EXTENDED REPORT

Nail-patella syndrome and its association with glaucoma: a review of eight families

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Background: Nail-patella syndrome (NPS) is a rare autosomal dominant syndrome, characterised by dysplasia of the nails, patellae, elbows and iliac horns. Mutations in the *LMX1B* gene were found in four North American families in whom glaucoma cosegregated with NPS.

Aims: To investigate the association of glaucoma with NPS in Australian families and to determine how common NPS is in Australia.

Methods: One family with NPS and glaucoma was identified from the Glaucoma Inheritance Study in Tasmania. A further 18 index cases of NPS were identified from the genetics database for southeastern Australia. Eight of these pedigrees were available for comprehensive glaucoma examination on available family members. DNA was sequenced for mutations in *LMX1B*.

Results: In total, 52 living cases of NPS were identified suggesting a minimum prevalence of at least 1 in 100 000. 32 subjects from eight NPS pedigrees (four familial and four sporadic cases) were examined. 14 subjects had NPS alone. 4 subjects had NPS and glaucoma or ocular hypertension. Five pedigrees with NPS had a reported family history of glaucoma, although some of these people with glaucoma did not have NPS. *LMX1B* mutations were identified in 5 of the 8 index cases—three sporadic and two familial. Two of the six (33%) participants over 40 years of age had developed glaucoma, showing increased risk of glaucoma in NPS.

Conclusion: Patients with NPS should be examined regularly for glaucoma. However, because the families with NPS are ascertained primarily from young probands or probands who are isolated cases, the exact level of risk is unclear.

Nail-patella syndrome (NPS) is a rare autosomal dominant condition estimated to occur in 1 in 50 000 live births.¹ NPS was originally described as a familial patellar abnormality in 1883² and as a familial nail abnormality in 1897.³ Manifestations of NPS include nail dystrophy⁴ (98%; fig 1 A–D); absent or hypoplastic patella (92%; fig 2A,B); arm or elbow abnormalities (90%; fig 3A); iliac horns (70%); soft tissue abnormalities (fig 4); nephropathy⁵ (38%) that may manifest in infancy as proteinuria or haematuria, or in adults as marked renal impairment; epilepsy (6%); and neurological or vasomotor abnormalities of the peripheral extremities (25%).¹

Renwick and Lawler⁶ linked the NPS1 gene to 9q34 and Lichter *et al*⁷ described cosegregation of primary open-angle glaucoma (POAG) with NPS. In another study of 29 additional families, 28 families ascertained on the basis of NPS and glaucoma was present in 9 (31%) families.⁸ A large review of subjects with NPS found that 8 of 83 (9.6%) subjects with NPS had glaucoma and an additional 6 of 83 (7.2%) had ocular hypertension (OHT).¹ The mean age at diagnosis for glaucoma or OHT was 48 (range 23–78) years. Anterior segment ocular abnormalities occur in mice, with targeted disruption of the *LMX1B* gene.⁹ Other rare ocular manifestations of NPS include ptosis, hypertelorism, epicanthal folds, bilateral sclerocornea, microcornea, keratoconus, cataracts, microphakia, anisocoria or pupillary ectopia.¹⁰

The gene causing NPS encodes the transcription factor *LMX1B*,¹¹ which determines dorsal limb patterning during vertebrae development,¹² controls the initial trajectory of motor axons in developing limbs¹³ and is also necessary for development of the anterior segment of the murine eye.¹⁴ It has a crucial role in the formation of podocytes in the kidney

and regulates expression of type IV collagen.¹⁵ *LMX1B* knockout mice have decreased expression of type IV collagen in glomerular basement membrane.¹⁶ *LMX1B* binds to a putative enhancer sequence in intron 1 of Col4A4.¹⁶ Most mutations occur in the LIM or homeodomain of the protein, and mutations are thought to act by haploinsufficiency.^{15 17}

The first report of an Australian family with NPS was published in 1970.¹⁸ Our study aimed to identify people with NPS in the Australian population, evaluate the minimum prevalence of NPS, identify the causative *LMX1B* mutations, and determine the extent of the association between NPS and glaucoma.

