

REVIEW ARTICLE

Nail patella syndrome: a review of the phenotype aided by developmental biology

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Nail patella syndrome (NPS) is an autosomal dominant condition affecting the nails, skeletal system, kidneys, and eyes. Skeletal features include absent or hypoplastic patellae, patella dislocations, elbow abnormalities, talipes, and iliac horns on x ray. Kidney involvement may lead to renal failure and there is also a risk of glaucoma. There is marked inter- and intrafamilial variability. The results of a British study involving 123 NPS patients are compared with previously published studies and it is suggested that neurological and vasomotor symptoms are also part of the NPS phenotype. In addition, the first data on the incidence of glaucoma and gastrointestinal (GI) symptoms in NPS are presented. NPS is caused by loss of function mutations in the transcription factor *LMX1B* at 9q34. The expansion of the clinical phenotype is supported by the role of *LMX1B* during development.

genetic analysis to a 1 cM interval on 9q34.1.^{6,7} The NPS gene was identified as that encoding the transcription factor *LMX1B* subsequent to the finding of phenotypic abnormalities in *lmx1b* null mice^{8,9} and independently by positional cloning.¹⁰ Subsequently, a series of studies have identified 83 mutations.^{11–16} The nature of the mutations and their distribution throughout the gene is consistent with a heterozygous loss of function aetiology. No genotype-phenotype correlation has been identified.

This study was undertaken to reassess the phenotype of NPS following the identification of *LMX1B* as the NPS gene and advances in molecular embryology illuminating its role in development. It is the largest clinical study to date to provide data on the variability and severity of the NPS phenotype.

METHODS

Ethical approval was obtained for the study from the relevant ethics committees. Patients were ascertained through clinical genetic departments in England, Scotland, and Wales, through patient contact groups, and through nephrologists. Informed consent was obtained from all participating patients.

All patients were visited at their home, with the exception of a small number of patients who lived locally to the Royal Liverpool Children's Hospital, who were seen in the clinical genetics department. All patients were seen by ES and a history was taken and examination performed. Each knee and elbow joint was assessed separately since the structural defects were often asymmetrical. Photographs were taken of any notable findings. A fresh urine sample was tested for the presence of protein and blood using urine analysis dipsticks. If abnormalities were found on urine analysis, patients were advised to visit their GP for repeat testing and, if necessary, further investigation and management by a local renal physician. Renal involvement was assessed on the basis of clinical history and on urine analysis. During the course of the study the frequency of back involvement and neurological and vasomotor symptoms became apparent. Therefore not all subjects were assessed in these areas. Adults who had not been screened for glaucoma in the previous two years were offered a test to detect raised intraocular pressure. This was done using a Tonopen after proxymetacaine local anaesthetic drops were instilled into the eyes. Patients with readings over 21 mm Hg were advised to see their opticians for a repeat test using an alternative method of tonometry and, if necessary, referred to an ophthalmologist for further investigation

Nail patella syndrome (NPS) (OMIM 161200), also known as hereditary osteoonychodysplasia (HOOD), Fong disease, Turner-Kieser syndrome, and Österreicher-Turner syndrome, is a pleiotropic condition with a classical clinical tetrad involving the nails, knees, elbows, and the presence of iliac horns. There are, however, many other features that may be seen in this condition and involvement of other body systems such as the kidneys and eyes is well documented. In the skeletal system, tendons, ligaments, and muscles can be affected as well as bones. Clinical manifestations are extremely variable in both frequency and severity and there is inter- and also intrafamilial variability.^{1,2} Patients may be severely affected by one aspect of NPS but have much milder or no manifestations elsewhere. Although the diagnosis may be made at birth,³ it is very common for families to remain undiagnosed for several generations despite having been seen by doctors from a variety of disciplines.⁴ NPS is an autosomal dominant condition^{2,4} and there have been no reported cases of non-penetrance or of germline mosaicism. The frequency of NPS has not been determined accurately. The incidence is widely reported at approximately 1 in 50 000 but the basis for this figure remains obscure.

NPS was one of the first disorders in humans for which a linkage relationship was established, in this case with the ABO blood group.⁵ Localisation of the NPS gene was refined by molecular

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Table 1 Patient measurements

	Males	Females
Mean birth weight in term babies (g)	3370 (2650–5050) (50th centile) n=32	3270 (2300–4140) (50th centile) n=47
Mean head circumference in term babies (cm)	34.9 (33–36) (50th centile) n=8	35.1 (33.8–37) (75th centile) n=5
Mean adult weight (kg)	66.9 (50.8–88) (50th centile) n=29	55.7 (41–77.1) (50th centile) n=60
Mean adult height (cm)	170.9 (152–188) (25th centile) n=29	158.5 (141–178) (25th centile) n=60
Mean adult head circumference (cm)	57.9 (55–60.8) (50th centile) n=23	55.5 (51.5–58.5) (50th centile) n=60

and management. Where relevant and possible, patient records and radiological investigations were reviewed.

PATIENT DEMOGRAPHICS

One hundred and twenty-four patients were initially recruited into the study. One patient was excluded as not having NPS. She had been diagnosed with NPS owing to the presence of iliac horns on pelvic *x* ray. She had no external signs of NPS, no family history, and on reviewing the pelvic *x* rays there were no iliac horns, only a non-specific flaring of the iliac bones laterally. Patients were recruited from 44 families. However, later it was discovered that two of these families were related. The study group therefore consisted of 123 patients from 43 families. There were 70 females and 53 males. The average age of patients in the study was 32.6 years (4 months–80 years). NPS had been inherited in 87.5% of patients (105/120) and had occurred sporadically in 12.5% (15/120). Three patients did not know whether their parents had been affected. As in previous studies, there was a wide degree of intrafamilial variability in the NPS phenotype although there were no incidences of non-penetrance or germline mosaicism.

PATIENT ASCERTAINMENT AND DIAGNOSIS

The majority of families (28/43) were ascertained through clinical genetic departments. Thirteen families were contacted through the NPS patient support group and two families through nephrologists.

In 18 families, the diagnosis had been made by orthopaedics, followed by clinical genetics in six families, paediatrics in five families, and dermatology in four families. One family was diagnosed by a radiologist while a family member was having an intravenous pyelogram for the investigation of nephrotic syndrome, and another family by a general surgeon. Six families did not know who had originally made the diagnosis and two families had made the diagnosis themselves.

