

## Exceptional Case

# Nail-patella syndrome—a novel mutation in the *LMX1B* gene

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### Abstract

Nail-patella syndrome (NPS) is an autosomal-dominant pleiotropic disorder characterized by dysplasia of finger nails, skeletal anomalies and frequently renal disease. In the reported case, genetic analysis revealed a new missense mutation in the homeodomain of *LMX1B*, presumed to abolish DNA binding (c.725T>C, p.Val242Ala). A missense mutation at codon 725 was identified, where thymine was replaced by cytosine which led to the replacement of valine by alanine at position 242. It was not detected in both parents. A 2005 study by Bongers *et al.* described a significant association between the presence of clinically relevant renal involvement in an NPS patient and a positive family history of nephropathy, which was lacking in our case.

**Keywords:** *de novo* *LMX1B* mutation; end-stage renal disease (ESRD); Nail-patella syndrome (NPS); renal transplantation

### Introduction

Nail-patella syndrome (NPS) is a rare autosomal-dominant genetic disorder (1 in 50 000 live births) due to heterozygous mutations in the *LMX1B* gene resulting in symmetrical nail, skeletal, ocular and renal abnormalities [1, 2]. This gene is a transcription factor involved in the normal dorso-ventral patterning of limb and development of glomerular basement membrane (GBM) in the kidney [3]. Renal involvement is found in 60% of cases, of which 15% progress to end-stage renal disease (ESRD) [4]. We report a case of NPS complicated by severe ocular anomalies and ESRD caused by a *de novo* mutation in the *LMX1B* gene; the patient underwent a successful renal transplantation.

### Case report

A 29-year-old male was referred to our hospital with end-stage renal failure. At 6 months of age he was diagnosed with sclerocornea and congenital glaucoma; he had a progressive loss of vision and became blind by eight years of age. He had limited extension of the elbows and recurrent subluxation of both knee joints since birth. He was found to have proteinuria at 9 years of age. Six years later, he was detected to have hypertension. At the age of 25 years, he developed pedal oedema and renal insufficiency. A renal biopsy showed severe glomerulosclerosis and interstitial fibrosis and he was on conservative management for chronic kidney disease. He developed ESRD and was initiated on hemodialysis at the age of 28 years. Neither of his parents nor his younger sister have similar clinical features. He had a normal

scholastic performance and had a post-graduate qualification.

Physical examination revealed pallor, bilateral pedal oedema and systemic hypertension. Ophthalmological examination showed sclerocornea of both eyes with spontaneous nystagmus and bilateral ptychosis bulbi (Figure 1a). He had antecubital pterygium, bilateral small and dislocated patellae, and nail dysplasia comprising of longitudinal ridging and splitting of the thumbnails (Figure 1b). Systemic examination was unremarkable.

Biochemical investigations and ultrasonogram of kidneys confirmed chronic kidney disease (Stage 5). Radiography of the knee and elbows joints revealed hypoplastic and dislocated patellae (Figure 2a) and ankylosis of elbow joints (Figure 2b). No iliac horns were observed.

DNA analysis was done. Direct sequencing of the eight-coding exons and flanking introns of the *LMX1B* gene was carried out [5]. In this patient, a new missense mutation in the homeodomain of *LMX1B* was identified, presumed to abolish DNA binding (c.725T>C, p.Val242Ala). The patient had a missense mutation at codon 725 where thymine was replaced by cytosine. This missense mutation led to a replacement of valine by alanine at position 242. This mutation was not detected in either parent.

His mother aged 46 years volunteered to donate a kidney. A live-related donor renal transplantation was performed for this patient at the age of 29 years. He had an uneventful postoperative period and the graft function is normal 4 years after transplantation.

### Discussion

NPS or osteo-onychodysplasia is an autosomal-dominant disorder characterized by hypoplastic or absent patellae,



Fig. 1. (a) Photograph showing the patient's sclerocornea and ptosis bulbi. (b) showing dystrophic thumb nail.

dystrophic fingernails and/or toenails, elbow dysplasia, iliac horns, frequently glaucoma and progressive nephropathy due to the mutations in the *LMX1B* gene on human chromosome 9q34 [6].

The *LMX1B* gene consists of 372 amino acids and encodes a transcription factor with two zinc binding LIM domains at the NH<sub>2</sub>-terminal, a DNA-binding homeodomain in the middle and a putative activation domain at the COOH<sup>-</sup> terminal. Most mutations in the *LMX1B* gene have been detected in those regions encoding the LIM domains and the DNA-binding homeodomain. Individuals with an *LMX1B* mutation located in the DNA-binding homeodomain showed significantly more frequent and more severe proteinuria and renal failure compared with subjects carrying mutations in the LIM domains [7].

Our patient with NPS had a *de novo* missense mutation in the homeodomain of *LMX1B*, not previously described in the literature; he had severe ocular and renal complications. The *LMX1B* gene is involved in the correct binding of DNA in the transcriptional regulation of key eukaryotic developmental processes. Both parents of the patient have been tested to exclude the possibility of a rare polymorphism, and found not to have this mutation, proving that this is a *de novo* mutation.

