Case Report

Retinitis pigmentosa and renal failure in a patient with mutations in \textit{INVS}

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Abstract

\textbf{Background.} Nephronophthisis (NPHP) is an autosomal recessive disease, which is the most common genetic cause of end-stage renal disease in the first three decades of life. The disease is caused by mutations in the \textit{NPHP} 1–5 genes, and is referred to as NPHP types 1–5, respectively. The association of NPHP and retinitis pigmentosa (RP) is known as Senior-Loken syndrome (SLS). The RP is associated with 10\% of cases of NPHP types 1, 3 and 4, and all cases of NPHP type 5, but never in NPHP type 2, the infantile form of NPHP. The NPHP type 2 is distinguished from other types of NPHP by its early age of onset and by cystic enlargement of the kidneys.

\textbf{Methods.} Mutational analysis of all five NPHP genes was performed by exon sequencing in a child with infantile NPHP and RP from a consanguineous kindred.

\textbf{Results.} A homozygous mutation was identified in exon 13 of inversin (\textit{INVS}) (C2719T, R907X) in this child.

\textbf{Conclusions.} This is the first report of the presence of RP in a patient with NPHP type 2 and \textit{INVS} mutations. This report now extends the association of RP with NPHP type 2.

\textbf{Keywords:} chronic renal fibrosis; genetics; kidney cysts; mutation; nephronophthisis; renal failure

Introduction

Nephronophthisis (NPHP) is an autosomal recessive kidney disease, characterized by a histological triad of renal fibrosis, tubular basement membrane disruption and renal cyst formation. It is the most common genetic cause of end-stage renal disease (ESRD) in the paediatric population. Five genes have been identified, in which mutations result in a renal NPHP phenotype [1–6]. Mutations in \textit{inversin}, also known as \textit{INVS} or \textit{NPHP2}, have recently been identified in patients with NPHP type 2, infantile form of NPHP [2].

The NPHP type 2 differs from the other four types of NPHP in two respects, infantile onset of ESRD and enlarged kidney size. The age of onset of ESRD in NPHP type 2 is < 5 years in all cases reported to date [2], whereas the median age of ESRD in other types of NPHP is 13 years. While the kidney size in NPHP types 1, 3, 4 and 5 is normal to small, the kidney size in NPHP type 2 is increased. Detailed analysis of a murine model of NPHP type 2 demonstrates cystic dilatation of Bowman's capsule, proximal tubule, thick ascending limb and collecting duct [7].

The patients described in the original report of human \textit{inversin} mutations associated with NPHP type 2 demonstrated extrarenal manifestations, which included hypertension and \textit{situs inversus} with a ventricular septal defect [2], but never retinitis pigmentosa (RP). Neither has ocular involvement been described in two mouse models of recessive \textit{INVS} mutations [8,9].

The association of NPHP with RP, known as Senior-Loken syndrome (SLS), is seen in all patients with mutations in \textit{NPHP5} and in about 10\% of patients with mutations in \textit{NPHP1}, \textit{NPHP3} or \textit{NPHP4}, but this has never been described in patients with \textit{INVS} mutations. We here report the first patient with RP and NPHP type 2 who has mutations in \textit{INVS}.

Case

A 2-year-old boy of Arab descent presented with anaemia and short stature. His family history was remarkable for consanguineous parents and for a brother who succumbed to an undiagnosed kidney disease at the age of 2 years. Our patient was found...
to be in advanced renal failure stage and deteriorated to ESRD at the age of 2.5 years. Renal ultrasound showed enlarged kidneys with increased echogenicity and without cysts. His ophthalmologic examination revealed bilateral RP, which was confirmed by electroretinogram testing. The child had a normal chest radiograph, excluding the possibility of situs inversus. The presumed clinical diagnosis was of the infantile form of NPHP associated with RP. He was maintained on chronic haemodialysis until deceased donor renal transplantation was undertaken at the age of 9 years. His graft function has been excellent until he started to demonstrate the first signs of non-compliance with immunosuppressive medications and experienced several episodes of late acute rejection. The unaffected siblings underwent complete physical examination including ophthalmological examination, renal ultrasound, blood and urine testing. All results from unaffected siblings were within normal limits. DNA was submitted for mutational analysis in the NPHP1–5 genes.

