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Nephronophthisis-a genetic cause of ciliopathy

Keywords: nephronophthisis, ciliopathies, nephrocystin-1, etiologies, oligogenicity, polyuria, polydipsia, nocturia

Abbreviations: NPHP, nephronophthisis; BBS, alström and bardet-biedl syndrome; LCA, leber congenital amaurosis

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Introduction

In the last-stage kidney defect the most expected Genetic cause is Nephronophthisis (NPHP) in kids and young ages. It is a recessive cystic kidney disease. Functional assuming and Nine genes positional cloning (*NPHP1* through 9) of the proteins that are encoded have confer towards a consolidate hypothesis that assign diseases related to cyst of kidney as "ciliopathies." It refers a congregation of overlapping syndromes and disorders whose etiologies lie in ciliary function and structure which are imperfect.[1] The Cilia can be motile or non-motile (primary) on the basis of their function and structure. Both the types has a basal body which lies below the surface of cell and structure which stretch to a distance from the cell. Ciliopathies are fast growing type of human physical condition in which there is disturbance of normal function by malfunction of non-motile cilia, or these conditions recently describe. The part of all non-motile cilia have a basic common pattern which consist a rounded array of nine microtubule doublets forming the axoneme, which is supported in the basal body, a transmogrify centriole.[2–4] The NPHP incidence varies worldwide from 1 in 50,000 to 1 in 90,0000 children. The last stage kidney disease among pediatric patients in the USA reported 5% prevalence.[5] NPHP and cystic kidney of medulla which is autosomal dominant disease are often characterize commonly because of similar morphological features. The age of onset is major difference between NPHP and MCKD. Due to NPHP the median age is 13years of ESRD, while in adulthood the MCKD usually progresses to ESRD. NPHP is a genetic based heterogeneous disease along with 13 identified genetic mutations calculating for 30% of all influenced patients.[6] The protein compounds of maximum mutated genes localize to the non-motile cilium in conformance with the conception of ciliopathies. Infantile NPHP has been associated with NPHP2 mutations, while the more normal juvenile type has mutations in various genes including NPHP 1, 4, 5 and 6. Mutation in Nephrocystin-1 (*NPHP1*) accounts for majority of isolated incidence of NPHP.[7,8]

Ciliopathies have share clinical aspects like as cysts in kidney, retinal defects, obesity and diabetes and mental retardation.[9] Alström and Bardet-Biedl syndrome (BBS) are ciliopathies that include multi organ systems and share similar clinical aspects of blindness because of defect in retina, diabetes and before the expected time of onset obesity.[10,11] Both syndromes are confirmed by genetic testing.[12,13] The clinical findings of Nephronopathisis (NPHP) are kidney cysts, retinal dystrophy, and the gene associated in NPHP are *XPNPEP3/NPHPL1, TMEM67/NPHP11, SDCCAG8/NPHP10, NEK8/NPHP9, RPGRIP1L/NPHP8 GLIS2/NPHP7, CEP290/NPHP6, IQCB1/NPHP5, NPHP4, NPHP3, INV/NPHP2*. An assortment of additional renal manifestation can happen with NPHP including retinitis pigmentosa, oculo motor apraxia, cerebellar vermis hypoplasia, occipital encephalocele, coloboma of the optic nerve, Leber congenital amaurosis (LCA), hepatic fibrosis and situs in versus demonstrate the multitude of downstream outcome of ciliopathies.

Genetic basis, clinical features and syndromes associated with nephronophthisis (NPHP)

A short account of the syndromes aligned with NPHP and added renal features common in those syndromes is explained below. Oligogenicity, in which allelic version at different locations can present to the disease, and epistasis in which modifier genes can alter phenotype, have been identified with NPHP.[14,15] Oligogenicity and epistasis describe the broad range of clinical dissimilarity that can be related with any variant gene in NPHP (Table 1).

Table 1 Genetic basis, clinical features and syndromes associated with nephronophthisis (NPHP)

Syndromes & deformity	Gene	Clinical aspects
Joubert syndrome (JBTS)	Nephrocystin1 (NPHP1), Abelson Helper Integration Site 1, Inositol poly phosphate 5-phosphate E, Transmembrane protein216, Transmembrane protein67, FTM, ADP-ribosylation13, CCD2D2A, Oral-facial digital syndrome type 1, Tetratricopeptide repeat domain 21 B, KIF7, Tectonic family member1, Transmembrane protein 237, Centrosomal protein41, Transmembrane protein138, C5Orf42, Tectonic family member 3, Zinc finger protein423, Transmembrane protein 231, Tectonic family member 2, Meckel syndrome type1, B9D1.	Hypotonia and ataxia, delayed motor development,

Table continued...

