Sleep disordered breathing in an adult 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 swelling 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.

In addition to skin and/or eye lesions. We report a case of sarcoidosis presenting as upper extremity venous thrombosis.

A 39 year old woman presented with sudden swelling of the right upper limb and right side of the neck and face. She reported no cough, dyspnoea, chest pain, or systemic symptoms of fever or weight loss. She had no previous medical history, smoked 20 cigarettes daily, and was on an oral contraceptive pill (levonorgestrel, Schering Health Care Ltd). On examination her body mass index was 31. She had extensive swelling of the right upper limb and right side of the neck and face. Her upper limb pulses were normal and she had no palpable lymphadenopathy.

Figure 1 CT scan of thorax showing thrombosed right brachiocephalic vein as indicated by arrow and mediastinal lymphadenopathy.

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Reference


Genotype-phenotype correlations in PCD patients carrying DNACHS 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. 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.

PCD represents a heterogeneous group of genetic disorders. Distinct PCD loci have been mapped to chromosome 9p13-p21 (DNAH5, 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 γ-dynein heavy chain. Mutants of the Chlamydomonas orthologue show a slow swimming phenotype and are characterised by axonemal abnormalities consisting of outer dynein arm (ODA) defects. This phenotype appears similar to that observed in a large Arab family.

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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 (1855delA, 2814delX) result in a complete absence of all ODA in respiratory cilia (fig1–K). In contrast, a splice site mutation predicting a loss of exon 75 (JVS74+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 both total and partial absence of ODA.

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**Figure 1** In situ hybridisation analysis of mouse Dnahc5 expression in the developing and adult respiratory system and ultrastructural defects in patients with PCD carrying DNAH5 mutations. **(A)–(F)** Section in situ hybridisation analysis of Dnahc5 expression in mouse 16 days post coitum embryos. Photographs show details of expression in the nasopharynx, larynx and trachea, respectively. Note cilia on epithelial cells in C (white arrows). **(G), (H)** Section in situ hybridisation analysis of Dnahc5 expression in mouse adult lung. Note epithelial expression in the whole bronchial system. **(I)** Electron micrograph of a cross section of a respiratory cilium from an affected individual from PCD family F658. Absence of outer dynein arms (ODA) is observed on all of the nine peripheral doublets. **(J)** Electron micrograph of a cross section of a cilium from the respiratory epithelium of an affected individual of PCD family UNC-7. The number of visible ODA on the peripheral doublets is reduced. The remaining ODA are shorter (arrows). **(K)** Electron micrograph of a cross section of a respiratory cilium from a healthy individual (control). Arrows indicate the location of ODA.

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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 IA–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
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