GENERAL APPEARANCE

It was evident that there was a lean body habitus associated with NPS and patients often have difficulty putting on weight (particularly muscle) despite adequate dietary intake and exercise. There is a particular decrease in muscle mass in the upper arms (fig 1) and upper legs. One patient was thought to have some form of muscular dystrophy in the past because of having almost absent biceps and triceps muscles with full development of the deltoids and forearm muscles. Some female patients described poor breast development and one patient had had cosmetic surgery for this. The tendency to be very lean was most evident in adolescents and young adults and became less apparent after middle age. The increased lumbar lordosis that was frequently present tended to make the buttocks appear prominent. Also, the legs often appeared short compared to the torso. No data were gathered during



Figure 1 Abnormal muscle distribution in upper arms.

this study to confirm any subjective assessment of disproportion, but this is planned for a future study. The head may appear large compared to the body. This appearance is supported by the data on height and head circumference (table 1). The high forehead and hairline, particularly at the temples, resembled a receding male pattern hairline when seen in women (fig 2). Some patients also reported that they had poor hair growth as a child and were apparently bald for quite some time in infancy. When their hair did grow it had a tendency to be fine.

NAIL AND DIGITAL CHANGES

Nail changes are the most constant feature of NPS. Nails may be absent, hypoplastic, or dystrophic, ridged longitudinally or horizontally, pitted, discoloured, separated into two halves by a longitudinal cleft or ridge of skin, thin or, less often, thickened. Nail changes may be observed at birth and are most often bilateral and symmetrical. The thumbnails are the most severely affected, and the severity tends to decrease towards the little finger. Each individual nail is usually more severely affected on its ulnar side. The nail changes may be limited to triangular lunules (or lunulae), a characteristic feature of



Figure 2 High, broad forehead and male pattern hairline.



Figure 3 Thumbnails showing the most severe dysplasia on the ulnar border of the thumbnail.

NPS. Dysplasia of the toenails is usually less marked and less frequent than that of the fingernails, but if the toenails are involved, it is often the little toenail which is affected.

In this study, nail changes were seen in 98% (120/123) of patients (figs 3, 4, and 5). The thumbnails were the only nails to be involved in 42% (52/123) of patients; 26% (32/123) of patients had involvement of their thumbs and index fingernails only, whereas 29% (36/123) had more extensive nail involvement. Nail involvement could be very subtle with the only manifestation being the presence of just one triangular lunula or a slightly smaller ulnar border of thumbnail. Triangular lunulae (fig 6) were seen in 88% of patients (106/121) but were not necessarily seen on all nails. The toenails were involved in 67% (82/122) of patients. The most common toenail finding was a small, dystrophic little toenail (a finding also common in the general population), but other toenails could also be thickened, discoloured, thin, dystrophic, or hypoplastic (fig 7).

A sensitive sign of digital involvement in NPS is loss of the creases in the skin overlying the distal interphalangeal (DIP) joints of the fingers (fig 5). This sign follows the same gradient



Figure 4 Thumbnails showing increased dysplasia on the ulnar border of each thumbnail.



Figure 5 Decreased severity of nail dystrophy towards the fifth finger and loss of skin creases over the distal interphalangeal joints.



Figure 6 Triangular lunules.



Figure 7 Dystrophic toenails.

of involvement as is seen in the nails so that the most frequently affected fingers are the index fingers. This loss of DIP skin creases was seen in 96% of patients (114/119). In addition to loss of skin creases there was often an associated reduction in flexion of the DIP joints and, again, this followed the same pattern of distribution (fig 8). Occasional patients also had decreased flexion of the proximal interphalangeal (PIP) joints, an inability to actively extend their DIP joints, fixed flexion of the DIP joints, and fixed flexion of the PIP



Figure 8 Decreased flexion of the distal interphalangeal joints.



Figure 9 Swan necking of the fingers.

joints of the middle and ring fingers. Hyperextension of the PIP joint and flexion of the DIP joints, resulting in "swan necking", was seen in 58% (69/118) of patients (fig 9). Fifth finger clinodactyly was seen in 35% (42/119).

KNEE INVOLVEMENT

The patellae may be small, irregularly shaped, or absent and patella involvement may be asymmetrical.^{3,17} Recurrent subluxation or dislocation of the patella is common in NPS and may be associated with poor development of the vastus medialis muscle. The displacement of the patella is lateral and superior, and the hypoplastic patella is often located laterally and superiorly even when not actually dislocated. There may be prominent medial femoral condyles, hypoplastic lateral femoral condyles, and prominent tibial tuberosities. Together with a hypoplastic or absent patella, this gives the knee joint a flattened profile (fig 10). Tight hamstring muscles may cause flexion contractures of the knees. There may also be osteochondritis dissecans, synovial plicae, and absence of the anterior cruciate ligament. Early degenerative arthritis is not uncommon.

Symptoms associated with knee abnormalities in NPS included pain, giving way, a feeling of instability, locking, clicking, patella dislocation, and the inability to straighten the knee joint. In this study, knee symptoms were reported in 74% of patients (89/120). Of these, nearly half were assessed subjectively as being mild. Patellae were clinically of normal size in 16% (37/237), were hypoplastic in 75% (179/237), and undetectable by palpation in 9% (21/237). Patella dislocations had been experienced by 25% (30/118) of patients, often



Figure 10 Skyline view of knees showing subluxed patellae on knee flexion.

Table 2 Low frequency findings

Knees
Genu recurvatum
Genu valgum
Genu varum
Leg length discrepancy
Rotational deformities of the legs
Osgood-Schlatter's disease
Osteochondritis dissecans of the lateral femoral condyle
Prominent medial femoral condyles
Underdeveloped lateral femoral condyles
Widening or deepening of the intercondylar femoral notch
Absence or hypoplasia of the anterior cruciate ligaments
Presence of an abnormal band dividing the supra patella pouch
Pelvis
Narrow iliac wings
Flared iliac wings
Small iliac bones
Square iliac blades
Relative overgrowth of ischium
Scalloped margin of the iliac bone
Spine
Spondylolisthesis
Spondylolysis
Spina bifida occulta (cervical and lumbar)
Lumbosacral segmentation defect
An extra lumbar vertebra
Fused sacroiliac joints
Fusion of the fifth lumbar and first sacral joint
Dural ectasia
Degenerative changes of the spine
Ankles and feet
Metatarsus adductus
Metatarsus valgus
Supination of the forefoot
Fusion of cuboid and navicular bones
Prominent medial malleoli
Shoulders
Narrow sloping shoulders
Dislocatable shoulders
Small scapulae
Raised and abnormally orientated scapulae
Thick lateral margins of the scapulae
Prominent acromioclavicular joints
Inferiorly subluxed humeral heads
Hypoplastic glenoid with a flattened humeral head

recurrently. It was not uncommon for patients to be unable to extend the knee joint fully, which seemed to be because of tight hamstrings. Fixed flexion deformities of up to 90 degrees were observed. Some patients had unexpected, abnormal anatomy at operation, including ectopic muscle attachments. Low frequency findings are listed in table 2.



Figure 11 X ray of elbow showing a dysplastic, dislocated radial head and hypoplasia of the capitellum.



Figure 12 Decreased extension of the elbows and bilateral pterygia. Note also high hairline at the temples.

