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# Hereditary Neuropathy with Liability to Pressure Palsies

Synonym: HNPP

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## Summary

### Clinical characteristics

Hereditary neuropathy with liability to pressure palsies (HNPP) is characterized by recurrent acute sensory and motor neuropathy in a single or multiple nerves. The most common initial manifestation is the acute onset of a non-painful focal sensory and motor neuropathy in a single nerve (mononeuropathy). The first attack usually occurs in the second or third decade but earlier onset is possible. Neuropathic pain is increasingly recognized as a common manifestation. Recovery from acute neuropathy is usually complete; when recovery is not complete, the resulting disability is mild. Some affected individuals also demonstrate a mild-to-moderate peripheral neuropathy.

### Diagnosis/testing

The diagnosis of HNPP is established in a proband with suggestive clinical and electrophysiologic findings and either the 1.5-Mb recurrent deletion or a novel deletion involving *PMP22* (in 80%), or a *PMP22* sequence variant (in 20%) identified by molecular genetic testing.

### Management

**Treatment of manifestations:** Treatment is symptomatic and involves occupational therapy and physical therapy as needed to address issues with fine motor and gross motor skills, including activities of daily living. Bracing, such as with a wrist splint or ankle-foot orthosis, may be useful transiently or in some instances permanently. Special shoes, including those with good ankle support, may be needed. Neuropathic pain can be treated with analgesic medications. Protective pads at elbows or knees may prevent pressure and trauma to local nerves.

**Surveillance:** Routine screening neurologic examination focused on muscle atrophy, strength, sensory loss, and neuropathic pain; physical and occupational therapy assessments of gross motor and fine motor skills and activities of daily living; foot examinations for pressure sores or poorly fitting footwear.

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*Agents/circumstances to avoid:* Prolonged sitting with legs crossed; prolonged leaning on elbows; occupations requiring repetitive movements of the wrist; rapid weight loss; vincristine.

*Evaluation of relatives at risk:* Asymptomatic relatives at risk may wish to clarify their genetic status by undergoing molecular genetic testing for the *PMP22* pathogenic variant identified in an affected family member in order to be advised about agents and circumstances to avoid.

## Genetic counseling

HNPP is inherited in an autosomal dominant manner. Approximately 20% of individuals with HNPP have the disorder as the result of a *de novo* *PMP22* pathogenic variant. Each child of an affected individual is at a 50% risk of inheriting the *PMP22* pathogenic variant. Once the *PMP22* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

## Diagnosis

### Suggestive Findings

Hereditary neuropathy with liability to pressure palsies (HNPP) **should be suspected** in individuals with the following clinical findings, electrophysiologic studies, imaging studies, and family history.

#### Typical clinical findings

- Recurrent acute focal sensory and motor neuropathies mainly at entrapment sites
- Painless nerve palsy after minor trauma or compression
- Evidence on physical examination of previous nerve palsy such as focal weakness, atrophy, or sensory loss
- Complete spontaneous recovery from neuropathies (in 50% of occurrences) within weeks
- Mild-to-moderate *pes cavus* foot deformity (in 4%-40% of individuals)

#### Electrophysiologic studies

- Prolongation of distal nerve conduction latencies (e.g., of the median nerve at the wrist and of common peroneal nerve at fibular head) is observed in most individuals, whether symptomatic or asymptomatic.
- Electrophysiologic criteria to consider in the diagnosis of HNPP include bilateral increase in median nerve motor and distal sensory latencies with at least one additional abnormal motor conduction finding in one peroneal nerve (89%) [Dubourg et al 2000].
- Absent or reduced sural responses are observed in one third of affected individuals [Robert-Varvat et al 2018].
- Nerve conduction velocity may be delayed at the site of compression even with conduction block [Robert-Varvat et al 2018].

#### Imaging studies

- Ultrasonography shows multifocal increase in nerve cross-sectional area at and outside entrapment sites [Bayrak et al 2015, Padua et al 2018].
- MRI may show increased nerve caliber and asymmetric swelling and hyperintensities of fascicles at entrapment sites [Yurrebaso et al 2014].

**Family history** is consistent with autosomal dominant inheritance (e.g., affected males and females in multiple generations). Absence of a known family history does not preclude the diagnosis.

