

# A study of new *NEK8* mutations in patients with severe renal cystic hypodysplasia and ciliopathy-associated defects

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*NEK8/NPHP9* encodes a NIMA (Never-In-Mitosis A) protein essential for cell cycle control. *NEK8* is composed of kinase and *RCC1* domains, the latter involved in centrosomal localization. It localizes into the nucleus and at the inversin compartment in the primary cilium. Using ciliary gene-enriched exome sequencing, we identified recessive *NEK8* mutations in 3 cases with severe overlapping phenotypes including renal cystic (hypo)dysplasia, *situs inversus*, cardiopathy and paucity of bile ducts. Two patients who died early after birth carried missense mutations in the kinase and/or *RCC1* domains. A homozygous splice mutation was identified in a fetus with Meckel-like phenotype. Analyses of patient fibroblasts and IMCD3 cells expressing mutated *NEK8*-GFP revealed that the mutations affect *NEK8* nuclear and ciliary localization. The number of ciliated cells was reduced and ciliary localization of *NEK8* partner *ANKS6/NPHP16* was lost, demonstrating the key role of *NEK8* in cilia function. Surprisingly, in patient fibroblasts, *NEK8* accumulates at the Golgi that appeared dispersed into the cytoplasm suggesting a role in vesicular trafficking. Cell cycle defects associated with abnormal nuclear accumulation of YAP, a transcriptional co-activator of the Hippo pathway was also observed, together with dysregulation of several Hippo effector/target genes. Finally, injection of *nek8* morpholinos in zebrafish embryos led to ciliopathy-related phenotype (curly body axis, laterality defects, pronephric cysts) that could be rescued by RNA expression of WT *NEK8* but not by the mutated forms,

further demonstrating pathogenicity of the mutations. Altogether, we demonstrate that human *NEK8* mutations alter developmental ciliary and non-ciliary processes, thus leading to multisystemic defects.

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