ELBOW INVOLVEMENT

Elbow abnormalities, like knee abnormalities, may be asymmetrical. There may be limitation of extension, pronation, and supination, or cubitus valgus. Typical radiological findings include dysplasia of the radial head, hypoplasia of the lateral epicondyle and capitellum and prominence of the medial epicondyle. These abnormalities may result in dislocation of the radial head, usually posteriorly (figure 11). Pterygia may occur and are usually antecubital, but axillary pterygia have also been described.

In this study, symptoms from the elbows were reported in 33% (39/120) of patients. Of these, most were subjectively assessed as mild. Loss of elbow extension was found in 70% of elbows (167/240). This was less than 15° in 36% of elbows (86/240), between 15 and 45° in 27% (64/240), between 45 and 90° in 5% (13/240), and over 90° in 2% (4/240) of elbows. When present, elbow contractures were usually present from birth, and the tendency was for the degree of contracture to remain the same over time. Elbow pterygia were present in 12% of patients (15/123) and could be bilateral or unilateral (fig 12). When pterygia were present, the neurovascular bundles could run superficially in the web, which made operative treatment to extend the elbow difficult. Even if patients had full range of extension, their ability to supinate their forearm was often limited.

The prevalence of pterygia of the elbow in this study was greater than that previously reported.¹⁸ It is unclear how detailed the clinical descriptions were in the papers reviewed by Carbonara *et al.*¹⁷ Rizzo *et al.*¹⁸ had previously suggested that the presence of pterygia was a predictor of renal involvement in NPS and that all patients with pterygia had renal disease. However, results from this study do not support this hypoth-



Figure 13 X ray of pelvis showing iliac horns.



Figure 14 X ray of pelvis showing iliac horns in early childhood.

esis (data not shown) and from what is known about the variability and pathogenesis of this condition, it seems extremely unlikely that the presence of pterygia would predict renal disease.

ILIAC HORNS

Iliac horns are bilateral, conical, bony processes that project posteriorly and laterally from the central part of the iliac bones of the pelvis and are considered pathognomonic of NPS¹⁷⁻¹⁹⁻²¹ (figs 13 and 14). Large horns may be palpable²²⁻²⁴ but are asymptomatic. They may be seen on third trimester ultrasound scanning,²⁵ on x ray at birth,¹ and in children there may be an epiphysis at the apex.^{4 19 23 26}

In this study, iliac horns were present in 68% (34/50) of the pelvic x rays that were available for examination and could be subtle. Seven women had required caesarean sections because of a narrow pelvis.

INVOLVEMENT OF THE ANKLES AND FEET

Talipes was a feature in 19% (23/122) of patients and was bilateral in 70% of these (16/23). Talipes equinovarus, calcaneovarus, calcaneovalgus, equinovalgus, and hyperdorsiflexion of the foot were all reported. Severe bilateral talipes had been detected at the 20 week scan in one patient. Tight Achilles tendons were a common finding, contributing to talipes and to toe walking, and Achilles tendon lengthening operations were sometimes necessary. Pes planus was present in 64% of patients (76/118). Other low frequency findings are listed in table 2. The 19% frequency of talipes in this study contrasts

Table 3 Frequency of types of renal involvement in different age categories

	Patients overall	Over age 18 years	Over age 40 years
No renal involvement	62.5% (75/120)	56.8% (50/88)	54.5% (24/44)
Pregnancy only	12.5% (15/120)	17% (15/88)	18.1% (8/44)
Proteinuria only	12.5% (15/120)	10.2% (9/88)	9.1% (4/44)
Haematuria only	0.8% (1/120)	1.1% (1/88)	2.2% (1/44)
Proteinuria + haematuria	10% (12/120)	12.5% (11/88)	13.6% (6/44)
Transplant	1.6% (2/120)	2.2% (2/88)	2.2% (1/44)

with 50% of patients in the study by Guidera *et al*,³ although that study was biased as ascertainment was from orthopaedic patients.

SPINAL AND CHEST WALL PROBLEMS

Back pain was a problem for 55% of patients (66/120). This was subjectively assessed as moderate or severe in over half of the patients. Back pain could start during childhood and was the reason that several people had been registered disabled. An increased lumbar lordosis was seen in 47.1% (41/87) of patients. Scoliosis, which was usually mild, was a feature in 23% (8/35) patients. Pectus excavatum was seen in 36% of patients (14/39) and one of these patients required operative treatment for dyspnoea.

OTHER SKELETAL MANIFESTATIONS

Bilateral congenital dislocated hips were reported in three patients and others reported clicking in their hips or the ability to sublunate their hip joints. Fixed flexion deformities of the hip occurred in three patients. Two patients were noted to have coxa valga on x ray. Occasional patients described that they had had rotational deformities of the leg, and this could be up to 180° of external rotation. This seemed to be the result of a combination of talipes, marked external rotation at the hips, and tibial torsion. Other low frequency findings are listed in table 2.

The joint contractures were of sufficient severity in two patients that a description of arthrogyriposis multiplex had been used at birth. Generalised joint hyperextensibility could also occur, most commonly in children, and particularly in the fingers. In the study population five patients, all of them male, had had inguinal herniae, four of them as children, and one patient had an epigastric hernia.

Some patients described generalised muscular pains, usually worse in cold, damp weather. Specific diagnoses that had been made included fibromyalgia, polymyalgia rheumatica, and fibrositis. Two patients had been diagnosed with chronic fatigue syndrome or myoencephalomyalgia (ME).

The results of this study emphasise not only the variability in severity of joint problems, but also the unpredictability of the character of the joint abnormalities and anatomy of the joints. Therefore, it is strongly advised that before any treatment for joint abnormalities, particularly surgery, a magnetic resonance imaging scan (MRI) is undertaken to provide the clinician with essential information about the anatomy of the joint.

THE ROLE OF *LMX1B* IN DORSOVENTRAL PATTERNING IN THE LIMB

A series of experiments in animal model systems have shown a crucial role for *LMX1B* in determination of dorsoventral patterning in the developing limb.^{8, 27–29} Although the defects observed in distal limb development in homozygous mutant *lmx1b*^{-/-} mice⁸ are more severe than typically observed in NPS patients, the parallels are clearly apparent. In addition, parallels can be drawn between the expression pattern of *lmx1b*

across the anterior-posterior axis of the distal limb and the decreasing severity of nail dysplasia in NPS from thumb to little finger.³⁰ It has been shown that expression of *lmx1b* in the distal limb mesenchyme is induced by dorsal ectoderm expression of *wnt7a* and repressed by ventral ectoderm expression of *en1*.^{29, 31} There are, therefore, marked similarities between the distal limbs of *wnt7a*^{-/-} and *lmx1b*^{-/-} mice.^{8, 32} It should be noted, however, that abnormal development is more severe in the proximal limbs of *lmx1b*^{-/-} mice and can be compared to the abnormal development of the proximal musculature observed in NPS patients.

