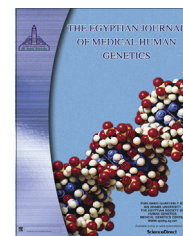




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CASE REPORT

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

Makia J Marafie ^{a,*}, Fahd Al-Mulla ^b

^a Kuwait Medical Genetics Centre, Maternity Hospital, Sabah Medical Area, P.O. Box 5833, Safat 13059, Kuwait

^b Department of Pathology, Faculty of Medicine, Kuwait University, P.O. Box 24923, Safat 13110, Kuwait

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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.

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1. Introduction

Senior-Loken (S-L) is an autosomal recessive syndrome and a variant of the nephronophthisis-associated disorders, in

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

* Corresponding author. Tel.: +965 24814328; fax: +965 24842073.

E-mail addresses: mj_marafie@yahoo.com (M.J Marafie), fahd@al-mulla.org (F. Al-Mulla).

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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.

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, RPGRI1L/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 supra-molecular 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 μ mol/L, serum calcium of 4.09 mmol/L and phosphorus of 0.56 mmol/L. Unfortunately, his condition deteriorated rapidly; his renal function was impaired, having

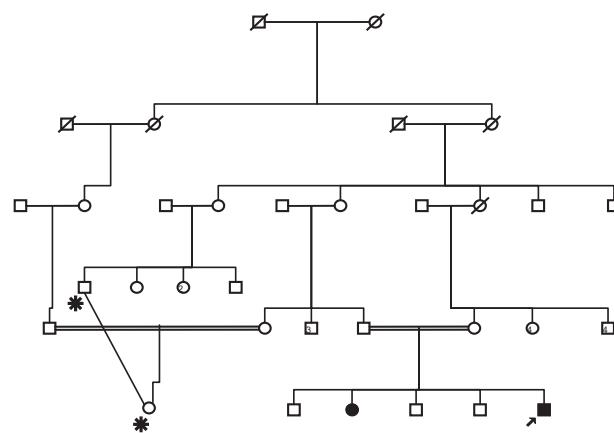


Figure 1 Family pedigree. The proband is indicated by an arrow. The couples embarking on marriage are indicated by the star signs.

uraemia, hyper-phosphatemia, anaemia (Hb 7 g/L) and hypertension, which then progressed to ESRD in a very short period. Initially, he was managed with standard medical anti failure treatment and dialysis, then underwent pre-emptive cadaveric renal transplant few months later.

2.2. Patient 2

His sister was 18 years old at the time of the counselling visit. She was born at full term after an uneventful pregnancy, by normal vaginal delivery. Her general condition was good with normal developmental milestones. Her parents noticed her poor vision at the age of 3 months. Eye examination at the age of 22 months revealed a very poor eye fixation with a high frequency nystagmus, hypermetropic vision (+8.0) and normal fundi. Retinoscopy of both eyes indicated severe retinal dysfunction, with an evidence of rudimentary activation of post retinal pathway. The electrodiagnostic picture was suggestive of Leber congenital amaurosis as it showed low amplitude scotopic and photopic response. All other investigations including brain and eye CT scan were normal. There was no history of polyuria, polydipsia, urinary tract infection or change in urine colour in her childhood and was normotensive. Her intellectual abilities were within normal. At the age of 13 years, her height was 131 cm and the weight was 31 kg, which were significantly below the fifth percentile for her age. She described periods of pain and tingling of fingers with dysuria. Her urine analysis showed excess white cells, but urine culture was negative. The level of urea nitrogen blood (BUN) was 19 mmol/L and creatinine 379 $\mu\text{mol/L}$. Her condition deteriorated, further investigations showed deterioration of the renal function, as her serum creatinine was $> 500 \mu\text{mol/L}$

and BUN was 25 mmol/L. She also had severe hypocalcaemia (1.7 mmol/L), which explained her tingling and pain sensations in the fingers, the carpedal spasm, and renal osteodystrophy. Complete blood cell count showed microcytic, hypochromic anaemia (Hb 7 g/L). Also, the biochemistry test revealed mild hypophosphatemia, hypomagnesaemia, but normal electrolytes. Other biochemical and haematological indices were within the normal limits. Renal ultrasound showed hyper-echogenic renal parenchyma, poor cortico-medullary differentiation, but normal sized kidneys. There was a medullary cyst of 1.3 cm was located in the right kidney. Roentgenograms of both hands showed generalised osteopenia, widening of epiphysis, irregular metaphyseal surface, erosion of diaphysis of ulnar bones and delayed bone age, which was corresponding to 11.5 years. Her condition then rapidly progressed to the ESRF. One month later, she underwent pre-emptive cadaveric renal transplant. However, she developed post-transplant diabetes mellitus.