METHODS

We reviewed the glaucoma families seen in the Glaucoma Inheritance Study in Tasmania (GIST)¹⁹ and other NPS families seen by the Clinical Genetics Service in Tasmania and Victoria. Written informed consent was obtained from patients recruited through the GIST, which was approved by the ethics committees of The Royal Victorian Eye and Ear Hospital, Melbourne, Australia, and The Royal Hobart Hospital, Hobart, Australia. This study was conducted in accordance with the Declaration of Helsinki. Members of 350 glaucoma pedigrees containing 1700 glaucoma cases in Tasmania were ophthalmologically examined and questioned about other health problems (although not specifically about NPS). Our findings should be taken as a minimum

Abbreviations: GIST, Glaucoma Inheritance Study in Tasmania; IOP, intraocular pressure; NPS, nail-patella syndrome; OHT, ocular hypertension; POAG, primary open-angle glaucoma

Figure 1 (A) Nail splitting, (B) nail ridging, (C) absent thumbnails and (D) triangular lunula, apex distal.

prevalence figure as it is likely that some cases of NPS were missed.

Within the GIST we identified one family with four cases of NPS, including the proband with NPS and ocular hypertension. A further 18 index cases of NPS were identified from the Genetics Health Services Victoria database (nine sporadic and nine familial index cases). Eight of the pedigrees were available for examination. We performed a comprehensive glaucoma screen as with the GIST participants, including Goldmann applanation tonometry, Humphrey 24–2 visual field analysis and stereodisc photographs with a Nidek 3DX camera, on all available family members, as well as a general examination specifically of the hands and the musculoskeletal system. The GIST criteria²⁰ were used to evaluate the presence of glaucoma. Blood samples were taken for DNA extraction.

Participants were considered to have glaucoma if they had glaucomatous disc features such as cup:disc ratio ≥ 0.7 and visual field defects. They were considered to have OHT if their maximum known intraocular pressure (IOP) was >22 mm Hg. One affected participant from each of the families was screened for mutations in all eight exons of *LMX1B*, using previously described methods,¹¹ except for exon 2, which was screened using primers 5'CTGACGGCCGGGCTTTC3' and 5'AAGACGCGCAGCTCTCGGAA3'. Polymerase chain reaction products were purified with a QIAquick polymerase chain reaction purification kit (Quiagen, Santa Clarita, California, USA). Nucleotide sequences were determined by direct sequencing of both strands of the polymerase chain reaction product with a Big Dye Cycle Sequencing Ready Reaction DNA sequencing kit and an ABI377 DNA sequencer (PE Applied Biosystems, Foster City, California, USA).

RESULTS

The population of southeastern Australia served by the Genetics Health Victoria is 5–6 million. From the database and the pedigrees that were examined, we established that there were at least 52 cases of NPS. This included nine sporadic cases and at least 43 familial cases in 10 NPS pedigrees (including four cases in one family in Tasmania, population 475 000), thereby giving a minimum prevalence of 1 in 100 000.

LMX1B mutations

Thirty two participants from eight pedigrees (fig 5 A–H) were examined and screened for mutations in *LMX1B*. We found four different mutations in five of the eight families tested (table 1). In NPSV142, a CAA→CCA change at nucleotide position 195 (Gln65Pro; fig 6A) was identified. This novel mutation is close to one of the cystines believed to be involved in a LIM-A domain zinc finger, and may disrupt the zinc finger structure. In NPSV130, a GCC→CCC change in the nucleotide position 637 (fig 6B; Ala213Pro) was identified.

Figure 2 (A) Absent or hypoplastic patellae; (B) absent patella on x ray.

Figure 3 Posterior dislocation of radial head on x ray.

Figure 4 Underdeveloped triceps, flexion contracture of elbow.

Figure 5 (A–H) Nail-patella syndrome pedigrees 1–8. NPS, nail-patella syndrome; NTG, normal tension glaucoma; OHT, ocular hypertension; POAG, primary open-angle glaucoma.

The previously described Ala213Pro mutation⁹ is thought to disrupt DNA binding by the homeodomain. Two other mutations previously described were identified in three of the remaining families: Gln59Ter¹¹ in one family (NPSV133) and Arg198Ter²¹ in two unrelated families (NPSV136 and NPST399). The Arg198Ter mutation in NPSV136 was not identified in either parent and is believed to be a de novo mutation.

