GENEReviews
Funded by the NIH • Developed at the University of Washington, Seattle

Nail-Patella Syndrome

[*Fong Disease, Hereditary Osteo-Onychodysplasia*]

Elizabeth Sweeney, MB ChB, MRCP, DRCOG, MD

Consultant Clinical Geneticist
Royal Liverpool Children's Hospital
Elizabeth.Sweeney@RLC.NHS.UK

Julie E Hoover-Fong, MDPhD

Director, Greenberg Center for Skeletal Dysplasias, Institute of Genetic Medicine
Johns Hopkins University
Jhoover2@jhmi.edu

Iain McIntosh, PhD

Professor of Medical Genetics
Department of Molecular & Cell Biology
American University of the Caribbean
imcintosh@aucmed.edu

Initial Posting: May 31, 2003.
Last Update: July 28, 2009.

Summary

Disease characteristics. Nail-patella syndrome (NPS) involves a classic clinical tetrad of changes in the nails, knees, and elbows, and the presence of iliac horns. Nail changes are the most constant feature of NPS. Nails may be absent, hypoplastic, or dystrophic; ridged longitudinally or horizontally; pitted; discolored; separated into two halves by a longitudinal cleft or ridge of skin; and thin or (less often) thickened. The patellae may be small, irregularly shaped, or absent. Elbow abnormalities may include limitation of extension, pronation, and supination; cubitus valgus; and antecubital pterygia. Iliac horns are bilateral, conical, bony processes that project posteriorly and laterally from the central part of the iliac bones of the pelvis. Renal involvement, first manifest as proteinuria with or without hematuria, occurs in 30%-50% of affected individuals; end-stage renal disease (ESRD) occurs in about 5% of affected individuals. Primary open-angle glaucoma and ocular hypertension occur at increased frequency and at a younger age than in the general population.

Diagnosis/testing. The diagnosis of nail-patella syndrome is based on clinical findings. Molecular genetic testing of *LMX1B*, the only gene known to be associated with NPS, is available on a clinical basis.

Management. *Treatment of manifestations*: Orthopedic problems may be helped by analgesics, physiotherapy, splinting, bracing, or surgery; ACE inhibitors to control blood pressure and possibly to slow progression of proteinuria; renal transplantation as needed. *Surveillance*: annual monitoring for hypertension and renal disease; screening for glaucoma as soon as a child is compliant. *Agents/circumstances to avoid*: chronic use of NSAIDs because of the detrimental effect on kidney function.

Genetic counseling. Nail-patella syndrome is inherited in an autosomal dominant manner. Eighty-eight percent of individuals with NPS have an affected parent. Twelve percent of affected individuals have a *de novo* mutation. The offspring of an affected individual are at a 50% risk of inheriting NPS. Prenatal diagnosis for pregnancies at increased risk is possible if the disease-causing mutation in the family has been identified.

Diagnosis

Clinical Diagnosis

No clinical diagnostic criteria for nail-patella syndrome (NPS) exist; however, the combination of clinical features seen in this condition is characteristic. The classic clinical tetrad comprises:

-

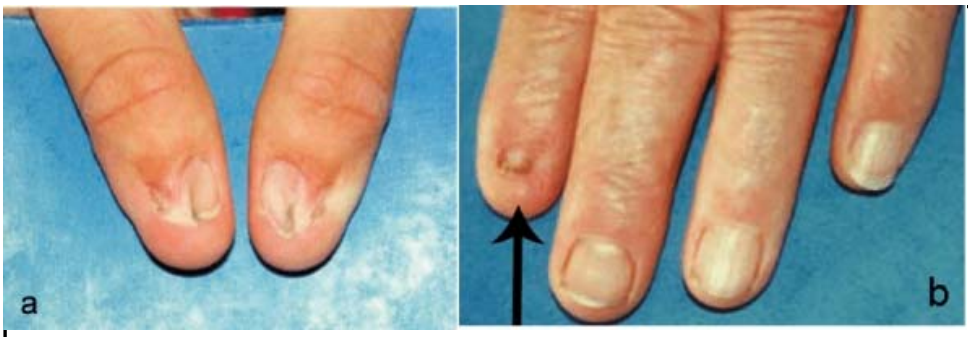

Figure 1. Typical presentation of thumb nails (a) and finger nails (b) in NPS. The arrow points to the index finger. Note decrease in severity of nail involvement from 2nd to 5th finger and lack of creases over the distal interphalangeal joints.

