

Case Report

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LMX1B gene mutation in a Saudi patient with bilateral symmetrical hypoplastic nails of the hands

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Abstract

Nail-patella syndrome (NPS) is a rare autosomal dominant disorder that is highly penetrant with marked phonotypical variability among inter- and intra-familial cases. We describe here a full-term newborn baby girl with a characteristic phenotype of familial bilateral symmetrical hypoplastic nails of the upper limbs and small patellae were displaced by ultrasound. This patient has a homozygous mutation in the gene encoding LIM homeobox transcription factor 1 beta (*LMX1B*).

Molecular DNA sequencing revealed that this is the first report in the literature linking a homozygous c.268C>T (p.Phe90Leu) mutation located within the highly conserved LIM-A domain of the *LMX1B* gene with presentation of NPS. Familial molecular analysis showed that both parents are heterozygous for the c.268C>T mutation. Therefore, prenatal diagnosis and genetic counselling are important considerations for family future planning.

Keywords: Nail-patella syndrome (NPS); Hypoplastic nails; Clubfoot; *LMX1B*

Introduction

Nail-patella syndrome (NPS) (OMIM 161200), also known as Osteo-onychodysplasia is a rare autosomal dominant disorder that is clinically associated with absent or hypoplastic finger and toe nails, absent or hypoplastic patellae, elbow dysplasia, and iliac horns. Variable clinical presentation has been reported in NPS, with some association with nephropathy, hypoplasticity of the posterior subluxation of the radial head and glaucoma. Males and females are equally affected with an estimated prevalence of 1 in 50,000 livebirths [1]. Genetic studies have demonstrated that loss function of the LIM homeobox transcription factor 1 beta (*LMX1B*) gene is responsible for NPS. *LMX1B* was mapped on to the long arm of chromosome 9 (9q34) [2] and is required essentially for the normal development of dorsal limb structures, the glomerular basement membrane and the anterior segment of the eye [3-6].

Materials and Methods

A full-term newborn baby girl was delivered via normal spontaneous vaginal delivery by a 29-year-old mother (Gravida 4, Para 3) without any complication and with no history of any medication during pregnancy. The birth weight was 2.47 kg, in the 10th to 25th percentile range; the length was 49 cm, in the 50th to 75th percentile range; and the head circumference was 31 cm, at the 10th percentile. Her heart rate was 140/minute, and her Apgar score was 9 at the first minute and 10 at fifth minute. Generally, the baby appeared well and active with no dysmorphic features noted other than a clubfoot.

On the second day after delivery, the baby presented with hyperbilirubinemia and ABO blood incompatibility. Her 8 year male brother was reported to have bilateral hypoplasticity of the posterior subluxation of the radial head, hypoplastic nail, and minimal valgus on left knee with cortical defect at the medical distal aspect of right femoral shaft. His renal function, ophthalmological finding and hearing were unremarkable. But no final diagnosis was made because the family lived in a rural area where no tertiary health services were available. There was no known consanguinity among the parents. Blood samples were obtained from the patient with informed consent from her parents and healthy controls. Genomic DNA was extracted from peripheral blood leukocytes using standard techniques. The *LMX1B* gene was amplified by PCR and bi directionally sequenced using an ABI Prism Big Dye Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems, Foster City, CA) in an ABI 3130 Genetic Analyzer sequencer (Applied Biosystems). Mutations were identified by comparison to a reference sequence (GenBank Accession No. NM_002316.3; http://www.ncbi.nlm.nih.gov) using CLC Genomics Workbench v4.0 (CLC bio, Aarthus, Denmark) and were checked against the updated SNP database (dSNPs; http://www.ncbi.nlm.nih.gov).

Results

Upon further physical examination, bilateral hypoplastic nails of the hands with absent nails on both thumbs were noted. The elbows showed cubitus valgus, and a right clubfoot was observed. There was no organomegaly. A hip x-ray showed the presence of iliac horns with normally located femoral heads. Knee ultrasound showed cartilaginous patellae bilaterally and no effusion. The baby's head showed a large anterior and a posterior fontanel. Brain magnetic resonance imaging showed focal cystic changes in the deep white matter of the left temporal lobe and no other significant abnormality. Renal and abdominal ultrasounds were normal. In addition, blood and urinalyses were

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normal, and no proteinuria was observed. The baby's blood group was A+, and a direct Coombs test was positive. Patient karyotype analysis revealed normal female (46, XX) chromosomes. Ophthalmologic examination revealed no abnormality. The parents and the rest of the patient siblings were well and healthy with normal renal function.