RENAL INVOLVEMENT

It is the renal manifestations of NPS that influence mortality. The main pathology involves a defect in the glomerular basement membrane.³³ The first sign of renal involvement is usually proteinuria, with or without haematuria.³³ Proteinuria may present at any age from birth onwards and may be intermittent. Renal problems may present, or be exacerbated, during pregnancy.³⁴ Once proteinuria is present, it may remit spontaneously,^{35, 36} remain as asymptomatic proteinuria, progress to nephrotic syndrome or nephritis, and occasionally to renal failure. Progression to renal failure may appear to occur rapidly or after many years of asymptomatic proteinuria.^{37, 38} The factors responsible for this progression are yet to be identified. Death from renal failure has occurred in patients as young as 8 years old.³⁹ When renal transplantation takes place in NPS, results are usually favourable.^{40, 41} Ultrastructural (electron microscopy) abnormalities are the most specific histological changes seen in NPS and are well described elsewhere.⁴² They include irregular thickening of the glomerular basement membrane with electron lucent areas giving a mottled “moth eaten” appearance, and the presence of collagen-like fibres within the basement membrane and the mesangial matrix. Structural renal tract changes have been reported infrequently^{1, 3, 21, 36, 42, 43} and may be coincidental. The main renal abnormality in NPS is a functional defect.

In this study, the incidence of renal involvement, including that occurring in pregnancy only, was 37.5% (45/120) in the patient group overall. When patients with involvement in pregnancy only were excluded, renal involvement occurred in 25% (30/120) of patients overall and in 33% (12/44) of those patients over the age of 40 years (table 3). The mean age that renal involvement was detected was 21.7 years (1–51 years). Renal failure had occurred in 3% (3/123) of patients. In those women who had been pregnant, 29% (14/48) had had pre-eclampsia, an increased incidence when compared with the general population.⁴⁴

Previous studies have estimated renal involvement to occur in between 12% to 55% of patients with NPS^{1, 17, 22, 27, 29, 35, 41} and renal failure in between 5% and 14% of NPS patients.^{42, 45} Renwick³⁴ performed urine analysis in an unselected series of 75 patients from eight NPS families and found that only 12% had evidence of renal involvement. Although this represents an unselected series, the relatively low numbers involved could lead to an inaccurate estimate of the frequency of renal

involvement. Looij *et al*⁴⁵ combined the data from the family they reported with those from other published reports and found that nephropathy occurred in 48% (114/236) and renal failure in 14% (33/239) of cases of NPS.⁴⁵ However, families in which renal involvement did not occur were excluded from the study of Looij *et al*⁴⁵ because the authors felt that NPS was heterogeneous, with one form being associated with renal problems and another form not. Excluding the families who did not have evidence of renal disease will have led to a considerable overestimate of the incidence of renal involvement in NPS. The highest reported frequency of renal involvement originates from a paper by Bennett *et al*⁴² who found renal involvement in 55% (20/36) and death from renal failure in 5% (2/36) of NPS patients from 11 families. Their method of classifying patients as having renal involvement could be considered rather oversensitive and non-specific. Ascertainment bias in some studies and reviews may lead to the reporting of more severely affected families and the over-representation of renal disease. However, as renal involvement is an age dependent finding, any cross sectional study will inevitably underestimate the lifetime risk of renal problems. Reported frequencies of renal involvement will also depend on the tests performed to detect any renal dysfunction.

Lmx1b mutant mice show renal changes similar to those seen in humans with NPS. Ultrastructural examination of mutant mice kidneys shows irregular thickening of the glomerular basement membrane with occasional regions of membrane discontinuity and abnormal podocytes with a lack of foot processes and slit diaphragms,⁴⁶ an appearance which correlates with the ultrastructural changes seen in the kidney of an NPS patient. LMX1B is important in regulating type IV collagen gene expression in the glomerular basement membrane of the developing kidney⁴⁷ and also has a likely role in regulating additional genes important in podocyte function and maintenance.^{48, 49} It seems, therefore, that abnormal development of the podocyte foot processes and the slit diaphragm are likely to contribute, along with reduced levels of glomerular basement membrane collagens, to the nephropathy of NPS.

OPHTHALMOLOGICAL FINDINGS

Glaucoma has recently been recognised as a feature of NPS.^{10, 50} Primary open angle glaucoma is the most frequent abnormality, although ocular hypertension may also be seen.⁵⁰

The prevalence of glaucoma and ocular hypertension in this study was 9.6% (8/83) and 7.2% (6/83) respectively. When participants under the age of 40 were excluded, these figures rose to 16.7% (7/42) and 11.9% (5/42). The mean age at which glaucoma or ocular hypertension had been detected was 47.9 years (23-78 years). The presence of glaucoma or ocular hypertension in 29% (12/42) of patients over 40 confirms that these are significant features in NPS. However, this aspect of NPS is treatable and therefore screening for glaucoma in NPS patients should be strongly encouraged. There is also an earlier onset of these problems in NPS patients than in the general population. The pathogenesis of the ocular hypertension and glaucoma in NPS is yet to be determined. While it is known that *lmx1b* is expressed in the trabecular meshwork of the developing eye,⁵¹ there are no published reports describing histological changes in the trabecular meshwork in NPS patients. This would usually necessitate the study of post-mortem material, and therefore a limited availability of tissue. The defect in collagen fibrillogenesis seen in the cornea of the *Lmx1b* *-/-* mutant mice may suggest a role for LMX1B in collagen regulation, similar to that seen in the kidneys.

Lester's sign consists of a zone of darker pigmentation around the central part of the iris, which is roughly a cloverleaf or flower shape (fig 15). This is most pronounced in blue eyes. Lester's sign was observed in 54% (64/119) of patients in this



Figure 15 Lester's sign of the iris.

study, usually bilaterally. Lester's sign was no more frequent among those with glaucoma or ocular hypertension than those without. In one review, Lester's sign was seen in 42% of NPS patients.¹⁷ Other authors have felt that Lester's sign was not a valid part of the syndrome and felt that the description of the iris anomaly given by Lester was consistent with the normal configuration of the collarette.⁵² It is now widely accepted that the iris configuration characteristic of Lester's sign is not pathognomonic of NPS and may be seen in the general population, although at considerably lower frequency.⁵² However, there are other iris appearances which may be seen in the general population but are much more common in particular syndromes, such as the stellate iris that is commonly seen in Williams' syndrome.⁵³ The expression of *lmx1b* in the anterior chamber of the developing eye, together with the iris abnormalities seen in *lmx1b* *-/-* mutant mice,⁵¹ supports the suggestion that Lester's sign is indeed a feature of NPS, albeit a non-specific one.