Nail changes. Nail changes are the most constant feature of NPS (98%). Nails may be absent, hypoplastic, or dystrophic; ridged longitudinally or horizontally; pitted; discolored; separated into two halves by a longitudinal cleft or ridge of skin; and thin or (less often) thickened. The nail changes may be limited to triangular lunules (or lunulae), a characteristic feature of NPS (Figure 1).

Nail changes may be observed at birth and are most often bilateral and symmetrical. The thumbnails are the most severely affected; the severity of the nail changes tends to decrease from the index finger toward the little finger. Each individual nail is usually more severely affected on its ulnar side. Dysplasia of the toenails is usually less marked and less frequent than that of the fingernails; if the toenails are involved, it is often the little toenail that is affected.

- **Knee involvement.** The patellae may be small, irregularly shaped, or absent. Patella involvement may be asymmetrical. 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; 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. These changes together with a hypoplastic or absent patella give the knee joint a flattened profile. Symptoms of knee involvement were apparent in 74% of cases in one study [Sweeney et al 2003].
- **Elbow involvement.** Elbow abnormalities may include limitation of extension, pronation, and supination; cubitus valgus; and antecubital pterygia. Elbow abnormalities may be asymmetrical. Typical radiologic 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. Approximately 70% of individuals with NPS exhibit some degree of elbow involvement [Sweeney et al 2003].
-