3. Methods and results

The written informed consent was obtained from the parents and their adult relatives for blood collection and molecular testing. The genomic DNA was extracted from the peripheral blood for defining the carrier status of the involved subjects. Sequence analysis of the entire coding region of the *IQCB1/NPHP5* gene was performed as described previously [22] and showed that the proband and his affected sister were homozygous carriers for the c.1241-1242delTC in exon 12 of the gene (Fig. 2). We confirmed the mutation in the proband and family members using the same standard sequencing protocol, which utilised the following forward and reverse primers

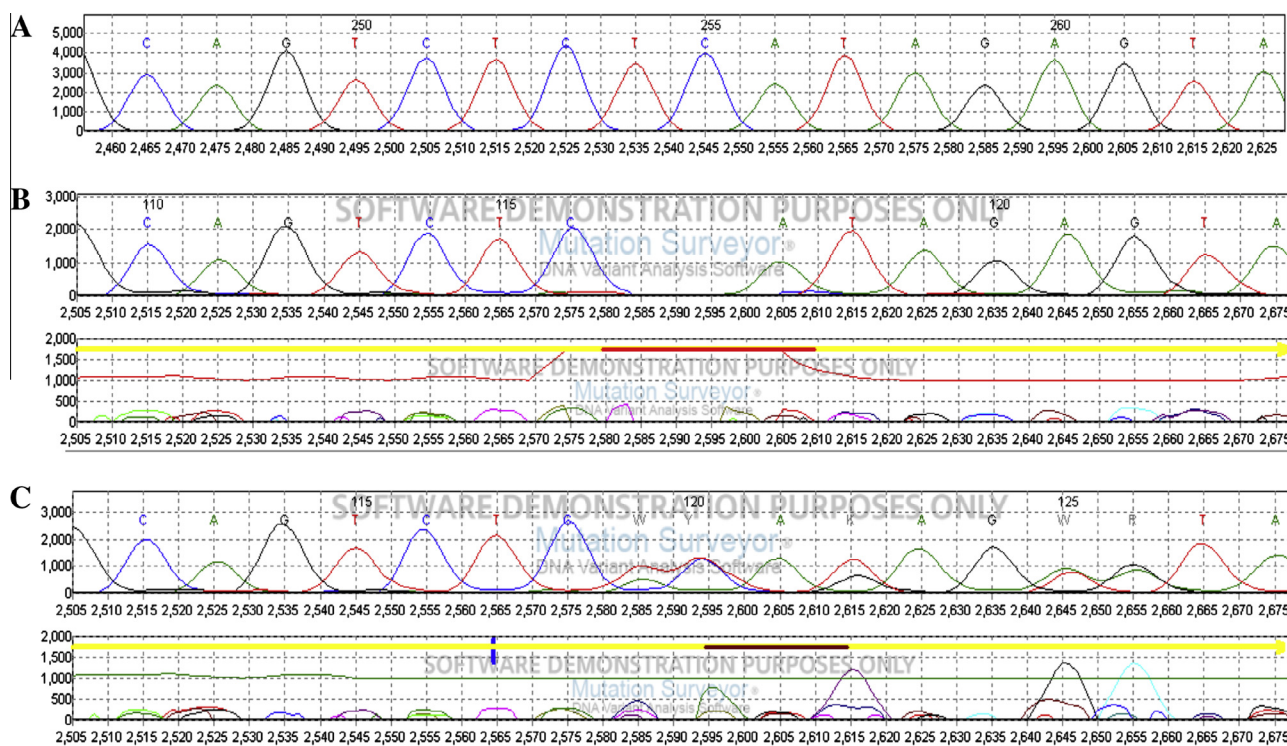


Figure 2 Electropherogram of the homozygous mutation c.1241-1242delTC, exon 12 of *IQCB1/NPHP5* gene found in the proband and his relatives. (A) Wild type (B) homozygous carrier. (C) Heterozygous carrier showing the frameshift.

respectively: F-5'- GCATGGCAGTGAGTATGTTGT-3' and R-5'- AGGCTCAAGAAAATAAGTGTCT-3'. The mutation (p.leu414HisfsStop4) is predicted to be pathogenic because it leads to protein truncation. Both parents and two other sibs were proved to be heterozygous carriers for the same mutation, while one brother was found normal. The proband's cousin was also heterozygous carrier for the same mutation, while her fiancé was normal (Fig. 1).