GASTROINTESTINAL INVOLVEMENT

The frequency and spectrum of bowel symptoms in NPS have not previously been assessed. Bowel symptoms were reported in 31% (36/117) of patients in this study. Irritable bowel syndrome, characterised by alternating constipation and diarrhoea with cramping abdominal pain, was reported in 13% of patients (15/117) and significant constipation requiring treatment was reported in an additional 18% (21/117) and was usually present from birth. Although these figures do not differ significantly from the general population,^{54, 55} these data together with case reports of NPS patients presenting with abdominal pain,⁵⁶ the coincidence of a Hirschsprung-like phenotype in another patient,⁵⁷ and the known requirement for *lmx1b* in the development of dopaminergic neurones⁵⁸ suggest that this is an area requiring further study.

Evidence for a role for LMX1B in the gut is found in chick and *C elegans* animal models. Chick *Lmx1* is expressed in the presumptive gut endoderm²⁷ and the *C elegans* orthologue of LMX1B, *lim-6*, is involved in regulating the outgrowth and differentiation of neurones controlling rhythmic enteric muscle contractions.⁵⁹ *Lim-6* mutants exhibit a bloated gut and defective defecation behaviour.

NEUROLOGICAL PROBLEMS

Neurological problems have not previously been reported as part of the phenotypic spectrum of NPS. During the course of the study, several patients spontaneously reported peripheral neurological symptoms and therefore other patients were subsequently asked about these symptoms, which were reported in 25% (28/110). The reported symptoms followed a pattern consisting of intermittent episodes of numbness and tingling and sometimes burning sensations in the hands and sometimes the feet, with no obvious precipitant. The symptoms did not follow the distribution of any particular dermatome or peripheral nerve, the distribution being more like a glove and stocking pattern. These symptoms could spread to the elbows and calves and could last from minutes to

Table 4 Differential diagnoses of NPS

Syndrome	Similarities	Differences	References
Small patella syndrome OMIM 147891 (ischioapatellar dysplasia, coxo-podo-patellar syndrome, Scott-Toar syndrome)	Small or absent patellae Recurrent patella dislocations Pelvic anomalies	Defective ossification at the ischiopubic junction and ischial hypoplasia Infra-acetabular "axe-cut" notch No nail changes No elbow changes No renal involvement No ocular involvement	67–70
Patella aplasia-hypoplasia OMIM 168860 PTLAH	Isolated aplasia or hypoplasia of the patella	No nail changes No elbow changes No renal involvement No ocular involvement	71–73
Familial recurrent dislocation of the patella OMIM 169000 Meier-Gorlin syndrome OMIM *224690	Familial tendency towards patella dislocation Absent patellae Dislocation of the radial head	Microtia Markedly short stature Delayed bone age Characteristic facial appearance Autosomal recessive inheritance	74 75–78
Genitopatellar syndrome OMIM *606170	Absent patellae Renal anomalies Flexion deformities of the knees and hips Club foot	Hypoplasia of the ischia and iliac bones Genital anomalies Facial dysmorphism Microcephaly Mental retardation renal manifestations are structural (multicystic kidneys or hydronephrosis) rather than functional	79
DOOR syndrome OMIM *220500	Absent or poorly formed nails	Long thumbs and big toes, often with triphalangism Other fingers and toes are short owing to an absent or hypoplastic distal phalanx Bilateral ptosis Short broad nose with a broad nasal tip and Large nostrils Structural renal tract abnormalities cataracts, optic atrophy Dandy-Walker malformation, seizures Autosomal recessive inheritance	80
Trisomy 8 mosaicism	Absent or hypoplastic patellae Limited elbow supination Abnormal nails	Significant learning difficulties and variable facial dysmorphism camptodactyly and progressive joint restriction usually of the fingers and toes	53
Coffin-Siris syndrome OMIM 135900	Absence or hypoplasia of the nails and patellae Elbow dislocation	Nail hypoplasia usually affects the little finger nails Facial dysmorphism Developmental delay	80
RAPADILINO syndrome OMIM 266280	Radial defects, absent or hypoplastic patellae Dislocated joints	Cleft palate, facial dysmorphism, short stature, radial defects include absent or hypoplastic thumbs and radii Autosomal recessive inheritance	80
Senior syndrome OMIM 113477	Small nails	Characteristic facial appearance, short stature, and mild intellectual impairment	81

hours. There was no history of associated motor weakness. Epilepsy was reported in 6% (7/123) of patients with a mean age of onset of 29 years (range 17 months–66 years). Unfortunately, available details of the particular types of epilepsy were limited. The 6% prevalence of epilepsy in the NPS study population was in contrast to the lifetime prevalence of epilepsy in the United Kingdom of 0.4%.⁶⁰ Since relatively little information about the character of the patients' epilepsy was available from their hospital records, this area needs further attention in future research studies.

There are a number of reasons why patients with NPS could have peripheral neurological symptoms, including trapped nerve roots from spinal problems, peripheral nerve entrapment, irritation around abnormal joints such as the elbow, or after joint surgery. However, all of these would be expected to cause symptoms in specific dermatomes or peripheral nerve distributions. Only occasional patients described such clearly demarcated neurological symptoms, which could clearly be related to coexisting orthopaedic problems, and these patients were not included in the data for neurological problems. Indeed, many of the patients who reported peripheral neurological symptoms did not have significant local orthopaedic problems.

The neurological symptoms reported by NPS patients are particularly interesting in the light of what is known about the role of *lmx1b* in neuronal migration in the mouse.⁶¹ Although

the work by Kania *et al*⁶¹ was based on the study of motor neurones, it opens the possibility of a wider role of *LMX1B* in peripheral nerve migration. There is a growing interest in the role of *LMX1B* in the developing brain. *Lmx1b* is already known to have an important role in the development of mesencephalic dopamine producing cells in mice, is highly expressed in the substantia nigra and ventral tegmental areas, and expression is present from an early stage in development and is maintained throughout life.⁵⁸ Recently, there has been a suggestion that attention deficit disorder/attention deficit hyperactivity disorder (ADD/ADHD) may be a feature of NPS, as could depression,⁶² and further studies in this area are under way.

VASOMOTOR PROBLEMS

Vasomotor problems have not previously been associated with NPS. During the course of the study several patients spontaneously reported having symptoms related to a poor peripheral circulation, such as having very cold hands and feet, even in warm weather. Of those patients asked, 55% (12/22) had these symptoms and two patients had specifically been diagnosed with Raynaud's phenomenon.

