

The nail points to the diagnosis

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Hong Kong Med J 2015;21:573.e3-5

DOI: 10.12809/hkmj154728

A 54-year-old man was referred to the genetic clinic with familial nail dysplasia in September 2012 (Fig 1). On further questioning, he reported recurrent knee pain due to patellar dislocation. There was no elbow involvement or renal problem. A skeletal survey was performed in view of his skeletal complaint (Fig 2). His family history was significant: his paternal grandfather, father, and two of his paternal uncles also had nail dysplasia and knee problems, but had undergone no formal medical assessment. What is the diagnosis?

What is his diagnosis?

The combination of nail dysplasia, patella hypoplasia, and iliac horn led to the clinical diagnosis of nail-patella syndrome (NPS). This syndrome is

also known as Fong disease or hereditary osteo-onychodysplasia. Multiple organ systems are affected including the nails, the eyes, the kidneys, and the skeleton. The clinical presentation of NPS can be highly heterogeneous and is summarised in the Table.^{1,2} It is a rare autosomal dominant disease with a prevalence of about 1 in 50000 newborn.¹ It is highly penetrant but with significant intra- and inter-familial variability in expression.

Is there any genetic testing available for such condition and what is the underlying pathogenesis?

The diagnosis of NPS is usually based on clinical findings. It is straightforward when the classic tetrad of abnormal nails, elbows, knees, and iliac horns

