

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



Nail-Patella Syndrome

[Fong Disease, Hereditary Osteo-Onychodysplasia]

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Initial Posting: 31 May 2003
Last Update: 26 July 2005

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; renal failure occurs in about 5% of [affected](#) individuals. Primary open-angle glaucoma and ocular hypertension also 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. *LMX1B* is the only [gene](#) known to be associated with NPS. [Sequence analysis](#) of [exons](#) 2 through 6 of the *LMX1B* [gene](#) detects 85% of [mutations](#). Such testing is available on a clinical basis.

Management. Management of NPS includes annual monitoring for hypertension and renal disease: ACE inhibitors may slow progression of proteinuria; if necessary, renal transplantation is usually favorable. [Screening](#) for glaucoma and subsequent treatment are done as soon as a child is compliant with the examination. Orthopedic problems may be helped by analgesics, physiotherapy, splinting, bracing, or surgery. Chronic use of NSAIDs should be avoided because of their detrimental effect on kidney function.

Genetic counseling. Nail-patella syndrome is inherited in an [autosomal dominant](#) manner. Eighty-eight percent of individuals diagnosed 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.

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:

- **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. 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 a recent 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](#)].
- **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. 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 [[Beals & Eckhardt 1969](#)], and by bone

scan [[Goshen et al 2000](#)]. In children, iliac horns may have an epiphysis at the apex.

Testing

Cytogenetic testing. Chromosome [translocations](#) disrupting the [gene](#) have also been reported [[Silahtaroglu et al 1999](#)] but represent a rare pathogenetic 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 at least one US CLIA-certified laboratory or a clinical laboratory outside the US. GeneTests does not independently verify information provided by laboratories and does not warrant any aspect of a laboratory's work. Listing in GeneTests does not imply that laboratories are in compliance with accreditation, licensure, or patent laws. Clinicians must communicate directly with the laboratories to verify information. —Ed.

Gene. *LMX1B* is the only [gene](#) known to be associated with NPS.

Molecular genetic testing: Clinical uses

- Confirmatory [diagnostic testing](#)
- [Prenatal diagnosis](#)

Molecular genetic testing: Clinical method

- **Sequence analysis.** Sequence analysis of [exons](#) 2 through 6 of the *LMX1B* [gene](#) detects approximately 85% of *LMX1B* [mutations](#). The other 15% of [mutations](#) presumably lie deep in [introns](#) or involve [deletion](#) of all or part of the [gene](#) [[Clough et al 1999](#)].

Table 1 summarizes [molecular genetic testing](#) for this disorder.

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

Test Method	Mutations Detected	Mutation Detection Rate ¹	Test Availability
Sequence analysis	<i>LMX1B</i> mutations in exons 2 through 6	85%	Clinical Testing

1. Proportion of [mutations](#) identified by [sequence analysis](#) of [exons](#) 2-6 [[Clough et al 1999](#) , [Sweeney et al 2003](#)].

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click [here](#).

Testing Strategy for a Proband

[Cytogenetic](#) testing is appropriate if signs and symptoms beyond the typical NPS [phenotype](#) are present.

Genetically Related Disorders

No other disorders 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 [[Beals & Eckhardt 1969](#) , [Sweeney et al 2003](#)]. The clinical manifestations are extremely variable in both frequency and severity, with inter- and intra-familial 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. 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 also 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.

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; renal failure occurs in approximately 5% [[Sweeney et al 2003](#)]. The first sign of renal involvement is usually proteinuria, with or without hematuria [[Gubler et al 1980](#)].

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 renal failure. Progression to renal failure may appear to occur rapidly or after many years of asymptomatic proteinuria [[Hoyer et al 1972](#) , [Vernier et al 1974](#)]. The factors responsible for this progression are yet to be identified. Nephritis may also occur in NPS.

Ultrastructural (electron microscopic) 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 [[Bennett et al 1973](#)].

Ophthalmologic findings. Primary open-angle glaucoma and ocular hypertension also 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 glaucoma has been reported in individuals with NPS [[Lichter et al 1997](#)], and the onset of symptoms may be earlier than in the general population [[Sweeney et al 2003](#)]. 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 A δ 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 [[Renwick & Izatt 1965](#)] 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 (ischioapatellar dysplasia, coxo-podo-patellar syndrome, Scott-Taor syndrome)	<ul style="list-style-type: none"> • Small or absent patellae • Recurrent patella dislocations • Pelvic anomalies 	<ul style="list-style-type: none"> • 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 	<p>OMIM 147891 Scott & Taor 1979 Bongers et al 2004</p>
Patella aplasia-hypoplasia (PTLAH)	<ul style="list-style-type: none"> • Isolated aplasia OR • Hypoplasia of the patella 	<ul style="list-style-type: none"> • No nail changes • No elbow changes • No renal involvement • No ocular involvement 	<p>OMIM 168860 Bernhang & Levine 1973</p>
Familial recurrent dislocation of the patella	<ul style="list-style-type: none"> • Familial tendency toward patella dislocation 		<p>OMIM 169000 Borochowitz et al 1988</p>
Meier-Gorlin syndrome	<ul style="list-style-type: none"> • Absent patellae • Dislocation of the radial head 	<ul style="list-style-type: none"> • Microtia • Markedly short stature • Delayed bone age • Characteristic facial appearance 	<p>OMIM 224690 Boles et al 1994</p>