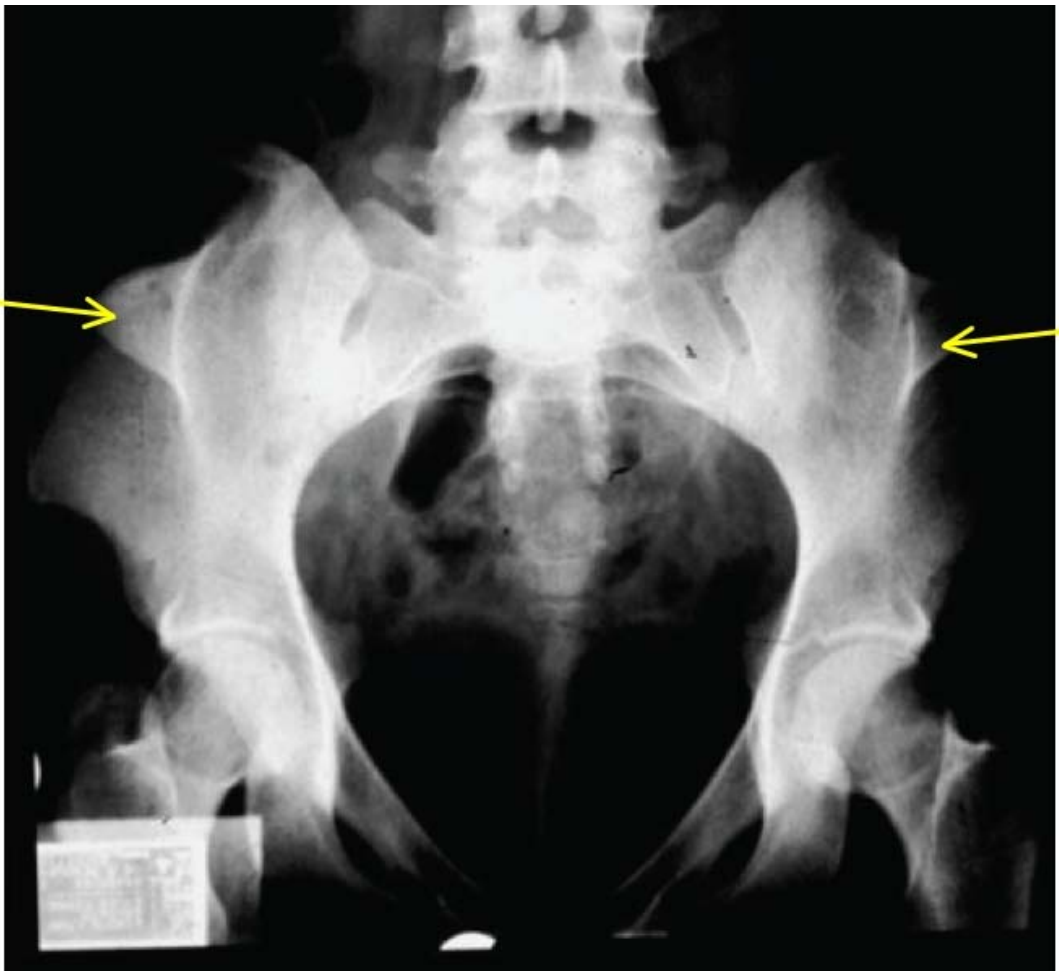

Figure 2. Iliac horns (arrows) in an individual with NPS

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. They are present in about 70% of individuals with NPS and are considered pathognomonic of NPS [Sweeney et al 2003]. Pelvic x-ray is usually necessary for their detection (Figure 2). Although large horns may be palpable, they are asymptomatic. Iliac horns may be seen on third-trimester ultrasound scanning [Feingold et al 1998], on x-ray at birth, and by bone scan [Goshen et al 2000]. In children, iliac horns may have an epiphysis at the apex.

Additional findings are not really considered as part of the diagnosis but the main clinical features should be looked for in an individual presenting with glaucoma or proteinuria as a primary feature.

Testing

Cytogenetic testing. Chromosomal translocations disrupting the gene have also been reported [Silahtaroglu et al 1999] but represent a rare pathogenic mechanism.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.—ED.

Gene. *LMX1B* is the only gene known to be associated with NPS.

Clinical testing

- **Sequence analysis.** Sequence analysis of *LMX1B* exons 2 through 6 and their intronic junctions detects approximately 85% of *LMX1B* mutations. The other 15% of mutations presumably lie elsewhere in the *LMX1B* gene [Clough et al 1999].

:

- **Deletion/duplication testing.** It appears that about 5% of individuals with nail-patella syndrome have a deletion of a substantial part of *LMX1B* detected using Southern blot analysis [Dunston et al 2004; Author, personal observation].
- **FISH analysis.** No studies have been published on the frequency of whole-gene deletions.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in Nail-Patella Syndrome

Gene Symbol	Test Method	Mutations Detected	Mutation Detection Frequency by Test Method	Test Availability
LMX1B	Sequence analysis	Sequence variants exons 2 through 6	85% [1]	Clinical
	Deletion/duplication analysis [2]	Exonic or whole-gene deletions	5%	
	FISH analysis	Large deletions	Undetermined	

1. Proportion of affected individuals with mutations identified by sequence analysis of exons 2-6 [Clough et al 1999, Sweeney et al 2003]
2. Testing that detects deletions/duplications not readily detectable by sequence analysis of genomic DNA; a variety of methods including quantitative PCR, real-time PCR, multiplex ligation-dependent probe amplification (MLPA), or array GH may be used.

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Testing Strategy

Confirmation of the diagnosis in a proband may require molecular genetic testing if the phenotype is atypical or cytogenetic testing if signs and symptoms beyond the typical NPS phenotype are present.

Prenatal diagnosis/preimplantation genetic diagnosis for at-risk pregnancies requires prior identification of the disease-causing mutation in the family.

Genetically Related (Allelic) Disorders

No other phenotypes are known to be associated with mutations in *LMX1B*.