There are two possible reasons for the increased incidence of peripheral circulatory problems seen in NPS. Firstly, there may be a defect in neuronal migration affecting the digital cutaneous neurones. This hypothesis is supported by the role of

Table 5 Recommendations for the care of patients with NPS

- Annual screening for renal disease from birth. This should include blood pressure and urine analysis. A urine albumin:creatinine ratio on a first morning urine is preferable to urine analysis dipsticks as it is a more sensitive measure and corrects for concentration of the urine. If any abnormalities are detected the patient should then be referred to a renal physician for further investigation and follow up.
- Screening for glaucoma every two years in adulthood. This should include measurement of intraocular pressure, examination of the optic disc, and assessment of visual fields in order to detect normal pressure glaucoma. If any abnormalities are detected, patients should be referred to an ophthalmologist.
- Before treatment such as surgery or intensive physiotherapy is considered for orthopaedic abnormalities, it is recommended that information on possible abnormal anatomy of both bone and soft tissue is acquired by magnetic resonance imaging (MRI).
- Genetic counselling should be offered to all patients with NPS.

lmx1b in neuronal migration in the developing limb.⁶¹ Secondly, there may be a confounding connective tissue problem in NPS that may predispose to the development of peripheral circulatory problems and Raynaud's phenomenon. Any involvement of lmx1b in the regulation of collagen gene expression other than in the kidney remains to be determined.

DENTAL PROBLEMS

Dental problems were reported in 23% (27/117) of patients. The most common problems were weak, crumbling teeth. Some patients had been told they had very thin enamel. This is an area that requires further study.

MOLECULAR ANALYSIS

A combination of SSCP and direct sequence analysis identified mutations in *LMX1B* in 38/43 of the families studied. The nature and distribution of the mutations were in keeping with those described previously. Patients without a detectable mutation did not differ significantly in their phenotype from those in whom a mutation was found. Details of molecular analysis will be presented in a separate paper.

DIFFERENTIAL DIAGNOSES AND FEATURES NOT ASSOCIATED WITH NPS

The combination of features seen in NPS is very characteristic and the condition should therefore be easy to distinguish from other disorders. However, there are some conditions which merit discussion owing to areas of overlap with NPS. Major differentials are highlighted in table 4.

Although often quoted as being features of NPS, cleft lip and palate have been reported in one NPS patient only⁶³ and their absence in the large number of other published NPS patients suggests that this association was purely coincidental. Similarly, the occurrence of NPS in association with deafness,⁶⁴ cancer predisposition,⁶⁵ mental retardation, and psychosis⁶⁶ are likely to be coincidental.

RECOMMENDATIONS FOR THE CARE OF PATIENTS WITH NPS

Further research is required before truly evidence based guidelines can be applied to the monitoring of NPS patients. Until this is available the authors make recommendations shown in table 5.

FUTURE RESEARCH

This study highlights the need for further research into the NPS phenotype, including areas such as vasomotor, bowel,

neurological problems, and depression and ADHD. A prospective cohort follow up study would help to delineate the natural history of the NPS phenotype, particularly in areas such as the development of renal problems and glaucoma with increasing age.

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REFERENCES

- 1 **Beals RK**, Eckhardt AL. Hereditary onycho-osteodysplasia (nail-patella syndrome). A report of nine kindreds. *J Bone Joint Surg Am* 1969;**51**:505-16.
- 2 **Turner JW**. An hereditary arthrodysplasia associated with hereditary dystrophy of the nails. *JAMA* 1933;**100**:882-4.
- 3 **Guidera KJ**, Satterwhite Y, Ogden JA, Pugh L, Ganey T. Nail patella syndrome: a review of 44 orthopaedic patients. *J Pediatr Orthop* 1991;**11**:737-42.
- 4 **Lucas GL**, Opitz JM. The nail-patella syndrome. Clinical and genetical aspects of 5 kindreds with 38 affected family members. *J Pediatr* 1966;**68**:273-88.
- 5 **Renwick JH**, Lawler SD. Genetical linkage between the ABO and nail-patella loci. *Ann Hum Genet* 1955;**19**:312-31.
- 6 **Campeau E**, Watkins D, Rouleau GA, Babul R, Buchanan JA, Meschino W, Der Kaloustian VM. Linkage analysis of the nail-patella syndrome. *Am J Hum Genet* 1995;**56**:243-7.
- 7 **McIntosh I**, Clough MV, Schaffer AA, Puffenberger EG, Horton VK, Peters K, Abbott MH, Roig CM, Cutone S, Ozelius L, Kwiatkowski DJ, Pyeritz RE, Brown LJ, Pauli RM, McCormick MK, Francomano CA. Fine mapping of the nail-patella syndrome locus at 9q34. *Am J Hum Genet* 1997;**60**:133-42.
- 8 **Chen H**, Lun Y, Ovchinnikov D, Kokubo H, Oberg KC, Pepicelli CV, Gan L, Lee B, Johnson RL. Limb and kidney defects in *Lmx1b* mutant mice suggest an involvement of *LMX1B* in human nail patella syndrome. *Nat Genet* 1998;**19**:51-5.
- 9 **Dreyer SD**, Zhou G, Baldini A, Winterpacht A, Zabel B, Cole W, Johnson RL, Lee B. Mutations in *LMX1B* cause abnormal skeletal patterning and renal dysplasia in nail patella syndrome. *Nat Genet* 1998;**19**:47-50.
- 10 **Vollrath D**, Jaramillo-Babb VL, Clough MV, McIntosh I, Scott KM, Lichter PR, Richards JE. Loss-of-function mutations in the LIM-homeodomain gene, *LMX1B*, in nail-patella syndrome (published erratum appears in *Hum Mol Genet* 1998;**7**:1333). *Hum Mol Genet* 1998;**7**:1091-8.
- 11 **McIntosh I**, Dreyer SD, Clough MV, Dunston JA, Eyaid W, Roig CM, Montgomery R, Ala-Mello S, Kaitila I, Winterpacht A, Zabel B, Frydman M, Cole WG, Francomano CA, Lee B. Mutation analysis of *LMX1B* gene in nail-patella syndrome patients. *Am J Hum Genet* 1998;**63**:1651-8.
- 12 **Clough MV**, Hamlington JD, McIntosh I. Restricted distribution of loss-of-function mutations within the *LMX1B* genes of nail-patella syndrome patients. *Hum Mutat* 1999;**14**:459-65.
- 13 **Hamlington J**, Clough M, Dunston J, McIntosh I. Deletion of a branch-point consensus sequence in the *LMX1B* gene causes exon skipping in a family with nail patella syndrome. *Eur J Hum Genet* 2000;**8**:311-14.
- 14 **Hamlington J**, Jones C, McIntosh I. Twenty-two novel *LMX1B* mutations identified in nail patella syndrome (NPS) patients. *Hum Mutat* 2001;**18**:458.
- 15 **Seri M**, Melchionda S, Dreyer S, Marini M, Carella M, Cusano R, Piemontese MR, Caroli F, Silengo M, Zelante L, Romeo G, Ravazzolo R,

