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Title: CCDC103 encodes a novel cilia dynein arm factor that is mutated in primary ciliary dyskinesia

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Body: Primary ciliary dyskinesia (PCD) is a genetically heterogenous disorder characterized by chronic destructive respiratory tract disease. In about 50 % of cases it is associated with situs inversus, because embryonic cilia play a critical role in establishing organ left-right asymmetry. Zebrafish schmalhans mutants exhibit characteristic features of ciliopathy caused by a mutation in ccdc 103; in electron microscopy cilia lack inner (IDA) and outer (ODA) dynein arms. Screening individuals for CCDC103 (the human ccdc103 ortholog) identified ten patients with mutations. We found homozygous loss-of-function mutations in six individuals (c.383_384insG) predicting a frame shift and premature termination of translation. In four affected individuals a homozygous transversion (c.A461C; p.H154P) was identified. All affected individuals exhibited typical clinical findings for PCD. Three patients had situs inversus totalis, one had situs inversus abdominalis and two dextrocardia. High-speed videomicroscopy (HVM) of patient OP-1192II1 (c.383_384insG) showed ciliary immotiliy with only residual flickering. By contrast, in two patients with the p.H154P variant, HVM showed reduced beat amplitude and coordination and few immotile cilia. In patient OP-1192II1, Immunofluorescence microscopy demonstrated distal ODA deficiency. Cells from PCD patient OP-1194II1 (p.H154P variant) displayed a normal localization of ODA components. Both patients showed a normal localization of the IDA component DNALI1. Our findings indicate that CCDC103 mutations cause PCD in humans. Whereas the loss-of-function mutation results in ciliary immotility and distal ODA deficiency, the p.H154P variant presents as a hypomorphic mutation.