Clinical Description

Natural History

The classic clinical tetrad of nail patella syndrome involves changes in the nails, knees, and elbows, and the presence of iliac horns (see Clinical Diagnosis). Many other features may be seen in NPS, and involvement of other body systems such as the kidneys and eyes is well documented [Sweeney et al 2003]. The clinical manifestations are extremely variable in both frequency and severity, with inter- and intrafamilial variability. Individuals may be severely affected by one aspect of NPS but have much milder or no manifestations elsewhere. Males and females are affected equally. Although the diagnosis may be made at birth, it is common for families to remain undiagnosed for several generations despite having been seen by doctors from a variety of disciplines.

Digital changes. In NPS, a reduction in flexion of the distal interphalangeal (DIP) joints is associated with loss of the creases in the skin overlying the dorsal surface of the DIP joints of the fingers. The gradient of severity is the same as seen in the nails; therefore, the index fingers are the most affected. Hyperextension of the proximal interphalangeal (PIP) joints with flexion of the DIP joints (resulting in "swan-necking") and fifth finger clinodactyly may be seen.

Knee involvement. In addition to the previously mentioned patellar abnormalities, 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 common. Symptoms associated with knee abnormalities in NPS include pain, instability, locking, clicking, patella dislocation, and inability to straighten the knee joint.

Involvement of the ankles and feet. Talipes equinovarus, calcaneovarus, calcaneovalgus, equinovalgus, and hyperdorsiflexion of the foot may occur. Tight Achilles tendons are common, contributing to talipes equinovarus and to toe-walking. Pes planus is common.

Spinal and chest wall problems. Back pain occurs in half of individuals with NPS. There may be an increased lumbar lordosis, scoliosis (usually mild), spondylolisthesis, spondylolysis, or pectus excavatum.

Osteoporosis. Bone mineral density (BMD) is reduced by 8%-20% in the hips of individuals with NPS. An increased rate of

fractures has also been reported.

General appearance. A lean body habitus may be associated with NPS and affected individuals often have difficulty putting on weight (particularly muscle) despite adequate dietary intake and exercise. In particular, muscle mass in the upper arms and upper legs tends to be decreased. The tendency to be very lean is most evident in adolescents and young adults and becomes less apparent after middle age.

Increased lumbar lordosis may make the buttocks appear prominent.

The high forehead and hairline, particularly at the temples, resembles a receding male pattern hairline when seen in women.

Renal involvement. Renal involvement occurs in 30%-50% of individuals with NPS; end-stage renal disease (ESRD) occurs in approximately 5% [Sweeney et al 2003].

The first sign of renal involvement is usually proteinuria, with or without hematuria. Proteinuria may present at any age from birth onwards and may be intermittent. Renal problems may present, or be exacerbated, during pregnancy. Once proteinuria is present, it may remit spontaneously, remain asymptomatic, or progress to nephrotic syndrome and occasionally to ESRD. Progression to renal failure may appear to occur rapidly or after many years of asymptomatic proteinuria. The factors responsible for this progression are yet to be identified. Nephritis may also occur in NPS.

Ultrastructural (electron microscopic) renal abnormalities are the most specific histologic changes seen in NPS and include irregular thickening of the glomerular basement membrane with electron-lucent areas giving a mottled "moth-eaten" appearance, and the presence of collagen-like fibers within the basement membrane and the mesangial matrix.

Ophthalmologic findings. Primary open-angle glaucoma and ocular hypertension occur at increased frequency in NPS and at a younger age than in the general population [Lichter et al 1997, Sweeney et al 2003]. Congenital and normal-tension glaucoma have been reported in individuals with NPS [Lichter et al 1997].

Iris pigmentary changes (termed Lester's sign) consisting of a zone of darker pigmentation shaped like a cloverleaf or flower around the central part of the iris are seen frequently.

Gastrointestinal involvement. One-third of individuals with NPS have problems with constipation (often from birth) or irritable bowel syndrome [Sweeney et al 2003].