Syndromes & deformity	Gene	Clinical aspects
Senior Lsken síndrome (SLS)	Nephrocystin1, Nephrocystin2, Nephrocystin3, Nephrocystin4, Nephrocystin 5, Centrosomal protein290, Nephrocystin6, Nephrocystin7, Nephrocystin8, Nephrocystin9, Nephrocystin10, Transmembrane protein 67/ Nephrocystin11, Nephrocystin12, WD Repeat domain19/ Nephrocystin 13.	Nephronophthisis and retinal dystrophy.
Bardet-Biedl síndrome (BBS)	Bardet-Biedl syndrome1, Bardet-Biedl syndrome2, Bardet-Biedl syndrome3/ADP-ribosylation6, Bardet-Biedl syndrome 4, Bardet-Biedl syndrome5, Bardet-Biedl syndrome6, Bardet-Biedl syndrome 7, Bardet-Biedl syndrome8/ Tetratricopeptide repeat domain8, Bardet-Biedl syndrome 9, Bardet-Biedl syndrome 10, Bardet-Biedl syndrome 11/TRIM32, Bardet-Biedl syndrome 12, Bardet-Biedl syndrome 13/MKS1, Bardet-Biedl syndrome 14/Centrosomal protein 290/Nephrocystin6, Bardet-Biedl syndrome 15/WDPCP, Bardet-Biedl syndrome 16/ SDCCAG8, Bardet-Biedl syndrome 17/LZTFL1, Bardet-Biedl syndrome 18.	Obesity, polydactyly, mental retardation, retinal distrophy, nephronophthisi, genitourinary, abnormalities, anosmia, congenital heart disease.
Meckel Gruber síndrome (MKS)	Meckel syndrome type1, Transmembrane protein 216/ Meckel syndrome type2, Transmembrane protein 67/MKS3, Centrosomal protein290, Regulator interacting protein-1, CC2DA, Nephrocystin3, Tectonic family member2, B9D1, B9D2, Transmembrane protein 231, Transmembrane protein 138, Transmembrane protein 237, EVC ciliary complex subunit2 and C5orf42.	Cystic renal displasia, occipital encephalocele, polydactyly, hepatic ductal displasia, congenital heart defects, cleft palate and cleft lip.
Asphyxiating Thoracic Dystrophy (ATD) or Jeune síndrome (JATD)	Intraflagellar transport80, Intraflagellar transport 139/ Tetratricopeptide repeat domain21B, Dynein cytoplasmic 2 heavy chain 1, WD repeat domain1919/ Intraflagellar transport 144, WD repeat domain60, WD repeat domain 34	Narrow thorax, short ribs and skeletal abnormalities.
Cogan syndrome	Nephrocystin 1	Oculomotor recessive, nystagmus
Boichis syndrome	Nephrocystin1	Congenital hepatic fibrosis, skeletol dysplasia, pituitary deficiency.

Treatment

There is no conclusive cure for NPHP and other affiliated ciliopathies at present. We could expect some definitive therapy in slowing renal cyst formation and progression in the future with better understanding of ciliopathies and ongoing trial in animal models. Drugs of interest include but not limited to vasopressin receptor antagonist, mTOR inhibitors and cyclin dependent kinase inhibitors[16–19] in animal models of NPHP and ADPKD which have been tried with success.

Ciliotherapy

Other than renal replacement therapy and hemodialysis remains the only effectual cure in the intensive evolution of new treatment or therapy recourse, of the last-stage disease. However, currently there has been a significant progression in comprehension the molecular pathogenesis of the defect, in including the finding of the duty of the primary cilium. Current findings have unequivocally affirmed that the alteration in the length of the non motile cilium is an dominant stimulator of pathological processes that outcome in the evolution and progression of NPHP. The recommencement of the non-motile cilium length by pharmacological regulation can prevent fibrosis, stop cystic growth, and upgrade renal function. There has been a significant progress in recent year about the area that activate rigorous growth of targeted therapy. These results have choices a new era in the development of targeted drugs which is known as Ciliotherapy.[20]

Evaluation plannings

To impaired concentrating ability of the kidneys early presenting features in NPHP are usually subtle and are secondary. Early findings often include polyuria, nocturia, polydipsia and secondary enuresis. Anemia and lethargy presents early in the disease. Early morning urine will be inappropriately dilute due to the inability to concentrate in the setting of water restriction.[21] Slow declination of kidney function occurs with progression to ESRD by adolescence in juvenile NPHP. Children may reach renal failure by 3years of age in the infantile form. Diagnosis of NPHP based on a clinical presentation of the disease. Cystic kidney diseases will be included in the differential diagnosis in children having findings of polyuria, polydipsia, enuresis and low urine concentrating ability.

Conclusion

Our perception has upgrade tremendously on the molecular basis of NPHP over the past decade. The actuality that ciliopathies have a extensive spectrum of clinical exposition, the task of cystoproteins in pathogenesis and non motile or primary cilia, has been find out or learnt. To know the biological work of nephrocystins and the molecular mechanism behind cyst formation, the difficulties still remains. Ongoing or Further investigation is important to facilitate the evolution of novel therapy and understanding of the biology of cyst formation at a cellular level to reverse the disease process or delayed it.

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Conflict of interest

Author declares that there is no conflict of interest.

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