Primary ciliary dyskinesia with normal ultrastructure

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Case study – Subject DNAH11 #8

Asian female with a clinical phenotype of chronic productive cough and rhinosinusitis with CT evidence of bronchiectasis, in both lower and middle lobes, at point of diagnosis [aged 10 years]. The patient repeatedly isolates *H. influenza* and intermittently *S. aureus.* This patient has poor adherence with treatment and had reduced pulmonary function tests from the point of diagnosis with FEV1 ranging from 50-61% predicted despite multiple admissions for intensive physiotherapy and intravenous antibiotics.

Nasal nitric oxide 52nl/min (PCD ordinarily <77nl/min).

The nasal brushing sample showed several de-nuded strips of epithelium with copious mucus and evidence of bacterial infection. Ciliary beat pattern was mixed, some areas had preserved movement but were stiff at the base, others had a weak residual movement, some areas were static. Large range of ciliary beat frequencies (0-16Hz).

Electron microscopy revealed a small sample with de-nuded epithelium and only 25 cross sections for assessment. Those counted showed 80% normal ultrastructure, 16% shortened outer arms, 4% inner dynein arm absence. In total 71% cross sections showed normal (9+2) microtubular arrangement, 19% microtubular disarrangements.

Genotyping revealed two previously unreported heterozygous variants in *DNAH11*, a missense change (NM_001277115.1:c.13040T>C; p.Leu4347Pro) and a large genomic deletion across exons 68-75 of the gene of unknown consequence. In addition to these variants of uncertain significance, a heterozygous missense change was identified in the outer dynein arm gene *DNAH5* (NM_001369.2:c.12513C>A; p.Asp4171Glu).

Electron tomography showed ODA% of MTD volume at the base of the cilium to be 10.4 (pink column below) in keeping with a DNAH11 defect. According to current ERS guidelines this individual would require 3 nasal brushings demonstrating a similar mixed, non-specific beat pattern and then would be subsequently classed as 'PCD highly likely'. Tomography is able to confirm the defect without additional testing.