Neurologic problems. Many individuals with NPS exhibit reduced sensation to pain and temperature in the hands and feet, most likely because of the inability of Aδ and C fibers to connect with interneurons in the dorsal spinal cord [Dunston et al 2005]. Some affected individuals report intermittent numbness, tingling, and burning sensations in the hands and feet, with no obvious precipitant. Rarely, these symptoms may be secondary to local orthopedic problems or neurologic compromise from the spine or cervical ribs. In most cases, however, the paresthesia follows a glove and stocking pattern rather than the distribution of a particular dermatome or peripheral nerve.

Epilepsy was reported in 6% of affected individuals in one large study [Sweeney et al 2003].

Vasomotor problems. Some individuals have symptoms of a poor peripheral circulation, such as very cold hands and feet, even in warm weather. Some may be diagnosed with Raynaud's phenomenon [Sweeney et al 2003].

Dental problems. Dental problems may include weak, crumbling teeth and thin dental enamel [Sweeney et al 2003].

Genotype-Phenotype Correlations

There is no known genotype-phenotype correlation in NPS [McIntosh et al 1998].

Penetrance

NPS is fully penetrant, although the range and severity of symptoms may be extremely variable.

Anticipation

Anticipation does not occur in NPS.

Nomenclature

NPS is the most accepted term but has the disadvantage of implying that nail and patellar dysplasia are the most important features. Hereditary onycho-osteodysplasia (HOOD) may be more accurate, but is rarely used. Perhaps hereditary onycho-osteodysplasia with nephropathy and glaucoma would be the best term. The terms Fong's disease and Turner syndrome * have also been used.

* Note: Referring to JW Turner and not HH Turner, who described the phenotype associated with a 45,X karyotype

Prevalence

The prevalence of NPS has been roughly estimated at one in 50,000 but may be higher because of undiagnosed individuals with a mild phenotype.

NPS has been reported in a wide variety of ethnic groups.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Table 2. Differential Diagnoses of Nail-Patella Syndrome

Syndrome	Similarities	Differences	References
Small patella syndrome (ischiopatellar dysplasia, coxo-podo-patellar syndrome, Scott-Taor syndrome)	Small or absent patellae Recurrent patella dislocations Pelvic anomalies	Defective ossification at the ischiopubic junction Ischial hypoplasia Infra-acetabular "axe-cut" notch No nail changes No elbow changes No renal involvement No ocular involvement	[OMIM 147891, Bongers et al 2004]
Patella aplasia-hypoplasia (PTLAH)	Isolated aplasia OR Hypoplasia of the patella	No nail changes No elbow changes No renal involvement No ocular involvement	[OMIM 168860]
Familial recurrent dislocation of the patella	Familial tendency toward patella dislocation		[OMIM 169000]
Meier-Gorlin syndrome	Absent patellae Dislocation of the radial head	Microtia Markedly short stature Delayed bone age Characteristic facial appearance Autosomal recessive inheritance	[OMIM 224690]
Genitopatellar syndrome	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 Structural (multicystic kidneys or hydronephrosis) rather than functional abnormalities Renal manifestations	[OMIM 606170, Cormier-Daire et al 2000]
DOOR syndrome	Absent or poorly formed nails	Long thumbs and big toes, often with triphalangy Other fingers and toes short as the result of an absent or hypoplastic distal phalanx Bilateral ptosis Short broad nose with a broad nasal tip and large nostrils	[OMIM 220500, Winter & Baraitser 2000]