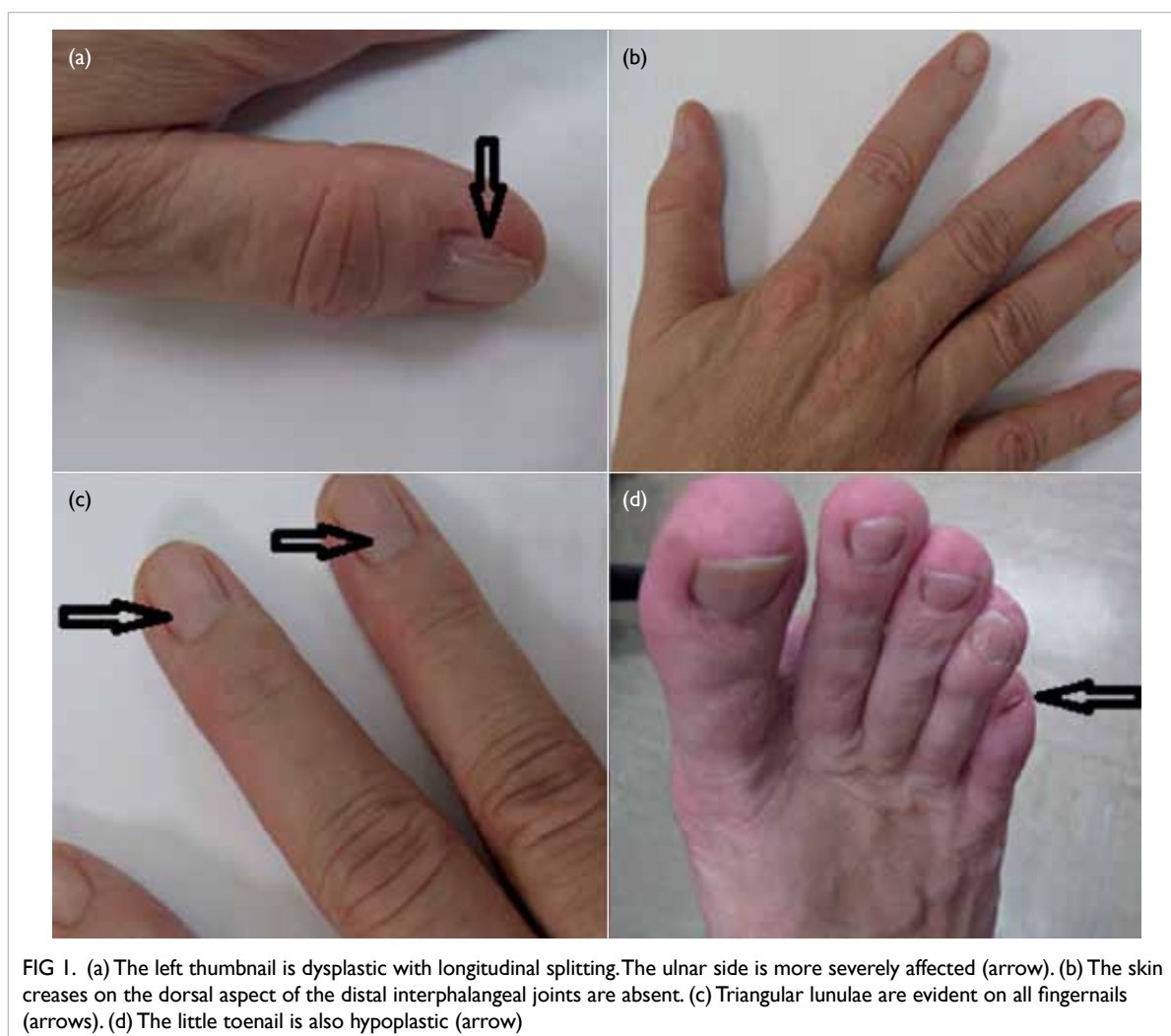




FIG 2. (a and b) The patellae are hypoplastic and laterally displaced (arrows). (c) A radiograph of the elbow showing no abnormalities. (d) Bilateral iliac horns on the posterolateral aspect of the pelvis are observed (arrows)

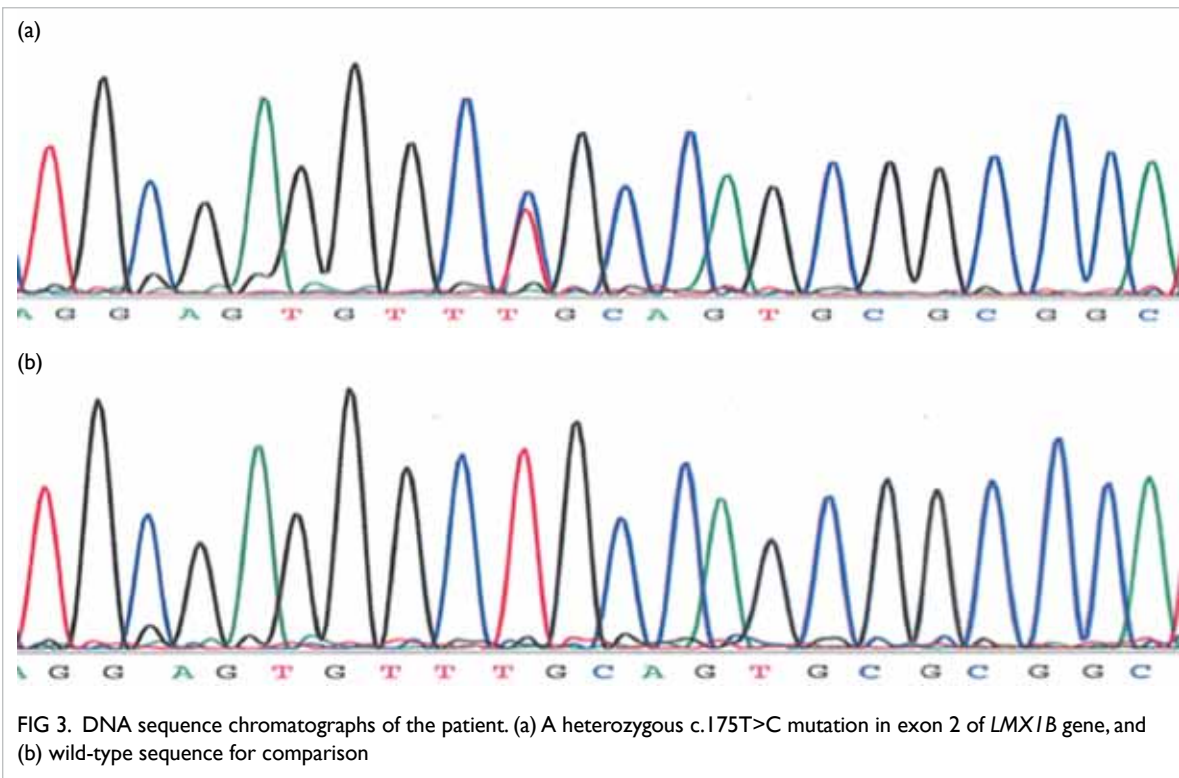
TABLE. Clinical manifestations of nail-patella syndrome^{1,2}

