Title: Nephronophthisis *GeneReview* (Overview) – Molecular Genetics: Animal Models
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Animal Models for Genes Associated with Nephronophthisis

NPHP1

Loss of NPHP1 in Madin-Darby canine kidney epithelial (MDCK) cells resulted in reduced cilia formation and length, delayed tight-junction formation, and disorganized multi-lumen cyst formation [Delous et al 2009]. A mouse model with homozygous deletions of exon 20 of *NPHP1* showed retinal degeneration with abnormal photoreceptor intraflagellar transport [Jiang et al 2009]. Interestingly, the mice did not have nephronophthisis but did show impaired spermatogenesis [Jiang et al 2008].

INVS (NPHP2)

Mouse embryonic fibroblasts (MEF) deficient for INVS showed normal cilia formation and cilia length but defective cilia orientation and directional cell migration [Veland et al 2013]. A mouse model of *Inv* mutation showed situs inversus and cystic renal disease [Yokoyama et al 1993, Morgan et al 1998]. Morpholino knockdown of Invs in zebrafish resulted in ventral axis curvature, left-right asymmetry and pronephric cysts [Simons et al 2005, Zhao & Malicki 2011].

NPHP3

Knockdown of *NPHP3* in a murine inner medullary collecting duct (IMCD3) cell model resulted in a reduced number of cilia and disrupted spheroid formation caused by polarity defects, effects that could be rescued by the somatostatin agonist octreotide [Ghosh et al 2012].

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Homozygous pathogenic variants in *Nphp3* were responsible for the phenotype in the pcy (polycystic kidney disease) mouse mutant [Olbrich et al 2003].

Homozygous null-mutations resulted in lateralization defects and were embryonically lethal in mice [Bergmann et al 2008].

Morpholino knockdown of *Nphp3* in zebrafish embryos caused abnormal body curvature, hydrocephalus, pronephric cysts, and situs inversus [Zhou et al 2010, Hoff et al 2013].

NPHP4

NPHP4 knockdown in Madin-Darby canine kidney (MDCK) cells resulted in significantly shorter cilia, delayed tight-junction formation, and disorganized multi-lumen structures when grown in three-dimensional collagen matrix [Delous et al 2009]. Unlike *NPHP1* knockdown, silencing of *NPHP4* did not lead to a reduced number of cilia [Delous et al 2009].

Morpholino knockdown of *Nphp4* in zebrafish caused abnormal body curvature, laterality defects, hydrocephalus, pericardial edema, retinal abnormalities, pronephric cysts and cloaca defects [Burcklé et al 2011, Slanchev et al 2011, Borgal et al 2012, French et al 2012].

Mouse KO, retinal involvement, and male infertility [Won et al 2011].

NPHP5 (IQCB1)

Depletion of Iqcb1 in zebrafish results in abnormal body curvature, cerebral anomalies, and development of pronephric cysts. This phenotype is aggravated by the combined knockdown of *CEP290*, suggesting a genetic interaction [Schäfer et al 2008].

NPHP6 (CEP290)

Knockdown of *CEP290* in an IMCD3 cell model caused reduced cilia formation and increased abnormal spheroid formation [Ghosh et al 2012].

Knockdown of *Cep290* in zebrafish caused abnormal body curvature, cerebral and retinal anomalies and development of pronephric cysts [Schäfer et al 2008].

Cep290 knockout in mice recapitulated the cerebellar Joubert phenotype and resulted in retinal and renal pathology [Lancaster et al 2011, Hynes et al 2014, Rachel et al 2015].

TMEM67 (NPHP11)

Morpholino knockdown of *Tmem67* in zebrafish resulted in a ciliopathy phenotype characterized by brain and eye abnormalities and pronephric cyst formation. Concommitant knockdown of *Flna* aggravated this phenotype [Adams et al 2012].

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Tmem67 knockdown mice manifested renal cystic dysplasia, neurologic features associated with ciliopathies, limb dysplasia, laterality defects, cardiac defects, pulmonary hypoplasia, and defective Wnt and Shh signaling [Abdelhamed et al 2013, Abdelhamed et al 2015].

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