Novel *LMX1B* variants in nail-patella syndrome

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Nail-patella syndrome (NPS, OMIM #161200) is a rare autosomal dominant multisystem disorder with an estimated prevalence of 1 in 50 000 population.[1] Despite its complete penetrance, underdiagnosis is suspected due to highly variable expressivity; presentations range from clinically significant skeletal anomalies accompanied by end-stage renal disease to isolated nail dystrophy. The achievement of a molecular diagnosis has broad implications for surveillance and management because ophthalmic and gastrointestinal involvement have been reported in association with NPS.[1]

In this commentary, we summarised the clinical and molecular characteristics of seven cases with molecularly confirmed NPS from five unrelated families at our hospital. The affected individuals ranged from 11 years to 73 years. All individuals in our cohort were male, except for Individual 2 (male-to-female ratio=6:1). A positive family history, with at least one clinically affected relative, was identified for each individual except Individual 5, who was subsequently confirmed to harbour a de novo *LMX1B* (LIM homeobox transcription factor 1 beta) variant.

Nail involvement was present in almost all affected individuals (6/7, 85.7%). Nail dystrophy with bilateral involvement, the most common manifestation, was associated with varying degrees of ridging and splitting. Triangular lunulae were identified in two affected individuals (28.6%), while knee involvement was observed in four affected individuals (57.1%). Three individuals (42.9%) displayed bilaterally small patellae, two of whom experienced complications with subluxation, whereas one exhibited bilaterally absent patellae. Elbow involvement was evident in only two individuals: one presented with bilateral elbow flexion contracture deformity and the other showed limited bilateral elbow movement. Bilateral iliac horns were detected in three affected individuals. Renal involvement was identified in only one individual (14.3%), who exhibited microscopic haematuria; the remaining individuals showed no renal manifestations. Three individuals presented with ocular manifestations. Notably, Individual 2 displayed ptosis and corneal opacity at birth; she was subsequently diagnosed with bilateral congenital ectropion uvea with glaucoma, which was complicated by high myopia and lattice degeneration of the retina in the right eye and rhegmatogenous retinal detachment in the left eye. Her father (Individual 3) had experienced blindness in his right eye since birth, as well as bilateral glaucoma. Individual 7 had underlying bilateral high myopia of -7.0 dioptres, which was complicated by cataract in the right eye at age 32 years. The variants were distributed across the *LMX1B* gene. Three affected families exhibited intragenic variants: two nonsense variants and one missense variant. Among these, two were novel variants, whereas the *LMX1B* c.745C>T nonsense variant had been previously reported.[2,3] Three individuals from two unrelated families harboured novel exon deletions. The clinical and molecular findings of these patients are summarised in the Figure, the online supplementary Figure and the online supplementary Table.

Nail-patella syndrome is a rare condition characterised by substantial inter- and intrafamilial variability. Some individuals in our cohort (Individuals 2, 3, and 5) showed symptoms from early infancy, whereas others (Individuals 4 and 7) were diagnosed in adulthood during incidental family screening or routine health checks. Nail anomalies are the most common feature, identified in >95% of affected individuals, consistent with observations in our cohort.[1,4] In particular, Individuals 1 and 2 had triangular lunulae, a feature considered pathognomonic for NPS. Skeletal anomalies involving the knee and elbow are described in 70% of affected individuals.[1,4] The detection of hypoplastic patellae may be challenging through physical examination alone, but iliac horns are often evident on radiographs. Although the proportion of knee involvement in our cohort aligns with previous literature reports, elbow involvement was considerably less frequent.[1,4]

The majority of individuals with NPS inherit pathogenic variants from a parent—an estimated 15% of cases in the literature have been attributed to de novo variants.[1] All individuals in our cohort had a positive family history except for Individual 5. Ascertainment bias is a concern because some at-risk relatives with mild symptoms, often comprising