Organ involvement	Clinical features	Prevalence
Nail	Nail dysplasia	93%
	Triangular nail lunulae	
	Nail hypoplasia	
	Longitudinal ridging	
	Anonychia, hemianonychia	
	Splitting spoon-shaped nail	
	Flaky nail	
Skeletal	Knee dysplasia	93%
	Patella aplasia/hypoplasia	
	Hypoplasia of lateral femoral condyle	
	Elbow dysplasia	93%
	Radial head hypoplasia	
	Capitellum hypoplasia	
	Pelvic dysplasia	70-80%
	Iliac horns	
	Foot dysplasia	
	Equinovarus, equinovalgus	
Ophthalmological	Primary open-angle glaucoma	10%
	Ocular hypertension	
	Lester's sign of iris	42-54%
Renal	Proteinuria +/- haematuria	12-55%
	Renal failure	

are present. Nonetheless molecular genetic testing should be considered when the diagnosis is in doubt, or when prenatal or pre-implantation diagnosis is desired. The *LMX1B* gene is the only gene known to be associated with NPS. Sequence analysis would identify the *LMX1B* gene mutation in 85% of cases of NPS.

LMX1B gene sequencing was performed for this patient (Fig 3) and revealed a missense mutation *LMX1B* NM_002316.3:c.[175T>C];[=];*LMX1B*{NP_002307.2}:p.[Cys59Arg];[=]. This changed the 59th amino acid from cysteine to arginine in the LIM-A domain of the *LMX1B* protein. It was located in an evolutionarily highly conserved region and has been reported in the literature to be associated with NPS. Therefore, it was considered to be pathogenic.³

To date, more than 150 mutations of the *LMX1B* gene have been reported, but no clear genotype-phenotype correlation has been demonstrated. *LMX1B* has been demonstrated in animal models to be involved in multiple developmental functions including dorso-ventral patterning of the limb



BOX. Recommended management for patients with nail-patella syndrome²

- Annual screening for renal disease from birth that includes urinalysis and blood pressure measurement. Referral to renal physician if abnormality is detected.
- Screening for intra-ocular pressure every 2 years from adulthood.
- Magnetic resonance imaging should be considered for abnormal anatomy of both bone and soft tissue if clinically indicated.
- Genetic counselling should be offered to all patients with nail-patella syndrome.

bud, and cellular differentiation in the kidney. Nonetheless the exact pathogenesis of NPS has not been elucidated.⁴

How to manage this patient?

Upon initial diagnosis, comprehensive renal, orthopaedic, and ophthalmological assessments are essential. The renal manifestation strongly affects the long-term prognosis. Kidney involvement occurs in 30% to 50% of patients, but kidney failure only occurs in 3% to 5%.² Since nephropathy may not develop until later in life, prospective monitoring is essential for all NPS patients. Primary open-angle glaucoma or ocular hypertension occurs in 10% of NPS patients so regular eye surveillance is also warranted. Nail-patella syndrome is an autosomal dominant disorder with a 50% chance of occurrence in offspring, thus genetic counselling is essential (Box³). Genetic testing of other at-risk family members, and prenatal and pre-implantation genetic diagnoses are possible only if the disease-causing mutation is known in the index patient.

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