We also identified synonymous nucleotide variants, including GAA→GAG at nucleotide position 373 (Glu124) and TCC→TCG at nucleotide position 657 (Ser219), as well as intronic nucleotide changes, G to T at intron 6 position –26 and G to C at intron 2 position +7, which were also present in the normal population (table 2).

Clinical features of the participants

Two participants with both NPS and glaucoma (NPSV131 II:5 and NPSV142 II:6) were found (fig 7A–D), one with an *LMXB1B* mutation and one without. NPSV131 II:5 was diagnosed as having NTG with advanced disc cupping (fig 7A,B) in 1991 at 63 years of age. Subsequently, her visual field deteriorated, with involvement of central vision. She underwent bilateral trabeculectomies and was treated with topical ocular hypotensive agents. Her visual field has been stable since 1996. Her family report shows her

Figure 6 (A) Gln65Pro sequence. (B) Ala213Pro sequence. (A,B) Right and left optic disc photos of NPSV131, II:5, with nail-patella syndrome and normal-tension glaucoma.

Table 1 Summary of mutations and clinical features in eight families with nail-patella syndrome

Family no	Mutation	ID	Age (years)	Sex	NPS	Glaucoma	Family history of glaucoma	BCVA	IOP (mm Hg) highest recorded	CDR	Other ocular finding	Musculoskeletal abnormality
Families with <i>LMX1B</i> mutation												
G VIC130	WT	II:1	48	F	N	N	Y	6/5, 6/5	14, 16	0.4, 0.4	NAD	Nil
	Ala213Pro	III:3	17	M	Y	N	Y	6/5, 6/5	15, 15	0.5, 0.5	NAD	Nails, patella, arm in fixed-flexion, iliac horns
G VIC133	WT	III:1	21	F	N	N	Y	6/5, 6/5	16, 17	0.5, 0.4	NAD	Nil
	WT	II:2	51	M	N	N	N					
	Gln59Ter	IV:1	17	M	Y	N	Y	6/4, 6/4	16, 17	Small discs absent cups	NAD	Nails, patella, valgus elbows
	WT	III:2	45	F	N	N	Y	6/5, 6/4	14, 14	Small discs absent cups	NAD	Nil
G VIC136	Arg198Ter	II:2	10	M	Y	N	N	6/5, 6/4	18, 22	0.3, 0.3		
		II:2	10	M	Y	N	N	6/9, 6/9	12, 9	0.4, 0.4	NAD	Nails, patella, talipes equinovarus
	WT	II:1	12	F	N	N	N	6/5, 6/12	12, 17	0.2, 0.2	L amblyopia	Nil
GVIC142	WT	I:1	39	F	N	N	N	6/5, 6/4	18, 16	0.3, 0.3	NAD	Nil
	WT	I:2	40	M	N	N	N	6/24, 6/5	13, 14	0.8 (tilted), 0.4	NAD	Nil
	Gln65Pro	II:5	54	F	Y	N	Y	6/5, 6/5	17, 18	0.3, 0.5	Myopia L retinal toxoplasmosis scar	Nails
	Gln65Pro	II:6	52	M	Y	POAG Dx 33 years	Y	6/4.8, 6/4.827	23	0.8, 0.6	Mild myopia	Nails, patella, elbows
	Gln65Pro	II:8	50	M	Y	N	Y					
	Gln65Pro	III:5	33	F	Y	OHT Dx 24 years	Y	6/6, 6/6	24, 19	0.5, 0.6	NAD	Patella, radius
	Gln65Pro	III:6	32	F	Y	N	Y	6/4, 6/4	21, 21	0.6, 0.6	Myopia	Nails, patella
	Gln65Pro	III:10	24	M	Y	N	Y	6/4.8, 6/4.821	21	0.6, 0.6	NAD	Nails, patella
	Gln65Pro	III:12	17	F	Y	N	Y					
	WT	III:14	13	F	N	N	Y					
G TAS399	Gln65Pro	IV:1	10	M	Y	N	Y	6/6, 6/6	12, 12	0.5, 0.6	NAD	Nails, patella
	Arg198Ter	II:8	50	F	Y	N	Y	6/6, 6/6	14, 14	0.7, 0.7	NAD	Nails, patella
	Arg198Ter	III:1	25	F	Y	N	Y	6/6, 6/6	17, 17	0.7, 0.7	NAD	Nails, patella
	Arg198Ter	III:2	25	F	Y	N	Y	6/6, 6/6	18, 18	0.7, 0.7	NAD	Nails, patella
	Arg198Ter	III:5	18	F	Y	OHT Dx 14 years	Y	6/6, 6/6	23, 22	0.3, 0.3	Epicanthus	Nails, patella
	WT	II:1	59	F	N	POAG Dx 49 years	Y	6/7.5, 6/6	28, 19	0.8, 0.6	NAD	Nil
	WT	II:3	57	F	N	N	Y					
	WT	II:4	53	F	N	OHT Dx 37 years	Y					
	WT	II:5	52	M	N	POAG	Y					
	WT	II:5	52	M	N	POAG	Y					
Families with no detected <i>LMX1B</i> mutation												
G VIC131	??	II:5	77	F	Y	NTG Dx 63 years	Y	6/5, 6/5	18, 18	0.95, 0.95	Bil. trabeculectomy	Nails, patella
G VIC134	??	III:2	25	M	Y	N	N	6/9, 6/9	16, 16	0.3, absent	NAD	Nails, patella, webbed arms, absent triceps, dentition
G VIC135	??	II:2	54	F	N	N	N	6/5, 6/5	16, 17	0.7, 0.6	Myopia	Nil
	??	III:5	32	F	Y	N	N	6/4, 6/5	20, 19	0.5, 0.5	NAD	Nails, patella, elbows, scoliosis
	??	II:2	73	F	Y	N	N				CRVO	

