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Mechanism underlying inherited renal cystic diseases

Genetic bases and pathogenic mechanisms of nephronophthisis

Marion Delous[1,2], Helori M. Gaudé[2], Sophie Saunier[2,*]

[1]Max-Planck-Institute for Heart and Lung Development, Bad Nauheim, Germany[1]
[2]INSERM, U983, Paris Descartes, Sorbonne Paris Cité University, Imagine Institute, 75015 Paris, France

Nephronophthisis is a recessive cystic kidney disorder that belongs to the group of ciliopathies. Most of the causal gene products localize at the primary cilium, as components of either the transition zone or the retrograde intraflagellar transport IFT-A complex, where they control ciliary protein trafficking and modulate responses to various signaling pathways. In this review, we summarize the current literature on nephronophthisis-related disease genetics and outline the essential pathophysiological mechanisms underlying these disorders.

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Introduction

Nephronophthisis (NPH) is the major genetic cause of chronic kidney diseases in children [1], characterized by tubular atrophy with thickened tubular basement membrane, severe interstitial fibrosis and formation of medullary cysts. The juvenile form leads to end-stage renal disease within the first decades of life. Extra-renal symptoms, such as retinal dystrophy, cerebellar vermis hypoplasia/aplasia, hepatic fibrosis, skeletal abnormalities and *situs inversus* are present in a significant proportion of NPH patients and their association with NPH represents distinct clinical entities. More than 15 NPH-related genes encoding NPHP proteins have been identified. NPHP proteins localize at cell junctions and the primary cilium, thus defining NPH and associated disorders as ciliopathies. Primary cilia are cellular organelles located at the apical surface, which are essential for extracellular chemical and mechanical signal transduction, ensuring tissue morphogenesis and homeostasis [2]. In this review, we cover the latest insights into the molecular and cellular mechanisms underlying NPH.

Basic genetics of NPH and related ciliopathies (NPH-RC)

NPHP genes involved in NPH-RC

Nephronophthisis is a clinically and genetically heterogeneous recessive disorder. Genetic studies combining positional cloning and candidate gene approaches allowed the identification of eleven genes mutated in patients with NPH-RC, *NPHP1-11* [3] (Table 1). Each NPHP protein is localized at the primary cilium where they work in complex with other ciliopathy-related proteins to maintain cilia structure and function [4].

The identification of additional genes involved in NPH-RC has been facilitated by a combination of ciliary interactome and whole/ciliopathy candidate exome sequencing strategies. Notably, mutations in genes encoding components of the retrograde intraflagellar transport complex A (IFT-A) have been identified in patients with skeletal ciliopathies associated with NPH (Table 1). Mutations of *IFT140* cause Mainzer–Saldino Syndrome [5], characterized by cone-shaped epiphysis of the phalanges, NPH and retinal dystrophy. Conditional knockout of *Ift140* in mouse collecting ducts results

*Corresponding author.: S. Saunier (sophie.saunier@inserm.fr)
[1] Current address.

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Table 1. Genes mutated in isolated NPH and NPH-RC

GENE [3]	Protein	Isolated NPH	Infantile NPH	NPH-related ciliopathies									Other ciliopathies without NPH				
				With liver fibrosis	With situs inversus	With cardiac defects	SLS	JBTS-B	MSS	JATD	SS	BBS-like	LCA	JATD	JBTS	COACH	MKS
NPHP1	Nephrocystin-1	✓✓					✓	✓							✓		
INVS/NPHP2	Inversin, nephrocystin-2	✓	✓✓	✓	✓✓	✓											
NPHP3	Nephrocystin-3	✓	✓(tr)	✓(hyp)	✓	✓	✓										✓ (tr)
NPHP4	Nephrocystin-4	✓					✓	✓									
IQCB1/NPHP5	IQ-motif containing protein, nephrocystin-5						✓✓										
CEP290/NPHP6	Centrosomal protein 290						✓	✓✓				✓	✓✓				✓
GLIS7/NPHP7	GLI similar 2	✓															
RPGRIP1L/NPHP8/ MKS5	RPGRIP1-like							✓ (hyp)								✓	✓ (tr)
NEK8/NPHP9	NIMA-related kinase 8	✓	✓														
SDCCAG8/NPHP10/ SLSN7	Seralogically defined colon cancer antigen 8						✓					✓					
TMEM67/NPHP11/ MKS3	Transmembrane protein 67			✓ (hyp)				✓ (tr)				✓				✓	✓ (tr)
TTC21B/NPHP12 [7]	IFT139	✓	✓							✓				✓			
WDR19/NPHP13 [8]	IFT144	✓								✓	✓						
CEP164/NPHP15 [10]	Centrosomal protein 164						✓					✓					
TMEM216/MKS2/ JBTS2 [56]	Transmembrane protein 216							✓							✓		✓
ATXN10 [4]	Ataxin 10		✓	✓													
IFT140 [5]	IFT140								✓	✓							
AHI1 [14]	Jouberin	✓						✓							✓		
CC2D2A/MKS6 [56]	Coiled coil and C2 domain containing 2A	✓	✓												✓	✓	✓
ZNF423/NPHP14 [10]	ZNF423		✓		✓			✓									

✓: Involvement; ✓✓: main involvement; hyp, hypomorphe mutation; tr, truncating mutation; NPH, nephronophthisis; SLS, Senior–Løken Syndrome; JBTS-B, Joubert Syndrome type B; MKS, Meckel–Gruber Syndrome; MSS, Mainzer–Saldino Syndrome; JATD, Jeune Asphyxiating Thoracic Dystrophy; SS, Sensenbrenner Syndrome; BBS, Bardet–Biedl Syndrome; LCA, Leber's congenital amaurosis; COACH, Cerebellar vermis hypoplasia/aplasia, Oligophrenia, Ataxia, Coloboma and Hepatic fibrosis.