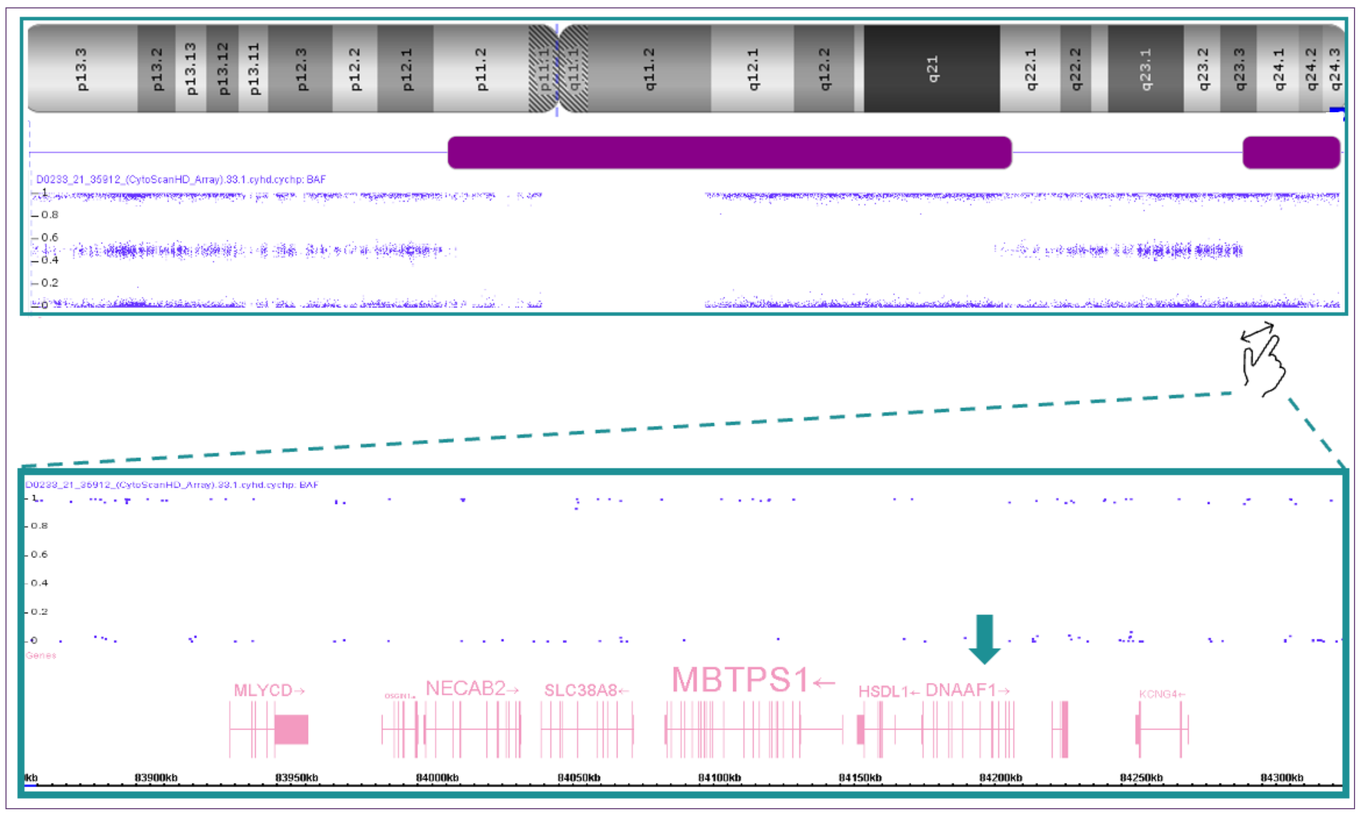

Figure 3. SNP-array results of the patient showing chromosome 16. Chromosome 16 is represented at the top and detected ROH are marked in purple. B-allele frequency (BAF) plot represents the SNP genotype. Following the formula: [B]/[A] + [B] BAF plot graphics homozygous AA SNPs with a score of 0, BB SNPs with 1 and heterozygous AB SNPs with 0.5[4]. Two big regions of homozygosity were detected involving cytobands 16p11.2-16q21 and 16q23.3-qter. Zooming at the telomeric ROH (bottom of the figure) the *DNAAF1* gene is found (blue arrow).

CONCLUSIONS

- PCD is a genetically heterogeneous disorder caused by defects in ciliary structure and function.
- Here we describe the first PCD patient due to a UPD of chromosome 16.
- This information is crucial for genetic counselling in terms of recurrence risk.

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