BCVA, best-corrected visual acuity; Bil., bilateral; CDR, cup:disc ratio; CRVO, central retinal vein occlusion; Dx, diagnosis; F, female; IOP, intraocular pressure; M, male; N, no; NAD, no abnormality detected; NPS, nail-patella syndrome; OHT, ocular hypertension; POAG, primary open-angle glaucoma; Y, yes; WT, wild type; ??, no mutation identified in pedigree.

54-year-old daughter as having both NPS and glaucoma, and her 52-year-old son as having NPS only. An *LMX1B* mutation has not been found in this family. NPSV142 II:6 had a maximum recorded IOP of 27 mm Hg diagnosed at age 33 years, and was treated with timolol 0.5% with good pressure control and cupped discs (fig 7C,D) but no visual field loss. This participant's niece (NPSV142 III:5) had a maximum IOP of 24 mm Hg with normal fields and abnormal discs (fig 8A,B). NPST399 III:5 was a teenager with one recorded IOP elevation of 23 mm Hg but otherwise healthy discs (fig 8C,D) and normal fields. This participant and his relatives with NPS were found to have a Gln65Pro mutation. Two participants had NPS and OHT (NPSV142 III:5, NPST399 III:5; fig 8A–D), both of whom have *LMX1B* mutations. Two participants had POAG only, without *LMX1B* mutation or NPS (NPST399 II:1, NPST399 II:5; fig 9A,B). One participant had OHT only, without *LMX1B* mutation or NPS (NPST399

II:4). Five of the pedigrees with NPS had a reported family history of glaucoma. Table 1 gives the clinical details.

DISCUSSION

The association of NPS with glaucoma in our study is more than would be expected in the general population 2–3% of people >40 years of age.^{22–23}

Our sporadic cases with *LMX1B* mutations probably represent de novo mutations, although we have proved this in only two of the four sporadic cases (NPSV130 and NPSV136). In southeastern Australia, 9 of 52 (17%) NPS cases were sporadic. Sweeney *et al*¹ reported 15 of 120 (12.5%) NPS cases as sporadic. In addition, they found mutations in 38 of 43 (88%) families, whereas in our group we found mutations in 5 of 8 (62.5%) families. Dunston *et al*²⁴ looked for mutations in 105 patients with NPS by sequencing and found them in 89 patients. In the remaining 16 patients and

Table 2 Normal population frequencies for polymorphisms in *LMX1B*

Glu124Glu	G/G 30%	G/A 61%	A/A 9%
Ser219Ser	G/G 33%	G/C 51%	C/C 16%
Int6 –26	G/G 67%	G/T 33%	T/T 0%
Int2 +7	G/C 37%	G/G 63%	C/C 0%