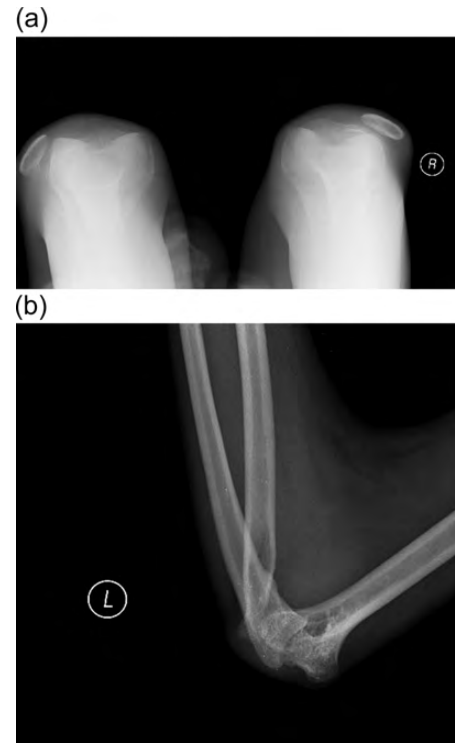


Fig. 2. (a) X-ray of knees showing bilateral dislocated patellae. (b) X-ray showing ankylosis of elbow joint.

The missense mutation in *LMX1B* gene product in the index case is shown (Figure 3). The position of intron-exon boundaries is indicated by dotted lines, and the boundaries between the domains are indicated by solid lines. HD denotes homeodomain [8].

Interestingly, nephropathy appeared to be more frequent in females. A significant association was described between the presence of clinically relevant renal involvement in an NPS patient and a positive family history of nephropathy [7], which was, however, lacking in our case.

Remarkable phenotypic variability at the individual, intrafamilial and interfamilial level was observed for different NPS manifestations [9]. Renal involvement determines the prognosis. The symptoms range from proteinuria and hematuria to features of chronic renal failure. Ultrastructurally, the thickened GBM has a moth-eaten appearance, the cause of which is the presence of electron-lucent areas containing fibrillar deposits resembling fibrillar collagen (Figure 4).

Renal transplantation is a viable therapeutic modality in the treatment of ESRD in patients with NPS, and the disease does not recur in the kidney grafts [10].

Whether the *de novo* mutation identified here is consistently associated with severe renal involvement and progression to ESRD remains to be studied in future. No clear genotype-phenotype association was apparent for extrarenal manifestations as phenotype is highly variable, and this is one sporadic case only. Further studies on modifier factors are needed to understand the mechanisms underlying phenotypic heterogeneity. A careful evaluation of potential living kidney donors for features of the disease is essential.

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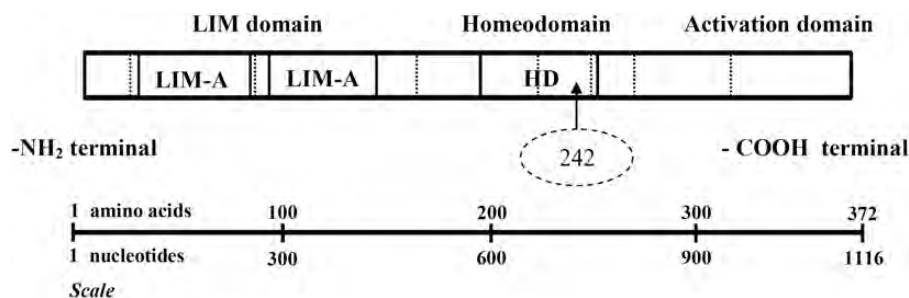


Fig. 3. *De novo* missense mutation in the homeodomain of LMX1B (at position 242).

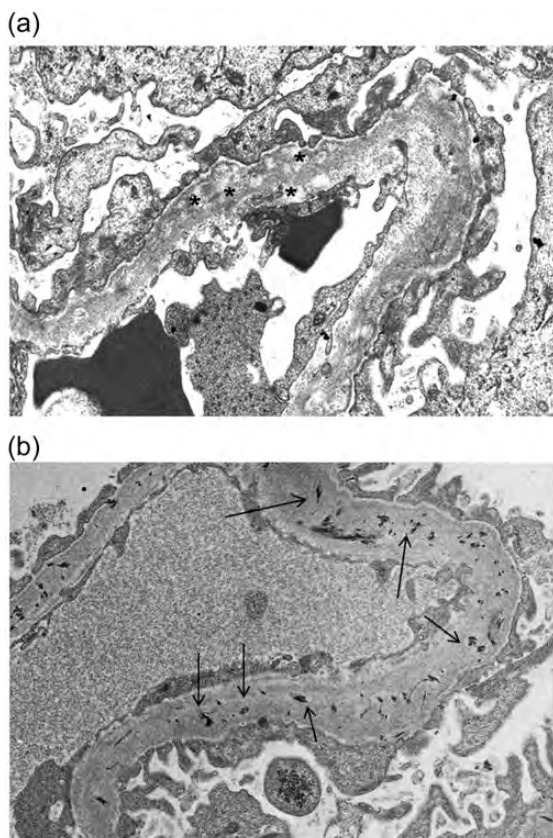


Fig. 4. (a) Electron microscopy image shows many electron-lucent areas in the thickened GBM that assumes a 'moth-eaten' appearance (\*), irregular effacement of foot processes. Uranyl acetate and lead citrate,  $\times 8500$  (Courtesy of Marie-Claire Gubler, Hôpital Necker and INSERM U983 Paris, France). (b) Electron microscopy image after phosphotungstic acid staining, detection of dark fibrillar material (arrows) within the GBM,  $\times 8000$  (Courtesy of Marie-Claire Gubler, Hôpital Necker and INSERM U983 Paris, France).

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*Conflict of interest statement.* None declared.

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