Sleep disordered breathing in a child with cherubism

Cherubism is a rare disorder with bilateral enlargement of the mandible that regresses with time. Bone degrading osteoclasts and bone building osteoblasts function abnormally causing the changes. It is an autosomal dominant condition which manifests in early childhood by the age of 2–5 years, but later regresses with time. Airway obstruction occurs due to backward displacement of the tongue affecting respiration.

An 18 year old male was referred to us for snoring. On inquiry the mother reported snoring of the lower face since childhood, which had progressed to its present size. The patient had difficulty in speech, mastication, and swallowing with mental retardation. There was a history of excessive daytime somnolence, nocturia, and increased irritability during the previous few years. On examination he had characteristic features of cherubism. The lower eyelids were retracted and his oral examination revealed gingival hypertrophy with most of the upper and lower teeth embedded in the gums. The tongue was enlarged and the posterior pharyngeal wall could not be visualised. Fine needle aspiration biopsy of the mandible revealed the presence of normal tissue, with most of the upper and lower teeth embedded in the gums. The tongue was enlarged, and the posterior pharyngeal wall could not be visualised.

Reference


Genotype-phenotype correlations in PCD patients carrying DNAHS mutations

Primary ciliary dyskinesia (PCD) is usually inherited as an autosomal recessive disorder. Affected individuals suffer from recurrent infections of the upper and lower respiratory tract due to reduced mucociliary clearance. Half of the affected offspring exhibit a complete situs inversus because of randomisation of left-right body asymmetry. 1 The PCD phenotype results from axonemal abnormalities in cilia and flagella. Total or partial absence of dynein arms are found in 70–80% of PCD cases. 2

PCD represents a heterogeneous group of genetic disorders. Distinct PCD loci have been mapped to chromosome 9p13-21 (DNAI), 19q13.3-qter and 5p15-p14, respectively. We identified DNAHS as the gene responsible for PCD located on 5p. DNAHS encodes a protein highly similar to the Chlamydomonas orthologue show a slow swimming phenotype and are characterised by axonemal abnormalities consisting of outer dynein arm (ODA) defects. 3 This phenotype appears similar to that observed in a large Arab family
used to map the PCD locus. Sequence analysis of the DNAH5 gene in PCD patients with randomisation of left-right asymmetry identified mutations resulting in non-functional DNAH5 proteins.

The murine orthologue of human DNAH5, called Dnahc5, is predominantly expressed in the lung as shown by Northern blot analysis. During gastrulation expression is confined to the node, which explains the randomisation of left-right asymmetry in PCD. Mice with a targeted mutation in Dnahc5 display a phenotype highly similar to that observed in patients with PCD. Dnahc5 deficient mice develop respiratory symptoms due to reduced mucociliary clearance, and half of the affected offspring have complete situs inversus.

In order to gain insight into the development of the disease phenotype and the function of DNAH5, we have studied the expression of Dnahc5 in the murine respiratory tract in both embryonic and adult tissue of mice using section in situ hybridisation analysis as described previously. We found that Dnahc5 expression is confined to ciliated epithelial cells of the upper and lower airways (fig.1A–H). This expression pattern is consistent with the PCD phenotype of humans resulting from mutations in DNAH5 and mice with a targeted disruption of Dnahc5, respectively.

Our expression data strongly suggest that ultrastructural abnormalities resulting from DNAH5 mutations should be present in ciliated respiratory epithelia of the nasopharynx, the larynx, and the bronchi. Sampling of respiratory cilia at different sites of the airway should not therefore affect ultrastructural findings caused by DNAH5 mutations.

Individuals of different PCD families exhibit various degrees of respiratory symptoms. We hypothesised that the severity of the disease phenotype might correlate with the molecular nature of the DNAH5 mutation in a family. Ultrastructural analysis of respiratory cilia in three families carrying homozygous mutations of DNAH5 indicated such a genotype-phenotype correlation. Electron microscopic photographs of respiratory cilia from families F373 and F658 have been reported previously and were compared with ultrastructural findings of the UNC-7 family.

Mutations causing premature translational termination of DNAH5 (1855NfsX5, 2814fsX1) result in a complete absence of all ODA in respiratory cilia (fig.11–K). In contrast, a splice site mutation predicting a loss of exon 75 (IVS74–1G>C) did not cause total absence of ODA. We semiquantitatively assessed ciliary axonemes from the affected siblings of UNC-7 for the presence of ODA in a blinded manner (n=36 cilia for one sibling, n=9 from the other). Both siblings had shortened stubby ODA compared with normal. Computer aided quantitative measurement showed that 54% of the ODA were less than half the average length of ODA in normal subjects, which indicates partial ODA deficiency.

We provide evidence for the first genotype-phenotype correlation in PCD. DNAH5 mutations should be considered in individuals with total and partial absence of ODA.

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