		<ul style="list-style-type: none"> • Autosomal recessive inheritance 	
Genitopatellar syndrome	<ul style="list-style-type: none"> • Absent patellae • Renal anomalies • Flexion deformities of the knees and hips • Club foot 	<ul style="list-style-type: none"> • 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 	<p>OMIM 606170 Cormier-Daire et al 2000</p>
DOOR syndrome	<ul style="list-style-type: none"> • Absent or poorly formed nails 	<ul style="list-style-type: none"> • Long thumbs and big toes, often with triphalangy • Other fingers and toes are short as the result of 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 	<p>OMIM 220500 Winter & Baraitser 2000</p>
Trisomy 8 mosaicism	<ul style="list-style-type: none"> • Absent or hypoplastic patellae • Limited elbow supination • Abnormal nails 	<ul style="list-style-type: none"> • Significant learning difficulties • Variable facial dysmorphism • Camptodactyly and progressive joint restriction, usually of the fingers and toes 	<p>Jones 1997</p>
Coffin-Siris syndrome	<ul style="list-style-type: none"> • Absence or hypoplasia of the nails and patellae • Elbow dislocation 	<ul style="list-style-type: none"> • Nail hypoplasia, usually affecting the little finger nails • Facial dysmorphism 	<p>OMIM 135900 Winter & Baraitser 2000</p>

<p>RAPADILINO syndrome (see Rothmund-Thomson syndrome)</p>	<ul style="list-style-type: none"> • Radial defects • Absent or hypoplastic patellae • Dislocated joints 	<ul style="list-style-type: none"> • Cleft palate • Facial dysmorphism • Short stature • Radial defects, including absent or hypoplastic thumbs and radii • Autosomal recessive inheritance 	<p>OMIM 266280 Winter & Baraitser 2000</p>
<p>Senior syndrome</p>	<ul style="list-style-type: none"> • Small nails 	<ul style="list-style-type: none"> • Characteristic facial appearance • Short stature • Mild intellectual impairment 	<p>OMIM 113477 Verloes et al 1993</p>

Management

Evaluations at Initial Diagnosis

- 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

Treatment of Manifestations

- Hypertension and renal disease are treated as in the general population. When renal transplantation is necessary, results are usually favorable [[Chan et al 1988](#) , [Bodziak et al 1994](#)]. ACE inhibitors are useful in slowing progression of proteinuria but their use should be monitored carefully in children.
- Glaucoma is treated as in the general population.
- Orthopedic problems may be helped by analgesics, physiotherapy, splinting, bracing or surgery. Because of the abnormal joint anatomy that may be present in NPS it is important to MRI joints prior to surgery so that appropriate surgical treatment can be planned in advance.
- Constipation is treated as in the general population.
- Dental problems are treated as in the general population.

Surveillance

- Annual [screening](#) of blood pressure and annual urinalysis
- Annual urine albumin:creatinine ratio on a first-morning urine. If any abnormalities are detected, the individual should then be referred to a nephrologist.
- Annual [screening](#) for glaucoma, as described above, from the time that a child is compliant with the examination
- Dental examinations at least every six months

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

Relatives should have a clinical examination to determine if they are [affected](#). In difficult cases in a family with a known [mutation](#), [molecular genetic testing](#) may be of benefit.

Therapies Under Investigation

Search [ClinicalTrials.gov](#) for access to information on clinical studies for a wide range of diseases and conditions.

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](#). —ED.

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 upon 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 upon the status of the proband's parents. If a parent is found to be **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 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.

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 in situations in which the **sensitivity** of currently available testing is less than 100%. See **DNA Banking** for a list of laboratories offering this service.

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 about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about 10-12 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 in

an [affected](#) family member in a research or clinical laboratory. For laboratories offering PGD, see [Testing](#) .

Molecular Genetics

Information in the Molecular Genetics tables may differ from that in the text; tables may contain more recent information. —Ed.

Molecular Genetics of Nail-Patella Syndrome

Gene Symbol	Chromosomal Locus	Protein Name
<i>LMX1B</i>	9q34.1	LIM homeobox transcription factor 1 beta

Data are compiled from the following standard references: Gene symbol from [HUGO](#); chromosomal locus, locus name, critical region, complementation group from [OMIM](#); protein name from [Swiss-Prot](#).

OMIM Entries for Nail-Patella Syndrome

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

Genomic Databases for Nail-Patella Syndrome

Gene Symbol	Entrez Gene	HGMD	GeneCards	GDB	GenAtlas
<i>LMX1B</i>	602575	LMX1B	LMX1B	9834526	LMX1B

For a description of the genomic databases listed, click [here](#).

Note: HGMD requires registration.

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 [polymorphisms](#) has been identified [[Clough et al 1999](#)]. All amino acid substitutions that have been observed cause NPS [[Dunston et al 2004](#)].

Pathologic allelic variants: Over 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](#)]. [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 NPS [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 [splicing](#) of [exon 7](#)).

Abnormal gene product: [Missense mutations](#) within the homeodomain reduce or eliminate [DNA binding](#) [[Dreyer et al 1998](#) , [McIntosh et al 1998](#) , [Bongers et al 2002](#) , [Dreyer et al 2000](#)]. [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](#)]. Nail-patella syndrome 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](#).

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. -Ed.

- **Nail Patella Syndrome UK**
PO Box 26415
East Kilbride
Glasgow G74 1YW
United Kingdom
Phone: 0800 121 82 98 (toll free line)
Email: info@npsuk.org
www.npsuk.org
- **Nail Patella Syndrome Worldwide, Inc**

25826 Norrington Square
South Riding VA 20152
Phone: 703-391-0690
Email: npsw@nailpatella.org
www.nailpatella.org

 [Resources Printable Copy](#)

References

[PubMed](#)

Published Statements and Policies Regarding Genetic Testing

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

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Funding Support
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