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CASE REPORT

Senior-Loken syndrome: A novel *NPHP5* gene mutation in a family from Kuwait

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KEYWORDS

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Abstract *Background:* Rare autosomal recessive disorders of variable severity are segregating in many highly consanguineous families from the Arab population. One of these deleterious diseases is Senior-Loken syndrome, a hereditary heterogeneous multiorgan disorder, which combines nephronophthisis with retinal dystrophy, leading to blindness and eventually end stage renal failure. This disorder has been reported in many cases worldwide, including two unrelated families from Arabian Gulf countries, which share the gene pool with Kuwait.

Case report: Here, we are reporting two children from an Arab family with a novel frameshift mutation found in IQCB1/NPHP5 gene; c.1241-1242delTC, predicted to cause protein termination p.Leu414HisfsStop4, and describing the associated clinical features.

Conclusion: Identification of this pathogenic mutation helped in confirmation of the clinical diagnosis and in providing a proper pre-marital genetic counselling and testing for a couple embarking on marriage from this highly consanguineous high-risk family.

1. Introduction

Senior-Loken (S-L) is an autosomal recessive syndrome and a variant of the nephronophthisis-associated disorders, in which the cystic kidney disease is associated with retinal dystrophy (retinitis pigmentosa or Leber congenital amaurosis). It is a deleterious disease that culminates in blindness and renal failure. Visual prognosis is usually poor and no definite treatment is available to date. However, renal transplantation appears to be the best option for the end stage renal failure (ESRF) [1–5]. This clinical association was described for the first time in 1961, in many patients and by two authors separately [1,2]. Consequently, more cases have been reported worldwide [6–8], including affected individuals in two separate unrelated families from Qatar and Saudi Arabia [9,10], being two Arabian Gulf countries, with a population that share the gene pool with the Arab population of Kuwait.

Abbreviations: ESRF, end stage renal failure; S-L, Senior-Loken; NPHP, nephronophthisis; BUN, blood urea nitrogen

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Nephronophthisis (NPHP), a heterogeneous ciliary dysfunction, or as named renal ciliopathy, is a disease causing cystic kidneys or renal cystic dysplasia, and the most common genetic cause of chronic renal failure in the first two decades of life [11–13]. Three clinical variants have been recognised; infantile, juvenile and adolescent types, depending on the age of onset of the manifestations and on the causative genes. The median age of onset varied, being 1, 13 and 19 years respectively [13,14]. The juvenile variant is the most common form of NPHP, it constitutes 5–10% of ESRF in affected children [15]. Furthermore, NPHP is frequently associated with a broad spectrum of extra-renal manifestations, constituting different clinico-pathological disorders, depending on the type of the mutated genes. Hence, molecular analysis of the relevant gene is important for confirmation of the clinical diagnosis and for providing effective genetic counselling.

A variety of ciliopathy disorders, other than Senior-Loken syndrome, have been described; including Bardet–Biedl syndrome (obesity, hypogonadism, retinal degeneration, polydactyly, mental retardation, and renal malformations), Jeune asphyxiating thoracic dystrophy (a lethal skeletal dysplasia condition with shortening of the bones and a narrow thorax), Joubert syndrome (cerebellar vermis hypoplasia and brainstem abnormalities; the primary hallmark is the molar tooth sign in the brain), Meckel–Gruber syndrome (a lethal disorder with occipital meningoencephalocele, cystic kidneys, hepatic developmental defect, post axial polydactyly, shortening and bowing of long tubular bones, congenital heart defects, microphthalmia, and cleft lip/palate), and Sensenbrenner syndrome or cranioectodermal dysplasia (retinal degeneration hepatobiliary disease, cerebellar vermis hypoplasia, and shortening of long bones in combination with craniosynostosis and ectodermal dysplasia such as skin laxity and abnormal dentition) [12,16,17].