## Establishing the Diagnosis

The diagnosis of HNPP is **established** in a proband with suggestive findings by identification of either the 1.5-megabase (Mb) recurrent deletion or a novel deletion involving *PMP22* (in 80%), or a pathogenic (or likely pathogenic) *PMP22* sequence variant (in 20%) by molecular genetic testing (see Table 1).

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variants" and "likely pathogenic variants" are synonymous in a clinical setting, meaning that both are considered diagnostic and both can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include any likely pathogenic variants. (2) Identification of a heterozygous *PMP22* variant of uncertain significance does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of single-gene testing and a multigene panel or comprehensive genomic testing. Individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those in whom the diagnosis of HNPP has not been considered are more likely to be diagnosed using a multigene panel or genomic testing (see Option 2).

### Option 1

**Single gene testing.** First, perform gene-targeted deletion/duplication analysis to detect the 1.5-Mb recurrent deletion or a novel deletion involving *PMP22*. If no deletion is detected, perform sequence analysis.

Sequence analysis of *PMP22* can detect missense, nonsense, frameshift, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected.

### Option 2

**A neuropathy multigene panel** that includes *PMP22* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

For an introduction to multigene panels click [here](#). More detailed information for clinicians ordering genetic tests can be found [here](#).

**Comprehensive genomic testing** does not require the clinician to determine which gene(s) are likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

If exome sequencing is not diagnostic – and particularly when evidence supports autosomal dominant inheritance – **exome array** (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

For an introduction to comprehensive genomic testing click [here](#). More detailed information for clinicians ordering genomic testing can be found [here](#).

**Table 1.** Molecular Genetic Testing Used in HNPP

Gene <sup>1</sup>	Method	Proportion of Probands with a Pathogenic Variant <sup>2</sup> Detectable by Method
<i>PMP22</i>	Deletion/duplication analysis <sup>3</sup>	~80% <sup>4</sup>
	Sequence analysis <sup>5</sup>	~20% <sup>6</sup>

1. See Table A. Genes and Databases for chromosome locus and protein.

2. See Molecular Genetics for information on variants detected in this gene.

3. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

4. van Paassen et al [2014]

5. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click [here](#).

6. Stögbauer et al [2000], van de Wetering et al [2002], Kleopa et al [2004]

## Clinical Characteristics

### Clinical Description

Hereditary neuropathy with liability to pressure palsies (HNPP) is characterized by recurrent acute sensory and motor neuropathy in a single or multiple nerves. The most common initial manifestation is the acute onset of a non-painful focal sensory and motor neuropathy in a single nerve (mononeuropathy) [Kumar et al 2002, Li et al 2004]. Some individuals experience transient sensory phenomena without weakness. A history of actual physical minor compression of the nerve may or may not be present.

The first attack generally occurs in the second or third decade (age range: 2-70 years; mean 37 years) but could be at any age. With the widespread availability of molecular genetic testing, reports of early onset have become increasingly common [Chrestian et al 2015].

While the nerve palsies often recur over a period of many years, some individuals have a single episode and some individuals with molecularly confirmed HNPP remain asymptomatic. Even within the same family extreme variability is seen. Nerve palsies and electrophysiologic abnormalities are more frequent in men than women [Manganelli et al 2013].

The most common sites of focal neuropathy (in decreasing order of frequency) are the following:

- Peroneal nerve at the fibular head causing foot drop
- Ulnar nerve at the elbow, causing hypothenar and interossei muscle weakness and atrophy with sensory loss over the lateral aspect of the hand
- Median nerve at the wrist causing carpal tunnel syndrome with thenar muscle weakness and atrophy and sensory loss over the thumb and index finger [Del Colle et al 2003]
- Brachial plexus and radial nerve, causing transient sensory symptoms and hand pain [Marriott et al 2002]

Involvement of other less commonly affected nerves includes the following:

- Motor brachial plexopathy [Kim 2014]
- Hypoglossal nerve paralysis affecting the tongue, including after carotid endarterectomy [Corwin & Girardet 2003, Winter & Juel 2003]
- Scapulo-peroneal syndrome [Barroso et al 2006]
- Sciatic neuropathy [Topakian et al 2014]
- Laryngeal and phrenic nerve involvement [Cortese et al 2016]

- Facial nerve involvement [Poloni et al 1998]

Pain is increasingly recognized as a common manifestation. In one study, 74% individuals had persistent pain lasting more than a week; of these, three quarters developed neuropathic pain and almost 90% were likely to have central sensitization (i.e., development and maintenance of chronic pain) [Beales et al 2017].