Int, intron; Ser, serine.

in an additional 12 whom they had previously sequenced, they found large deletions by Southern blotting or by looking at intragenic markers in 9 of 28; so deletions may account for some of the families in this study.²⁴

We identified several heterozygotic polymorphisms, ruling out the possibility that one allele was deleted. However, such polymorphisms were not available for every exon in every individual; so we cannot rule out the possibility that local deletion is responsible for the cases in which point mutations were not identified. Multiple studies reporting a lack of point mutations in the coding sequence for cases with NPS suggest a variety of possibilities, including misdiagnosis, undetected *LMX1B* mutations (deletions or additional exons), an additional NPS locus or the presence of some classes of mutations in *LMX1B* that are not being efficiently detected by sequencing of the coding region.

The fraction of glaucoma in participants with NPS as well as the fraction of participants with OHT in our study is 2 of 18 (11.1%). Sweeney *et al*¹ reported that 8 of 83 (9.6%) subjects with NPS had glaucoma and a further 6 of 83 (7.2%) subjects with NPS had OHT. Sweeney reported a mean age at diagnosis of their combined glaucoma and OHT groups to be 47.9 years. The mean age at diagnosis of glaucoma in our two participants was 48 years, and the one participant with OHT, for whom we have age information, was diagnosed at age 24 years. The fact that one of our participants with glaucoma had NTG is in keeping with a recent paper.²⁵

Sweeney *et al*¹ observed glaucoma or OHT in 29% of participants with NPS >40 years, which is consistent with our finding of two participants with open-angle glaucoma

among the 5 (33%) participants with NPS > 40 years. This is clearly higher than the frequency of glaucoma in populations that have not been selected for the presence of NPS, and indicates an increased risk of glaucoma for people with NPS.

LMX1B may have a role in a regulatory network associated with multiple genes. Of particular interest is the involvement of *LMX1B* in the regulation of expression of the *FOXC1* gene that is associated with glaucoma and anterior segment dysgenesis.²⁶ Both *LMX1B* and *FOXC1* are associated with eye development. Pressman *et al*¹⁴ found in a mouse model that in the presence of *LMX1B*, *FOXC1* and *FOXC2* are not found in the differentiating corneal stroma, whereas in the absence of *LMX1B*, *FOXC1* and *FOXC2* can both be detected in this tissue. Yeast 2 hybrid studies suggest an interaction between *LMX1B* and *PAX2*.²⁷ These three genes are also associated with renal development, or are expressed in the cornea.²⁸ The interaction of multiple regulatory genes, including *LMX1B*, may have a role in the variable expressivity and penetrance observed in subjects with NPS without glaucoma or NPS with OHT.

CONCLUSIONS

Glaucoma is associated with NPS, and thus family members should be screened for it in the same way that individuals with anterior segment dysgenesis or a positive family history of glaucoma are. Because NPS can include juvenile-onset glaucoma, Sweeney *et al*¹ recommend an annual glaucoma examination from the time a child with NPS can cooperate in the assessment. Presently, we do not know enough about relative risk with respect to age. Further research may allow

Figure 7 (A,B) Right and left optic disc photo of NPSN131, II:5, with nail-patella syndrome (NPS) and normal tension glaucoma. (C,D) Right and left optic disc photos of NPSV142, II:6, with NPS and primary open-angle glaucoma.

Figure 8 (A,B) Right and left optic disc photos of NPSV142, III:5, with nail-patella syndrome (NPS) and ocular hypertension (OHT). (C,D) Right and left optic disc photos of NPST399, III:5, with NPS and OHT.

less frequent examination for younger people. Genetic counseling in these families is valuable because patients with NPS may see several individual specialists—for example, orthopaedic, renal and ophthalmic—without the opportunity for a discussion about the full phenotype and need for screening for other health problems. Mutation analysis of *LMX1B* in more families should help clarify the association of glaucoma and NPS. Identifying the genes interacting with *LMX1B* may help to elucidate the mechanism of glaucoma development in NPS.

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Figure 9 (A,B) Right and left optic disc photos of NPST399, II:1, with primary open-angle glaucoma but not nail-patella syndrome.

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