- Gasparini P, Lee B. Identification of LMX1B gene point mutations in Italian patients affected with nail-patella syndrome. *Int J Mol Med* 1999;**4**:285-90.
- 16 **Knoers N**, Bongers E, van Beersum S, Lommen E, van Bokhoven H, Hol F. Nail-patella syndrome: identification of mutations in the LMX1B gene in Dutch families. *J Am Soc Nephrol* 2000;**11**:1762-6.
- 17 **Carbonara P**, Alpert M. Hereditary osteo-onycho-dysplasia (HOOD). *Am J Med Sci* 1964;**248**:139-51.
- 18 **Rizzo R**, Pavone L, Micali G, Hall JG. Familial bilateral antecubital pterygia with severe renal involvement in nail-patella syndrome. *Clin Genet* 1993;**44**:1-7.
- 19 **Williams HJ**, Hoyer JR. Radiographic diagnosis of osteo-onychodysostosis in infancy. *Radiology* 1973;**109**:151-4.
- 20 **Sartoris DJ**, Resnick D. The horn: a pathognomonic feature of paediatric bone dysplasias. *Aust Paediatr J* 1987;**23**:347-9.
- 21 **Darlington D**, Hawkins CF. Nail-patella syndrome with iliac horns and hereditary nephropathy. Necropsy report and anatomical dissection. *J Bone Joint Surg Br* 1967;**49**:164-74.
- 22 **Fong EE**. "Iliac horns" (symmetrical bilateral central posterior iliac processes): a case report. *Radiology* 1946;**47**:517-18.
- 23 **Hawkins C**, Smith O. Renal dysplasia in a family with multiple hereditary abnormalities including iliac horns. *Lancet* 1950;**i**:803.
- 24 **Cottreill CP**, Jacobs P. Hereditary arthro-osteo-onychodysplasia associated with iliac horns. *Br J Clin Pract* 1961;**15**:933-41.
- 25 **Feingold M**, Itzchak Y, Goodman RM. Ultrasound prenatal diagnosis of the nail-patella syndrome. *Prenat Diagn* 1998;**18**:854-6.
- 26 **Zimmerman C**. Iliac horns: a pathognomonic roentgen sign of familial onycho-osteodysplasia. *AJR* 1961;**86**:478-83.
- 27 **Riddle RD**, Ensinii M, Nelson C, Tsuchida T, Jessell TM, Tabin C. Induction of the LIM homeobox gene *Lmx1* by WNT7a establishes dorsoventral pattern in the vertebrate limb. *Cell* 1995;**83**:631-40.
- 28 **Vogel A**, Rodriguez C, Warnken W, Izpisua Belmonte JC. Dorsal cell fate specified by chick *Lmx1* during vertebrate limb development (published erratum appears in *Nature* 1996;**379**:8480). *Nature* 1995;**378**:716-20.
- 29 **Cygan J**, Johnson R, McMahon A. Novel regulatory interactions revealed by studies of murine limb pattern in *Wnt-7a* and *En-1* mutants. *Development* 1997;**124**:5021-32.
- 30 **Dreyer S**, Morello R, German M, Zabel B, Winterpacht A, Lunstrum G, Horton WA, Oberg KC, Lee B. LMX1B transactivation and expression in nail-patella syndrome. *Hum Mol Genet* 2000;**9**:1067-4.
- 31 **Johnson RL**, Tabin CJ. Molecular models for vertebrate limb development. *Cell* 1997;**90**:979-90.
- 32 **Parr B**, McMahon A. Dorsalising signal *Wnt-7a* required for normal polarity of D-V and A-P axes of mouse limb. *Nature* 1995;**374**:350-3.
- 33 **Gubler MC**, Levy M, Naizot C, Habib R. Glomerular basement membrane changes in hereditary glomerular diseases. *Ren Physiol* 1980;**3**:405-13.
- 34 **Renwick JH**. *The genetics of the nail-patella syndrome*. PhD thesis, University of London, 1957.
- 35 **Daniel CRD**, Osment LS, Noojin RO. Triangular lunulae. A clue to nail-patella syndrome. *Arch Dermatol* 1980;**116**:448-9.
- 36 **Simila S**, Vesa L, Wasz-Hockert O. Hereditary onycho-osteodysplasia (the nail-patella syndrome) with nephrosis-like renal disease in a newborn boy. *Pediatrics* 1970;**46**:61-5.
- 37 **Hoyer JR**, Michael AF, Vernier RL. Renal disease in nail-patella syndrome: clinical and morphologic studies. *Kidney Int* 1972;**2**:231-8.
- 38 **Vernier RL**, Hoyer JR, Michael AF. The nail-patella syndrome-pathogenesis of the kidney lesion. *Birth Defects* 1974;**10**:57-9.
- 39 **Leahy M**. The hereditary nephropathy of osteo-onychodysplasia. *Am J Dis Child* 1966;**112**:237.
- 40 **Bodziak KA**, Hammond WS, Molitoris BA. Inherited diseases of the glomerular basement membrane. *Am J Kidney Dis* 1994;**23**:605-18.
- 41 **Chan PC**, Chan KW, Cheng IK, Chan MK. Living-related renal transplantation in a patient with nail-patella syndrome. *Nephron* 1988;**50**:164-6.
- 42 **Bennett WM**, Musgrave JE, Campbell RA, Elliot D, Cox R, Brooks RE, Everett WL, Beals RK, Porter GA. The nephropathy of the nail-patella syndrome. Clinicopathologic analysis of 11 kindred. *Am J Med* 1973;**54**:304-19.
- 43 **Browning MC**, Weidner N, Lorentz WB Jr. Renal histopathology of the nail-patella syndrome in a two-year-old boy. *Clin Nephrol* 1988;**29**:210-13.
- 44 **Skjaerven R**, Wilcox A, Lie R. The interval between pregnancies and the risk of preeclampsia. *N Engl J Med* 2002;**346**:33-8.
- 45 **Looij BJ Jr**, te Slaa RL, Hogewind BL, van de Kamp JJ. Genetic counselling in hereditary osteo-onychodysplasia (HOOD, nail-patella syndrome) with nephropathy. *J Med Genet* 1988;**25**:682-6.
- 46 **Rohr C**, Prestel J, Heide L, Hossler H, Kriz W, Johnson R, Antignac C, Witzgall R. The LIM-homeodomain transcription factor *Lmx1b* plays a crucial role in podocytes. *J Clin Invest* 2002;**109**:1073-82.
- 47 **Morello R**, Zhou G, Dreyer S, Harvey S, Ninomiya Y, Thorner P, Miner JH, Cole W, Winterpacht A, Zabel B, Oberg KC, Lee B. Regulation of glomerular basement membrane collagen expression by *LMX1B* contributes to renal disease in nail patella syndrome. *Nat Genet* 2001;**27**:205-8.
- 48 **Morello R**, Lee B. Insight into podocyte differentiation from the study of human genetic disease: nail-patella syndrome and transcriptional regulation in podocytes. *Pediatr Res* 2002;**51**:551-8.
