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Identification of mutations in *DYNC2LI1*, a member of the mammalian cytoplasmic dynein 2 complex, expands the clinical spectrum of Jeune/ATD ciliopathies

K Kessler[1*], N Falk[2], I Wunderlich[1], M Fröhlich[1], N Hauer[1], A Gießl[2], JH Brandstätter[2], H Sticht[3], AB Ekici[1], S Uebe[1], E Seemanová[4], A Reis[1], R Roepman[5], C Thiel[1]

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Ciliopathies are caused by defects in formation, maintenance and function of the primary cilium and underlying genes affect the dynein motor, intraflagellar transport complexes, or the basal body. In a patient of non-consanguineous parents presenting an intermediate phenotype between asphyxiating thoracic dystrophy and Ellis-van Crefeld syndrome we performed exome sequencing. Variants were selected based on potential ciliary function as identified in a yeast two-hybrid screen with NEK1, a basal body protein involved in short rib-polydactyly type Majeweski (SRPSII). We identified compound heterozygous nonsense (p.R208X) and missense (p.T221I) mutations in *DYNC2LI1* segregating in the family. DYNC2LI1 is ubiquitously expressed and interacts with DYNC2H1 to form the dynein 2 complex important for retrograde intraflagellar transport. The hypothetical protein caused by the nonsense mutation lacks the coiled-coil domain involved in protein interaction and dimerization. The mutation p.T221I affects a highly conserved nucleoside triphosphate hydrolase domain responsible for GTPase driven dynein protein localization. Mutations in both *DYNC2LI1* interacting partners *DYNC2H1* and *NEK1* are associated with ATD and SRPSs. We screened further patients of our short stature cohort and identified in two siblings heterozygous mutations in *DYNC2LI1* (p.M1T) and its interaction partner *DYNC2H1* (p.K495T). The DYNC2H1 mutation was previously reported by El Hokayem et al. compound heterozygous with a splice site mutation in a patient with SRPSII. Our results might indicate a possible digenic diallelic inheritance in our patients. This is the first report of mutations in *DYNC2LI1* as part of the dynein 2 complex further expanding the clinical spectrum of ciliopathies.

Authors' details
[1]Institute of Human Genetics, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany. [2]Department of Biology, Animal Physiology, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany. [3]Institute of Biochemistry, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany. [4]Department of Clinical Genetics, Institute of Biology and Medical Genetics, 2nd Medical School, Charles University, Prague, Czech Republic. [5]Department of Human Genetics, Radboud University Medical Center, Nijmegen, The Netherlands.

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[1]Institute of Human Genetics, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany
Full list of author information is available at the end of the article