		Structural renal tract abnormalities Cataracts Optic atrophy Dandy-Walker malformation Seizures Autosomal recessive inheritance	
Trisomy 8 mosaicism	Absent or hypoplastic patellae Limited elbow supination Abnormal nails	Significant learning difficulties Variable facial dysmorphism Camptodactyly and progressive joint restriction, usually of the fingers and toes	[Jones 1997]
Coffin-Siris syndrome	Absence or hypoplasia of the nails and patellae Elbow dislocation	Nail hypoplasia, usually affecting the little finger nails Facial dysmorphism	[OMIM 135900, Winter & Baraitser 2000]
RAPADILINO syndrome (see Rothmund-Thomson syndrome)	Radial defects Absent or hypoplastic patellae Dislocated joints	Cleft palate Facial dysmorphism Short stature Radial defects, including absent or hypoplastic thumbs and radii Autosomal recessive inheritance	[OMIM 266280, Winter & Baraitser 2000]
Senior syndrome	Small nails	Characteristic facial appearance Short stature Mild intellectual impairment	[OMIM 113477]

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with nail-patella syndrome (NPS), the following evaluations are recommended:

- Blood pressure measurement and urinalysis to screen for renal disease, plus a urine albumin:creatinine ratio on a first-morning urine. The latter is a more sensitive measure of renal disease than urinalysis as it corrects for urine concentration. If any abnormalities are detected, the individual should then be referred to a nephrologist.
- Screening for glaucoma as soon as a child is able to cooperate with the examination. The examination 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, individuals should be referred to an ophthalmologist. Any infant or young child found to have an abnormal or absent red reflex on eye examination by a primary care physician should be referred to an ophthalmologist immediately.
- History and physical examination to detect orthopedic problems
- History to identify gastrointestinal, neurologic, or vasomotor abnormalities
- Before surgery or intensive physiotherapy is performed for orthopedic complaints, investigation via MRI of possible bone/soft tissue abnormalities
- History and examination to detect dental anomalies
- Consideration of formal quantification of bone mineral density (BMD) via DEXA as indicator of fracture propensity based on reported low BMD and increased fracture risk in NPS.
    - DEXA norms are readily available in most clinical settings for adults and may be pursued in all young adults (>age 18 years) at least once.
    - Pediatric DEXA norms are often less readily available, but may be obtained via local pediatric endocrinologist or machine manufacturer. No formal recommendations for DEXA scanning of pediatric patients exist at this time, but DEXA should be pursued if fractures or unexplained skeletal pain occurs with additional clinical evaluation.

Treatment of Manifestations

Hypertension and renal disease are treated as in the general population. When renal transplantation is necessary, results are usually favorable. ACE inhibitors are useful in slowing progression of proteinuria but their use should be monitored carefully in children.

Orthopedic problems may be helped by analgesics, physiotherapy, splinting, bracing, or surgery. Because of the abnormal joint anatomy that may be present in patients with NPS, MRI of joints is important prior to surgery so that appropriate surgical treatment can be planned in advance.

Treatment as in the general population for:

- Glaucoma
- Constipation
- Dental problems

Surveillance

Annual measurement of the following is appropriate:

- Measurement of blood pressure
- Urinalysis
- Urine albumin:creatinine ratio on a first-morning urine. If any abnormalities are detected, the individual should then be referred to a nephrologist.
- Screening for glaucoma from the time that a child is compliant with the examination

Dental examination is indicated at least every six months.

DEXA scanning frequency in adults is based on clinical symptoms, abnormalities detected on previous evaluations, and standard practice in peri-/post-menopausal females and older males.

Agents/Circumstances to Avoid

Chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided because of their detrimental effect on kidney function.

Testing of Relatives at Risk

Early diagnosis of NPS in at-risk family members allows for ophthalmologic and renal screening – especially in individuals with mild-moderate skeletal involvement who may not otherwise come to clinical attention. Molecular genetic testing can be used if the disease-causing mutation in the family is known; otherwise, monitor renal findings (i.e., blood pressure, urinalysis, and urine albumin:creatinine ratio on a first-morning urine) and screen for glaucoma.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Other

Genetics clinics, staffed by genetics professionals, provide information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

See Consumer Resources for disease-specific and/or umbrella support organizations for this disorder. These organizations have been established for individuals and families to provide information, support, and contact with other affected individuals.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

Nail-patella syndrome is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Eighty-eight percent of individuals diagnosed with NPS have an affected parent [Sweeney et al 2003].
- A proband with NPS may have the disorder as the result of a *de novo* gene mutation. Twelve percent of affected individuals have a *de novo* mutation [Sweeney et al 2003].
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include physical examination and molecular genetic testing if the family mutation is known, as mild symptoms may be overlooked.