- 49 **Miner J**, Morello R, Andrews K, Li C, Antignac C, Shaw A, Lee B. Transcriptional induction of slit diaphragm genes by *Lmx1b* is required in podocyte differentiation. *J Clin Invest* 2002;**109**:1065-72.
- 50 **Lichter PR**, Richards JE, Downs CA, Stringham HM, Boehnke M, Farley FA. Cosegregation of open-angle glaucoma and the nail-patella syndrome. *Am J Ophthalmol* 1997;**124**:506-15.
- 51 **Pressman C**, Chen H, Johnson R. LMX1B, a LIM homeodomain class transcription factor, is necessary for normal development of multiple tissues in the anterior segment of the murine eye. *Genesis* 2000;**26**:15-25.
- 52 **Flickinger RR Jr**, Spivey BE. Lester's line in hereditary osteo-onychodysplasia. *Arch Ophthalmol* 1969;**82**:700-3.
- 53 **Jones KL**. *Smith's recognizable patterns of human malformation*. 5th ed. Philadelphia: Saunders, 1997.
- 54 **Muller-Lissner SA**, Bollani S, Brummer RJ, Coremans G, Dapoigny M, Marshall JK, Muris JW, Oberndorff-Klein Wolthuis A, Pace F, Rodrigo L, Stockbrugger R, Vatn MH. Epidemiological aspects of irritable bowel syndrome in Europe and North America. *Digestion* 2001;**64**:200-4.
- 55 **Pare P**, Ferrazzi S, Thompson WG, Irvine EJ, Rance L. An epidemiological survey of constipation in Canada: definitions, rates, demographics, and predictors of health care seeking. *Am J Gastroenterol* 2001;**96**:3130-7.
- 56 **Lane JE**, Walker AN, Chandler PW, Gresen KW. Nail-patella syndrome: an incidental finding from abdominal discomfort. *South Med J* 1999;**92**:1213-5.
- 57 **Wright MJ**, McIntosh I. Hirschprung-like aganglionosis of the colon in patients with nail patella syndrome: extension of the NPS phenotype to a fourth organ system. *Am Soc Hum Genet* 1999;**A**:348.
- 58 **Smidt M**, Asbreuk C, Cox J, Chen H, Johnson R, Burbach J. A second independent pathway for development of mesencephalic dopaminergic neurons requires *Lmx1b*. *Nat Neurosci* 2000;**3**:337-41.
- 59 **Hobert O**, Tessmar K, Ruvkun G. The *Caenorhabditis elegans* *lim-6* LIM homeobox gene regulates neurite outgrowth and function of particular GABAergic neurons. *Development* 1999;**126**:1547-62.
- 60 **MacDonald B**, Cockerell O, Sander J, Shorvon S. The incidence and lifetime prevalence of neurological disorders in a prospective community-based study in the UK. *Brain* 2000;**123**:665-76.
- 61 **Kania A**, Johnson R, Jessell T. Coordinate roles for LIM homeobox genes in directing the dorsoventral trajectory of motor axons in the vertebrate limb. *Cell* 2000;**102**:161-73.
- 62 **McIntosh I**, Tierney E, Bukells I, Marsh L. Behavioural phenotype of nail-patella syndrome. *Am J Hum Genet* 2001;**69**:281.
- 63 **Richieri-Costa A**. Antecubital pterygium and cleft lip/palate presenting as signs of the nail-patella syndrome: report of a Brazilian family. *Am J Med Genet* 1991;**38**:9-12.
- 64 **Hussain SS**, Hope GA. Sensorineural hearing loss and nail patella syndrome. *Arch Otolaryngol Head Neck Surg* 1994;**120**:674-5.
- 65 **Gilula LA**, Kantor OS. Familial colon carcinoma in nail-patella syndrome. *Am J Roentgenol Radium Ther Nucl Med* 1975;**123**:783-90.
- 66 **Schroeder G**. Osteo-onycho-dysplasia hereditaria (albuminurica). *Konstitutionslehre* 1961;**36**:42.
- 67 **Morin P**, Vielpeau C, Fournier L, Denizet D. Le syndrome coxo-podo-patellaire. *J Radiol* 1985;**66**:441-6.
- 68 **Scott JE**, Taor WS. The "small patella" syndrome. *J Bone Joint Surg Br* 1979;**61**:172-5.
- 69 **Burckhardt A**. Eine Kombination von Knie- und Beckendysplasie. (The small patella syndrome). *Z Orthop* 1988;**126**:22-9.
- 70 **Vanek J**. Ischiopatellare Dysplasie: Syndrom der 'Kleinen Patella' von Scott und Taor. *Fortschr Roentgenstr* 1981;**135**:354-6.
- 71 **Bernhang AM**, Levine SA. Familial absence of the patella. *J Bone Joint Surg Am* 1973;**55**:1088-90.
- 72 **Kiss I**, Mandi A, Szappanos L. Patella aplasia or hypoplasia occurring in a family. Symposium 1976. Cited by Braun HS. *Clin Genet* 1978;**13**:350-2.
- 73 **Braun HS**. Familial aplasia or hypoplasia of the patella. *Clin Genet* 1978;**13**:350-2.
- 74 **Borochowitz Z**, Soudry M, Mendes D. Familial recurrent dislocation of patella with autosomal dominant mode of inheritance. *Clin Genet* 1988;**33**:1-4.
- 75 **Hurst J**, Winter R, Baraitser M. Distinctive syndrome of short stature, craniosynostosis, skeletal anomalies and malformed ears. *Am J Med Genet* 1988;**29**:107-15.
- 76 **Boles R**, Teebi A, Schwartz D, Harper J. Further delineation of the ear, patella, short stature syndrome (Meier-Gorlin syndrome). *Clin Dysmorphol* 1994;**3**:207-14.
- 77 **Loeys B**, Lemmerling M, Van Mol C, Leroy J. The Meier-Gorlin syndrome, or ear-patella-short stature syndrome, in sibs. *Am J Med Genet* 1999;**84**:61-7.
- 78 **Bongers E**, Opitz J, Fryer A, Sarda P, Hennekam R, Hall B, Superneau DW, Harbison M, Poss A, van Bokhoven H, Hamel BC, Knoers NV. Meier-Gorlin syndrome: report of eight additional cases and review. *Am J Med Genet* 2001;**102**:115-24.
- 79 **Cormier-Daire V**, Chauvet ML, Lyonnet S, Briard ML, Munnich A, Le Merrer M. Genitopatellar syndrome: a new condition comprising absent patellae, scrotal hypoplasia, renal anomalies, facial dysmorphism, and mental retardation. *J Med Genet* 2000;**37**:520-4.
- 80 **Winter R**, Baraitser M. *London dysmorphology database*. 2.2 ed. Oxford: Oxford University Press, 2000.
- 81 **Veroles A**, Bonneau D, Giudi O. Brachymorphism-onychodysplasia-dysphalangism syndrome. *J Med Genet* 1993;**30**:158-61.