4. Discussion

S-L syndrome is a rare entity that has been reported in many families worldwide [6–8], including two different Arab families from Qatar and Saudi Arabia [9,10]. Here, we have investigated an Arab family with two children affected with S-L syndrome. A novel mutation in exon 12 of *IQCB1/NPHP5* gene was identified; named c.1241-1242delTC, which is predicted to result in a premature protein truncation (p.leu414Hisfs-Stop4). The gene has been termed the classical S-L gene because its mutations have been only associated with renal-retinal phenotype [5]. Indeed, our affected family members showed diseases limited to the retina and kidney, albeit to a different extent. Previous work reported several mutations in the *IQCB1/NPHP5* gene [7,22,24]. However, to the best of our knowledge, this mutation has not been reported previously. Moreover, this is the first report of *IQCB1/NPHP5* gene mutation found in the Arabian Peninsula. The implication of this finding was discussed with the family members, who were cooperative and understanding of the preventive measures against recurrence of the disease in their future generations; hence a related couple approached the clinic requesting premarital genetic testing.

The prevalence of consanguineous marriages is high in the Arab population and it reached 54.3% in Kuwait, with estimated population incidence rates of 52.9–55.7% [25–27]. Consequently increasing the incidence of autosomal recessive diseases, some of which are very rare and their causative gene mutations have never been identified. For thousands of years, intra-familial and intra-tribal marriages are most traditionally practised; this creates the need for a proper premarital management of couples embarking on marriage, from families with hereditary diseases, and hence molecular screening should be provided to them as a preventive measure against recurrence in their future generations. There is a need for documentation of the mutations detected in all unfortunate families with rare diseases, which are scattered in the Arab world and Middle East to help clinicians provide well-tailored genetic counselling and reasonably priced molecular tests. The parental educational background, their cooperation and the gene mutation, which was identified in the proband and his relatives, further enhanced management of this family.

5. Conclusion

We have identified a novel pathogenic gene mutation in a highly consanguineous high-risk family with a rare devastating autosomal recessive disease. This finding has its serious implication for the future generations in case of intermarriages amongst the family members. Therefore, we used this information to guide us in providing a proper premarital genetic counselling. There is a need to educate the public and the clinicians

who are involved in providing the premarital genetic service, as the mandatory genetic screening covers only few common blood disorders. Hence the consanguineous couples should be referred to the genetic clinic if such diseases were found segregating within their families.

