Recessive HYDIN mutations cause primary ciliary dyskinesia without situs abnormalities

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Primary ciliary dyskinesia (PCD) is a genetically heterogenous disease characterized by reduced mucociliary clearance. This is caused by defects in cilia motility. Impaired sperm flagella motility contributes to male infertility. In about 50 % of cases PCD is associated with situs inversus or more rarely situs ambiguous as a result of embryonic cilia dysfunction leading to randomization of left-right body asymmetry. 70 years ago the hy3 mouse carrying hydin mutations has been described. These mutations lead to an abnormal composition of the central pair (CP) apparatus. Clinically, these mice suffer from lethal hydrocephalus. Now we report HYDIN mutations in human PCD patients without hydrocephalus and normal body composition. By using a homozygosity mapping strategy we identified a novel PCD locus on chromosome 16q21-q23 across the HYDIN locus. In three affected siblings genomic analyses showed homozygous c.3985G>T HYDIN mutations affecting the evolutionary conserved splice acceptor site of exon 27. We confirmed aberrant splicing with early stop of translation by cDNA analysis. High-speed videomicroscopy (HVM) of respiratory cells showed a reduced bending capacity. Sperm motility was markedly decreased with only 8% of sperms showing minimal progressive motility. Transmission electron microscopy (EM) appeared normal in most cross sections. 9 + 0 cilia and 8 + 1 cilia composition were found very rarely. EM tomography showed absence of the CP apparatus C2b projection resembling findings in Hydin-deficient mice. Our results expand the knowledge on PCD genetics. Careful diagnostic evaluation is obligate in this PCD variant as HVM and EM findings are subtle.