LMX1B molecular mutation analysis of the patient revealed the presence of two homozygous missense mutations, (c.268C>T, p.Leu90Phe) and (c.372A>G, p.Glu124Glu), in exon 2 and exon 3 of the *LMX1B* gene, respectively. The novel c.268C>T (p.Leu90Phe) mutation (Figure 1a) has not been previously reported in any public database and was not found in 50 healthy and ethnically matched control individuals. However, the c.372A>G mutation is considered a single nucleotide polymorphism (SNP) and is registered in dSNPs as rs227158. Both parents are heterozygous for both the c.268C>T and c.372A>G mutations. Protein sequence alignment showed that the leucine at position 90 mutation was identified in highly conserved amino acid within the LIM-A domain across different species (Figure 1b).

Discussion

NPS is inherited via autosomal dominance due to loss-of-function mutations of the *LMX1B* gene, which belongs to a family of LIM homeodomain transcription factors containing two N-terminal zinc-binding LIM domains (LIM-A, LIM-B), a homeodomain, and a C-terminal glutamine-rich domain. LIM domains are involved in interactions with other transcription factors and synergistic activation of transcription; therefore, *LMX1B* is required during developmental





В	Ļ
Patient	LQCAACQQA F TTSCYFRDRK
HUMAN	LQCAACQQA L TTSCYFRDRK
Mus musculus	LQCAACQQA L TTSCYFRDRK
Canis lupus familiaris	LQCAACQQA L TTSCYFRDRK
Gallus gallus	LQCAACQQA L TTSCYFRDRK
Rattus norvegicus	LQCAACQQA L TTSCYFRDRK

Figure 1b: Protein sequence alignment of *LMX1B* from different species showing the highly conserved amino acid sequence and the positions of p.Leu90Phe mutation in *LMX1B* as indicated by an arrow.

processes including dorso-ventral patterning of the limb and normal development of the kidney and eye [1,3-5]. Studies have shown that homozygous inactivation of *lmx1b* in mice and chickens resulted in nail and skeletal defects that were associated with renal abnormalities, as in humans [6-8]. Dysplastic or hypoplastic nails, absent or hypoplastic patella, dysplasia of the elbow and iliac horns are the major (in more than 98%) clinical findings seen in NPS patients [1,9]. Other skeletal abnormalities may be present, such as poorly developed shoulder blades, clinodactyly, clubfoot, scoliosis, and unusual neck bones [8,10].

There are more than 140 mutations in the *LMX1B* gene reported within the Human Gene Mutation Database at the Institute of Medical Genetics in Cardiff (http://www.hgmd.cf.ac.uk/ac/index. php). Recently, bilateral clubfeet were reported in four NPS patients with *LMX1B* mutations [7], and nephropathy and ocular anomalies were variably reported in some cases of NPS [1,8]. Our recent finding [11] and the current work demonstrate that the p.Leu90Phe mutation of *LMX1B* gene cause the presentation of a nail anomaly, a patella anomaly, an elbow anomaly, iliac horns and a unilateral clubfoot. Renal, ophthalmological and hearing anomalies were not seen in our patient or maybe the patient is too young yet to manifest these features. Molecular analysis revealed the presence of homozygous (c.268C>T, p.Leu90Phe) missense mutations within the highly conserved LIM-A domain of the *LMX1B* gene.

Conclusions

We conclude that our patient represents a number of clinical finding that shared with NPS such as (i) abnormal nails on the hands, (ii) one clubfoot, (iii) iliac horns and (iv) cubitus valgus on both elbows. The patient's head showed a large anterior and a posterior fontanel with focal cystic changes in the deep white matter of the left temporal lobe of the brain. This is the first report showing a mutation in the *LMX1B* gene that causes NPS with an autosomal recessive expression in a Saudi family with well healthy parents. This suggests further heterogenousity of NPS associated with different mutations spectrum in the *LMX1B* gene and provide insight into the underlining pathology of NPS.

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Statement of Competing Interests

The authors have no competing interests.

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