Nail Patella Syndrome: A Case Report and Review of Literature

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Abstract

Nail patella syndrome is a rare autosomal dominant disorder characterized by nail dysplasia, absent or hypoplastic patella, abnormality of the elbows and presence of iliac horns. Here, we report a case of a one-and-half-year-old girl with nail patella syndrome. Mutation analysis of the patient revealed a known *de novo* pathogenic variant, c.668G>A (p.R223Q) in exon 4 of the *LMX1B* gene.

Introduction

Nail patella syndrome (NPS) (OMIM 161200) is characterized by absent or hypoplastic, split or ridged and discolored nails, small and irregular or absent or dislocated patellae, elbow deformity that limits the movements of pronation or supination and the presence of bilateral iliac horns. Additional features like nephropathy and glaucoma are observed within the disease spectrum. The prevalence of this condition is about 1 in 50,000 individuals. Haploinsufficiency of *LMX1B* (OMIM 602575) due to the presence of pathogenic variants is known to cause this condition. *LMX1B* encodes an LIM homeobox transcription factor 1 beta, which is a member of LIM-homeodomain family. This transcription factor is essential for the dorsoventral patterning of the limbs, normal development of the kidney, eyes and dopaminergic and serotonergic neurons. In this article, we report a patient with NPS due to a known variant in *LMX1B*.

Case report

The patient was a one-and- half-year-old girl. She was the only child born to a non-consanguineous couple at term with no antenatal or neonatal complications. She had first presented at 19 days of age, with a left club foot deformity and bilateral dislocation of knee-caps. On examination she had prominent forehead, depressed nasal bridge, and dystrophic nails with longitudinal ridges (Fig 1 A-C). Ultrasound examination of both knees showed small patellae with bilateral dislocation. Radiologic examination of both hips showed bilateral iliac horns (Fig 1 D-G). Rest of the systemic examination was normal.

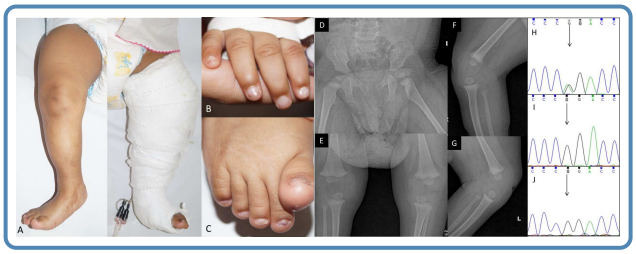

Figure 1 Clinical photographs of the patient showing skin dimpling due to the hypoplastic patella and cast application after tenotomy for congenital talipes equinovarus deformity of the left foot (A), and hypoplastic nails in the fingers (B) and toes (C). Radiographs showing bilateral iliac horns (D) and anteroposterior (E) and lateral view of knee joints (F and G). Electropherogram of exon 4 of *LMX1B* in the patient (H) showing the variant c.668G>A (indicated by black arrow) and electropherograms of the mother (I) and father (J) showing absence of this variant (indicating de novo occurrence of the variant).

At two months of age, Achilles tenotomy was done in view of left congenital talipes equinovarus (CTEV). Diagnosis of nail patella syndrome was made on clinical and radiological grounds.

Follow-up at 8 months of age showed normal developmental milestones and her length was 66cm (normal). Her renal function tests and ophthalmologic evaluations were within normal limits. The study has the approval of institutional ethics committee and written informed consent was taken from the patient. We performed Sanger sequencing of *LMX1B* which revealed a known pathogenic variant c.668G>A (p.R223Q) in exon 4. Sequence analysis of parents did not reveal this variant suggesting the *de novo* occurrence of the mutation (Fig 1 H-J).

Discussion

Clinically, the classical presentation of NPS involves changes in nails, knees, elbows and presence of iliac horns. However, the severity of the disease varies extremely within individuals of the same family also. Many families may remain undiagnosed because of the mild phenotype. As multiple systems are involved in NPS, there may be a predominance of disease in one system whereas others may be minimally affected. The spectrum of orthopedic afflictions includes 'swan necking' of index finger, patellar abnormalities (dysplasia, small patellae), tight hamstring muscles and congenital talipes equinovarus (CTEV). Pinette et al., reported a case of prenatal diagnosis of NPS by identifying skeletal dysplastic changes (absence of left patella and severe malrotation of left foot) in an anomaly scan establishing the importance of a targeted anomaly scan in afflicted families. Renal impairment complicates 40% cases of NPS. Primary open angle glaucoma and ocular hypertension are common ophthalmologic findings. Hence, annual screening for nephropathy (blood pressure monitoring, urinalysis and urine albumin/ creatinine ratio) and for glaucoma form part of NPS patient care. In the present study, the patient had three of the classic tetrad of features typical of NPS. However, there were no signs of elbow deformity, nephropathy, and glaucoma which have been reported as consistent features of this condition and she would require annual surveillance for the same.

More than 400 cases with NPS have been reported so far all over the world and more than 140 pathogenic variants have been identified in patients with NPS. Different types of mutations including missense, nonsense, frameshift, and splice site mutation, as well as partial and whole gene mutations have been identified in *LMX1B*. In majority of the cases (88%) the variants are inherited from a parent in an autosomal dominant manner and in some cases (12%) the mutation arises *de novo*. *LMX1B* regulates expression of genes encoding alpha 3 and alpha 4 chains of collagen IV, interstitial type III collagen, podocin and CD2AP that form slit pore membrane connecting podocytes. The pathogenic variant identified in this study is found in the mutation hotspot of *LMX1B* which spans exons 2-6. Missense mutations are found to be most commonly present at the mutation hotspot. Therefore, the diagnostic strategy would be to analyze the mutation hotspot. If no pathogenic variants are found, then deletion/duplication analysis is considered.

Identification of *LMX1B* pathogenic variants supports the role of this gene in the causation of NPS and reinforces the importance of molecular genetic testing as part of prenatal counseling for families with affected individuals.

References

1. Bongers EM, et al. Nail-patella syndrome. Overview on clinical and molecular findings. Pediatr Nephrol 2002; 17: 703-712.
2. Dunston JA, et al. The human *LMX1B* gene: transcription unit, promoter, and pathogenic mutations. Genomics 2004; 84: 565-576.
3. Figueroa-Silva O, et al. Nail-patella syndrome: report of 11 pediatric cases. J Eur Acad Dermatol Venereol. 2016; 30:1614-1617.
4. Lemley KV. Kidney disease in nail-patella syndrome. Pediatr Nephrol 2009; 24: 2345-2354.
5. Lichter PR, et al. Cosegregation of open-angle glaucoma and the nail-patella syndrome. Am J Ophthalmol 1997; 124: 506-515.
6. McIntosh I, et al. Mutation analysis of *LMX1B* gene in nail-patella syndrome patients. Am J Hum Genet 1998; 63: 1651-1658.
7. Miner JH, et al., Transcriptional induction of slit diaphragm genes by *LMX1B* is required in podocyte differentiation. J Clin Invest 2002; 109: 1065-1072.
8. Pinette MG, et al. Early prenatal diagnosis of nail-patella syndrome by ultrasonography. J Ultrasound Med 1999; 18: 387-389.
9. Sweeney E, et al. Nail patella syndrome: a review of the phenotype aided by developmental biology. J Med Genet 2003; 40: 153-162.
10. Sweeney E, et al. Nail-Patella Syndrome, GeneReviews(R). In: Pagon RA, et al (Eds.), 1993 -. University of Washington, Seattle. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1132/. Accessed on 10th March, 2017.