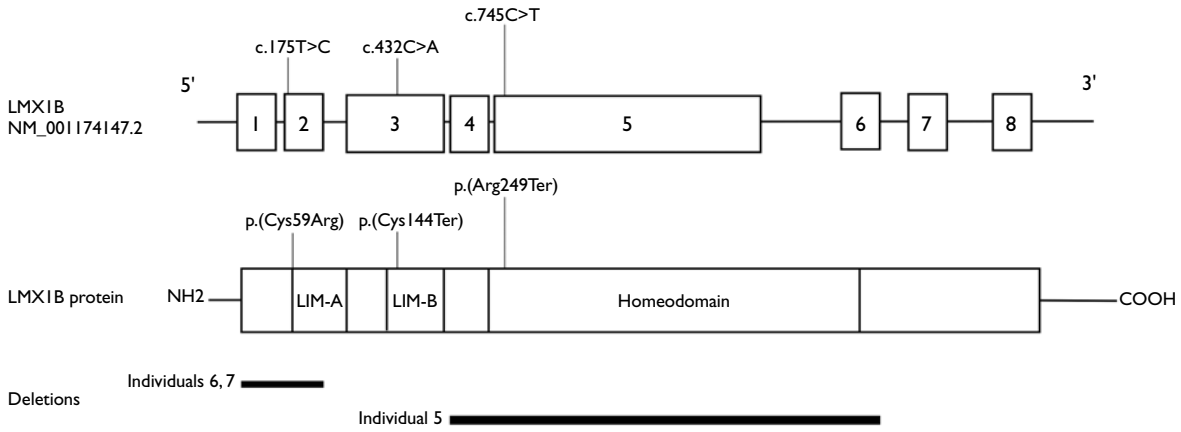

FIG. Distribution of *LMX1B* variants in our cohort

isolated nail dystrophy, declined molecular confirmation. Consequently, the clinical burden of NPS may be overestimated, but underdiagnosis remains prevalent. Renal involvement, reported in up to half of affected individuals and associated with the risk of end-stage kidney disease,[1,5] was identified in only one individual in our cohort (Individual 1), who displayed microscopic haematuria during surveillance. No individuals in our cohort showed renal impairment, which may be explained by the age-dependent penetrance of renal symptoms and the relatively young age of these individuals. Other rare features previously reported in association with NPS, such as vascular anomalies and reduced bone mineral density, were not observed in our cohort.

Thus far, *LMX1B* is the only gene implicated in NPS; it is typically interrogated through sequencing analysis, which detects up to 85% of variants, followed by dosage analysis using techniques such as multiplex ligation-dependent probe amplification.[1] Although most pathogenic variants (80%) reportedly occur in the LIM domain of *LMX1B*,[1] the variants identified in our cohort were distributed throughout the gene, with only c.175T>C and c.432C>A located in the LIM-A and LIM-B domains, respectively (Fig). Two families in our cohort harboured exon deletions. The mutation spectrum observed in our cohort does not entirely align with descriptions in the literature, but this discrepancy may reflect the relatively small number of patients included in the study. Ophthalmic involvement has been reported in 10% to 25% of affected individuals.[1,4] In our cohort, two affected individuals from the same family (Individuals 2 and 3), carrying the c.745C>T variant, exhibited severe ocular manifestations and impaired vision from early infancy. While this variant has been described in the literature, it was not previously linked to ophthalmic involvement in NPS.[2,3] Further research is required to determine whether ethnicity influences phenotypic and genotypic differences, considering that our cohort mostly comprised individuals of Chinese ethnicity.

Author contributions

Concept or design: LT Leung, SKL Ho.
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Analysis or interpretation of data: LT Leung, SKL Ho, WC Yiu.
Drafting of the manuscript: LT Leung, SKL Ho.
Critical revision of the manuscript for important intellectual content: SSW Cheng, IFM Lo, HM Luk.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

The authors declared no conflicts of interest.

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Ethics approval

The patients were treated in accordance with the Declaration of Helsinki and provided informed consent for publication of this commentary, including the publication of clinical photos.

Supplementary material

The supplementary material was provided by the authors, and some information may not have been peer reviewed. Accepted supplementary material will be published as submitted by the authors, without any editing or formatting. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by the Hong Kong Academy

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Answers to CME Programme

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I. Management of chronic kidney disease: a Hong Kong consensus recommendation

A	1. True	2. False	3. True	4. False	5. True
B	1. True	2. False	3. True	4. True	5. False

Hong Kong Med J 2024;30:488-97

II. 2024 Hong Kong College of Obstetricians and Gynaecologists Guidelines for cervical cancer prevention and screening

A	1. True	2. True	3. False	4. False	5. False
B	1. False	2. True	3. False	4. True	5. True