Methods

All exons of NPHP1, INVS, NPHP3, NPHP4 and NPHP5 were analysed by direct sequencing. Briefly, PCR primers flanking each exon were designed from genomic sequence (primer sequences available upon request). Direct sequencing of each amplicon was performed using the dideoxy chain termination method on an ABI capillary sequencer. Sequences were analysed using Sequencher® software.

Results

Results of mutational analysis of all INVS exons in F103 revealed a homozygous mutation in individual F103IL-1 in exon 13, C2719T, with a predicted coding sequence change of R907X (Figure 1). The truncation of the protein is predicted to occur before the second ‘destruction box’ and the second IQ domain. This mutation segregated from the mother. No DNA was available for analysis from the father. This mutation was previously published with the initial report of INVS mutations in NPHP type 2, in one family who had no evidence of retinal abnormalities. The mutation was not present in 100 healthy individuals.

Discussion

The RP was previously known to occur in NPHP types 1, 3, 4 and 5, but not in the infantile form (NPHP type 2). This report extends the association of RP with NPHP to include all the genes known to cause NPHP. We detected a homozygous mutation in the affected child, which segregates from the mother, as noted in the ‘Results’ section. The fact that NPHP type 2 is a recessive disease and the parents, who are first-degree cousins, had two affected offspring, supports the assumption that the father is a carrier of the same mutation, although we are unable to confirm this as DNA is unavailable for analysis.

Inversin has been localized to the primary cilia of polarized MDCK cells, a tissue culture model of renal epithelial cells [2]. The gene products of NPHP1, NPHP4 and NPHP5 have also been localized to the primary cilia in tissue culture models of renal epithelial cells. The primary cilia is analogous to the connecting cilium of the retina, a structure in photoreceptor cells, which connects the inner and outer segments of the photoreceptor cell. Introduction of an inversin:GFP construct into a transgenic mouse line results in the localization of the GFP signal to the primary cilia of renal tubular cells as well as ciliary structures in the

![Fig. 1. Pedigree of F103. Parents are first-degree cousins. Index case is individual II:1, depicted by solid square. Chromatograms are shown either below or beside individuals for whom DNA was available. The chromatograms demonstrate the nonsense mutation (C2719T) in exon 13, which is predicted to result in premature truncation of the protein (R907X). The position of the nucleotide change is indicated by the arrows above the chromatograms. The nucleotide sequence is represented below the chromatograms and codons are indicated by underlines. The mutation segregates from the mother and appears heterozygously in three unaffected siblings (II:2, II:3 and II:5).](https://academic.oup.com/ndt/article-abstract/21/7/1989/1821883)
The presence of inversin in the photoreceptor cell suggests that it has functional importance in this cell type.

The exact cause of RP in cases of NPHP remains elusive. In this case it seems likely that mutations in INVS are necessary for the manifestation of RP as the affected sibling with homozygous mutations in INVS is the only one with retinal findings. Siblings with only one heterozygous mutation in INVS had a normal ophthalmological examinations and no evidence of renal failure. However, we cannot definitively rule out the possibility that an additional independent mutation is segregating within this kindred, leading to the retinal findings. Regardless, mutations in the NPHP genes alone do not appear to be sufficient for the manifestation of RP in association with NPHP, as the incidence of RP varies among different families with the same causative NPHP mutation. The exception is mutations in the NPHP5 gene, which lead to RP in all patients. It is, therefore, speculated that modifier genes are possibly responsible for the phenotypic pleiotropy seen in NPHP types 1–4.

Conflict of interest statement. None declared.

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References

10. Watanabe D, Saijoh Y, Nonaka S et al. The left–right determinant inversin is a component of node monocilia and other 9+0 cilia. Development 2003; 130: 1725–1734

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