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References

- [1] Senior B, Friedmann AI, Braudo JL. Juvenile familial nephropathy with tapetoretinal degeneration: a new oculorenal dystrophy. *Am J Ophthalmol* 1961;52:625–33.
- [2] Loken AC, Hanssen O, Halvorsen S, Jolster NJ. Hereditary renal dysplasia and blindness. *Acta Paediatr* 1961;50:177–84.
- [3] Caridi G, Murer L, Bellantuono R, Sorino P, Caringella DA, Gusmano R, et al. Renal-retinal syndromes: association of retinal anomalies and recessive nephronophthisis in patients with homozygous deletion of the NPH1 locus. *Am J Kidney Dis* 1998;32:1059–62.
- [4] Otto EA, Loeys B, Khanna H, Hellemans J, Sudbrak R, Fan S, et al. Nephrocystin-5, a ciliary IQ domain protein is mutated in Senior-Loken syndrome and interacts with RPGR and calmodulin. *Nat Genet* 2005;37:282–8.
- [5] Hildebrandt F, Attanasio M, Otto E. Nephronophthisis: disease mechanisms of a ciliopathy. *J Am Soc Nephrol* 2009;20:23–35.
- [6] Roozbeh J, Sharifian M, Hosseini H, Sagheb MM, Behzadi S, Raeisjalali GA, et al. Senior-Loken syndrome in an Iranian family. *Saudi J Kidney Dis Transpl* 2010;21(4):735–7.
- [7] Haghghi A, Al-Hamed M, Al-Hissi A, Hynes A-M, Sharifian M, Roozbeh J, et al. Senior-Loken syndrome secondary to NPHP5/IQCB1 mutation in an Iranian family. *NDT Plus* 2011;4:421–3.
- [8] Aggarwal HarikrishanK, Jain Deepak, Yadav Sachin, Kaverappa Vipin, Gupta Abhishek. Senior-Loken syndrome with rare manifestations: a case report. *Eurasian J Med* 2013;45:128–31.
- [9] AlFadhel M, AlAmir A. Senior-Loken syndrome in a Saudi child. *Saudi J Kidney Dis Transpl* 2008;19(3):443–5.
- [10] Othman M, Rashed A, Bakr A. The Senior-Loken syndrome: two cases from the state of Qatar. *J Clin Diagn Res* 2012;6:1411–3.
- [11] Simms RJ, Hynes AM, Eley L, Sayer JA. Nephronophthisis: a genetically diverse ciliopathy. *Int J Nephrol* 2011;2011:527137.
- [12] Arts HH, Knoers NV. Current insights into renal ciliopathies: what can genetics teach us? *Pediatr Nephrol* 2013;28(6):863–74.
- [13] Hildebrandt F, Otto E. Molecular genetics of nephronophthisis and medullary cystic kidney disease. *J Am Soc Nephrol* 2000;11(9):1753–61.
- [14] Hurd TWb, Hildebrandt F. Mechanisms of nephronophthisis and related ciliopathies. *Nephron Exp Nephrol* 2011;118(1):e9–14. Review..
- [15] Salomon Rémi, Saunier Sophie, Niaudet Patrick. Nephronophthisis. *Pediatr Nephrol* 2009;24:2333–44.
- [16] Bergmann C. Educational paper. *Eur J Pediatr* 2012;171(9):1285–300.
- [17] Ronquillo CC, Bernstein PS, Baehr W. Senior-Loken syndrome: a syndromic form of retinal dystrophy associated with nephronophthisis. *Vision Res* 2012;75:88–97.
- [18] Antignac C, Arduy CH, Beckmann JS, Benessy F, Gros F, Medhioub M, et al. A gene for familial juvenile nephronophthisis (recessive medullary cystic kidney disease) maps to chromosome 2p. *Nat Genet* 1993;3:342–5.
- [19] Omran H, Sasmaz G, Haffner K, Volz A, Olbrich H, Melkaoui R, et al. Identification of a gene locus for Senior-Loken syndrome in the region of the nephronophthisis type 3 gene. *J Am Soc Nephrol* 2002;13:75–9.

- [20] Schuermann MJ, Otto E, Becker A, Saar K, Ruschendorf F, Polak BC, et al. Mapping of gene loci for nephronophthisis type 4 and Senior-Loken syndrome, to chromosome 1p36. *Am J Hum Genet* 2002;70:1240–6.
- [21] Halbritter J, Porath JD, Diaz KA, Braun DA, Kohl S, Chaki M, et al. GPN Study Group. Identification of 99 novel mutations in a worldwide cohort of 1,056 patients with a nephronophthisis-related ciliopathy. *Hum Genet* 2013;132(8):865–84.
- [22] Stone EM, Cideciyan AV, Aleman TS, Scheetz TE, Sumaroka A, Ehlinger MA, et al. Variations in *NPHP5* in patients with nonsyndromic leber congenital amaurosis and Senior-Loken syndrome. *Arch Ophthalmol* 2011;129(1):81–7.
- [23] Estrada-Cuzcano A, Koenekoop RK, Coppieters F, Kohl S, Lopez I, Collin RW, et al. *IQCB1* mutations in patients with leber congenital amaurosis. *Invest Ophthalmol Vis Sci* 2011;52(2):834–9.
- [24] Cideciyan AV, Rachel RA, Aleman TS, Swider M, Schwartz SB, Sumaroka A, et al. Cone photoreceptors are the main targets for gene therapy of *NPHP5* (*IQCB1*) or *NPHP6* (*CEP290*) blindness: generation of an all-cone *Nphp6* hypomorph mouse that mimics the human retinal ciliopathy. *Hum Mol Genet* 2011;20(7):1411–23.
- [25] Al-Awadi SA, Moussa MA, Naguib KK, Farag TI, Teebi AS, el-Khalifa M, et al. Consanguinity among the Kuwaiti population. *Clin Genet* 1985;27(5):483–6.
- [26] Tadmouri GO, Nair P, Obeid T, Al Ali MT, Al Khaja N, Hamamy HA. Consanguinity and reproductive health among Arabs. *Reprod Health* 2009;8:6–17.
- [27] Hamamy H, Bittles AH. Genetic clinics in Arab communities: meeting individual, family and community needs. *Public Health Genomics* 2009;12(1):30–40, Review.