To date, pathogenic mutations in at least 14 different NPHP genes have been identified, (named nephrocystin genes) including (NPHP1, INV/NPHP2, NPHP3, NPHP4, IQCB1/NPHP5, CEP260/NPHP6, GLIS2/NPHP7, RPGRIP1L/NPHP8 and NEK8/NPHP9, SDCCAG8/NPHP10, TMEM67/NPHP11, TTC21B/NPHP12, WDR19/NPHP13, and XPNPEP3/NPHPL1) [3,4,14,16–21]. These genes encode the cilia-associated proteins (nephrocystins) that form supramolecular complexes essential for cilia formation and its regulatory function in many organs; including retina, inner ear, kidney and brain. In general, all these identified genes explain the disease in only 30% of the affected patients, with NPHP1 being responsible for 20% of the genetically studied cases [13]. Nevertheless, further potential genes are expected to be discovered due to the enormous clinico-genetic (phenotype-genotype) heterogeneity of the disease that has a marked influence on its presentation and severity, and the massive phenotypic overlap that results in emerging of many syndromes [12,16]. Mutations in the *IQCB1*/*NPHP5* (SLN5/OMIM; 609237, on chromosome 3q21) are reported to be the most frequent causes of S-L syndrome [4], with a phenotypic variation between carriers of different mutations along the same gene [22,23]. We have investigated an Arab family from Kuwait having two children affected with S-L syndrome. Molecular analysis revealed a novel *IQCB1*/*NPHP5* gene mutation that we report for the first time. Identification of the causative gene mutation confirmed the clinical diagnosis and encouraged other family members to seek genetic counselling and testing.

2. Family data

The family presented here constitutes first cousin parents and five children, two of whom were affected with the S-L disorder. There was no family history of any hereditary disease such as renal, visual or hearing defect. Two more family members (a couple) embarking on marriage, approached the clinic for genetic counselling and testing, one being a female first cousin of the proband, and the second being a male first cousin of his father (Fig. 1).

2.1. Patient 1

The proband with a clinical diagnosis of nephronophthisis, congenital blindness and ESRF, was referred to the genetics clinic at the age of 9 years for genetic counselling and confirming the diagnosis of S-L syndrome by molecular analysis to avoid renal biopsy. At that time, he was on peritoneal dialysis, for few months, for his ESRF secondary to his condition. He was the product of full term pregnancy and normal delivery, with normal developmental milestones. He was blind since birth, with a high frequency nystagmus, and was diagnosed with Leber's congenital amaurosis at the age of 8 months. He was on regular follow up by a nephrologist since early life, where the renal function test, serum electrolytes and urine analysis were performed periodically because of the family history of a similar condition in his elder sister. At the age of 8 years, he looked well, with normal intellectual ability, but 1 year delayed bone age. His body weight was 24 kg, and height was 118 cm (25th percentile). Abdominal and pelvic ultrasound of all organs was normal, except for kidneys. Both kidneys were of normal size, but with increased echotexture, more pronounced on the right side. The right kidney measured 8.2 cm and the left one was 8.1 cm. The bladder was unremarkable. These findings were suggestive of early changes of chronic kidney disease. All other investigations were normal such as eye and brain CT scan. A few months later, his investigations showed Urea Nitrogen blood (BUN) of 27 mmol/L, serum creatinine of 547 μmol/L, serum calcium of 4.09 mm/l and phosphorus of 0.56 mmol/L. Unfortunately, his condition deteriorated rapidly; his renal function was impaired, having

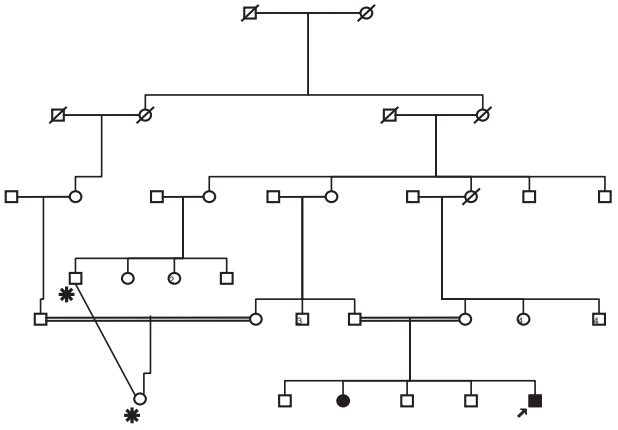

Figure 1 Family pedigree. The proband is indicated by an arrow. The couples embarking on marriage are indicated by the star signs.