Sibs of a proband

- The risk to the sibs of the proband depends on the genetic status of the proband's parents.
- If a parent of the proband is affected, the risk to the sibs is 50%.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low.
- If a disease-causing mutation cannot be detected in the DNA of either parent, two possible explanations are germline mosaicism in a parent or a *de novo* mutation in the proband. Although no instances of germline mosaicism have been reported, it remains a possibility.

Offspring of a proband. The offspring of a proband are at a 50% risk of inheriting NPS; disease severity cannot be predicted.

Other family members of a proband. The risk to other family members depends on the status of the proband's parents. If a parent is affected, his or her family members are at risk.

Related Genetic Counseling Issues

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation or clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) or undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected.

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant when the sensitivity of currently available testing is less than 100%. See for a list of laboratories offering DNA banking.

Prenatal Testing

Molecular genetic testing. Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15 to18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed. Although this testing can determine whether or not the fetus has inherited the *LMX1B* disease-causing mutation, it cannot predict the appearance or severity of clinical manifestations.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Ultrasound examination. Talipes equinovarus or large iliac horns may be detected on fetal ultrasound examination in the third trimester of pregnancy.

Preimplantation genetic diagnosis (PGD). Preimplantation genetic diagnosis may be available for families in which the disease-causing mutation has been identified. For laboratories offering PGD, see .

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. [PubMed]

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. [PubMed]

Dreyer SD, Morello R, German MS, Zabel B, Winterpacht A, Lunstrum GP, Horton WA, Oberg KC, Lee B. LMX1B transactivation and expression in nail-patella syndrome. *Hum Mol Genet.* 2000; 9: 1067–74. [PubMed]

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. [PubMed]

Dunston JA, Hamlington JD, Zaveri J, Sweeney E, Sibbring J, Tran C, Malbroux M, O'Neill JP, Mountford R, McIntosh I. The human LMX1B gene: transcription unit, promoter, and pathogenic mutations. *Genomics.* 2004; 84: 565–76. [PubMed]

Dunston JA, Reimschisel T, Ding YQ, Sweeney E, Johnson RL, Chen ZF, McIntosh I. A neurological phenotype in nail patella syndrome (NPS) patients illuminated by studies of murine Lmx1b expression. *Eur J Hum Genet.* 2005; 13: 330–5. [PubMed]

Feingold M, Itzchak Y, Goodman RM. Ultrasound prenatal diagnosis of the nail-patella syndrome. *Prenat Diagn.* 1998; 18: 854–6. [PubMed]

Goshen E, Schwartz A, Zilka LR, Zwas ST. Bilateral accessory iliac horns: pathognomonic findings in nail-patella syndrome. Scintigraphic evidence on bone scan. *Clin Nucl Med.* 2000; 25: 476–7. [PubMed]

Jones KL (1997) Smith's Recognizable Patterns of Human Malformation, 5th ed, Saunders, pp 24-27.

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. [PubMed]

McIntosh I, Dreyer SD, Clough MV, Dunston JA, Eyaid W, Roig CM, Montgomery T, 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. [PubMed]

Silahtaroglu A, Hol FA, Jensen PK, Erdel M, Duba HC, Geurds MP, Knoers NV, Mariman EC, Tumer Z, Utermann G, Wirth J, Bugge M, Tommerup N. Molecular cytogenetic detection of 9q34 breakpoints associated with nail patella syndrome. *Eur J Hum Genet.* 1999; 7: 68–76. [PubMed]

Sweeney E, Fryer A, Mountford R, Green A, McIntosh I. Nail patella syndrome: a review of the phenotype aided by developmental biology. *J Med Genet.* 2003; 40: 153–62. [PubMed]

Winter R, Baraitser M (2000) London Dysmorphology Database. 2.2 ed. Oxford University Press.

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

Suggested Reading

McIntosh I, Dunston JA, Liu L, Hoover-Fong JE, Sweeney E. Nail patella syndrome revisited: 50 years after linkage. *Ann Hum Genet.* 2005; 69: 349–63. [PubMed]

Chapter Notes

Revision History

- 28 July 2009 (me) Comprehensive update posted live
- 26 July 2005 (me) Comprehensive update posted to live Web site
- 31 May 2003 (me) Review posted to live Web site
- 14 April 2003 (im) Original submission

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Nail-Patella Syndrome: Genes and Databases

Gene Symbol	Chromosomal Locus	Protein Name	HGMD
LMX1B	9q34.1	LIM homeobox transcription factor 1-beta	LMX1B

Data are compiled from the following standard references: gene symbol from HGNC; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from UniProt. For a description of databases (Locus Specific, HGMD) linked to, click here.

Table B. OMIM Entries for Nail-Patella Syndrome (View All in OMIM)

161200	NAIL-PATELLA SYNDROME; NPS
602575	LIM HOMEOBOX TRANSCRIPTION FACTOR 1, BETA; LMX1B

Normal allelic variants. The *LMX1B* gene comprises eight exons covering more than 90 kb, transcribed and spliced to an ~7-kb mRNA. *LMX1B* is a member of the LIM-homeodomain family. Alternative splicing of 21 bp at the 3' end of exon 7 has been observed; the biologic significance of this event remains to be determined. A series of single-nucleotide normal variants has been identified [Clough et al 1999].

Pathologic allelic variants. More than 130 mutations have been identified. Nonsense, frameshift, splice site, and missense mutations have all been reported, as well as deletions of part, or all, of the gene [Dunston et al 2004]. All amino acid substitutions that have been observed cause NPS [Dunston et al 2004]. Missense mutations are concentrated within the homeodomain and the residues in the LIM domains essential for maintaining the zinc finger structures. A series of recurrent mutations within the homeodomain accounts for approximately 30% of all *LMX1B* mutations [Clough et al 1999]. No mutations have been identified in the terminal third of the gene.

Normal gene product. The predicted protein comprises 395 or 402 amino acids (depending on alternative splicing of 21 bp at the 3' end of exon 7).

Abnormal gene product. NPS is the result of heterozygous loss-of-function mutations within the gene encoding the transcription factor. Because all types of mutations (including large deletions and translocations) result in the same phenotype [Dunston et al 2004], it is believed that NPS is the result of haploinsufficiency for *LMX1B*. There is no evidence that transcripts bearing nonsense or frameshift mutations escape nonsense-mediated mRNA decay and cause any dominant-negative effects on the normal gene product. Missense mutations within the homeodomain reduce or eliminate DNA binding [Dreyer et al 1998, McIntosh et al 1998, Dreyer et al 2000, Bongers et al 2002]. Missense mutations within the LIM domains are believed to affect the secondary structure of the zinc fingers [McIntosh et al 1998, Clough et al 1999].

Resources

See Consumer Resources for disease-specific and/or umbrella support organizations for this disorder. These organizations have been established for individuals and families to provide information, support, and contact with other affected individuals. GeneTests provides information about selected organizations and resources for the benefit of the reader; GeneTests is not responsible for information provided by other organizations.—ED.

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page

Literature Cited

Bongers EM, Duijf PH, van Beersum SE, Schoots J, Van Kampen A, Burckhardt A, Hamel BC, Losan F, Hoefsloot LH, Yntema HG, Knoers NV, van Bokhoven H. Mutations in the human TBX4 gene cause small patella syndrome. *Am J Hum Genet.* 2004; 74: 1239–48. [PubMed]

Bongers EM, Gubler MC, Knoers NV. Nail-patella syndrome. Overview on clinical and molecular findings. *Pediatr Nephrol.* 2002; 17: 703–12. [PubMed]