Other manifestations can include:

- Rapid onset and progression of neuropathy early in military physical training [Horowitz et al 2004]
- Multifocal presentation
  - Progressive muscular atrophy [Tohge et al 2016]
  - Charcot-Marie-Tooth hereditary neuropathy-like pattern [Gouider et al 1995]
- Chronic inflammatory demyelinating polyneuropathy-like disorders [Rajabally et al 2016]
- Central nervous system white matter lesions compatible with demyelination (usually asymptomatic) [Novakova & Sussova 2012, Chanson et al 2013]

**Prognosis.** Full recovery over a period of days to months occurs in approximately 50% of episodes. While incomplete recovery is common and often associated with frustration and disability associated with recurrent pressure palsies, the degree of disability in performing activities of daily living is usually not severe. Poor recovery correlates with a history of prolonged focal compression of the nerve [Koike et al 2005]. Chronic neuropathic pain appears as a sequel to post-entrapment in 50% to 75% of affected individuals.

## Genotype-Phenotype Correlations

More than 26 single *PMP22* nucleotide variants have been reported to cause HNPP. It is not clear if there are genotype-phenotype correlations with these variants since each is limited to a few families [Li et al 2013].

Of note, six families with the *PMP22* frameshift variant p.Arg95Glnfs128 have a typical HNPP phenotype and are also more likely to have an associated clinically evident motor/sensory neuropathy mimicking Charcot-Marie-Tooth neuropathy type 1 (CMT1; see [CMT Overview](#)) [Lenssen et al 1998]. A similar phenotype has been described in individuals with other single-nucleotide variants in *PMP22* [Bellone et al 2006, Li et al 2007, Muglia et al 2007, Moszyńska et al 2009, Taioli et al 2011].

## Penetrance

Penetrance is 100% but expressivity is highly variable even within the same family.

For an unknown reason men typically have more severe clinical nerve palsies and electrophysiologic studies.

## Nomenclature

Hereditary neuropathy with liability to pressure palsies was previously referred to as hereditary pressure-sensitive neuropathy, tomaculous neuropathy,\* recurrent pressure-sensitive neuropathy, and "tulip-bulb digger's palsy" or "potato-grubbing palsy" [Koehler 2003]. Of note, a *PMP22* deletion was identified in the original Dutch family reported by De Jong in 1947 as having potato-grubbing palsy [Koehler & Baas 2012].

\* Sural nerve biopsy often shows evidence of demyelination and "tomaculous" change (focal, sausage-like enlargement of the nerve), a nonspecific finding noted occasionally in other neuropathies.

## Prevalence

The prevalence of HNPP is unknown; it is estimated at 7:100,000-16:100,000 population. The actual prevalence may be higher because of under-diagnosis.

The types of pathogenic variants and phenotypic spectrum are quite homogenous across different populations [van Paassen et al 2014, Karadima et al 2015].

## Genetically Related (Allelic) Disorders

The other phenotypes associated with heterozygous pathogenic variants in *PMP22* are Charcot-Marie-Tooth neuropathy type 1A (CMT1A) and Charcot-Marie-Tooth neuropathy type 1E (CMT1E) (see [CMT Overview](#)).

A severe CMT phenotype was reported in two children who were compound heterozygotes for two different *PMP22* deletions [Al-Thihli et al 2008, Abe et al 2010].

## Differential Diagnosis

The signs and symptoms of compression neuropathy in hereditary neuropathy with liability to pressure palsies (HNPP) are the same as those of the acquired type. Thus, HNPP is part of the broad differential diagnosis of both compression neuropathies and general peripheral neuropathies, including the hereditary neuropathies and Charcot-Marie-Tooth (CMT) syndrome (see [CMT Overview](#)).

## Acquired Disorders

**Compression neuropathies.** Pressure palsies are most commonly the result of environmentally acquired physical compression of peripheral nerves. The most common are carpal tunnel syndrome with compression of the median nerve at the wrist,\* peroneal pressure palsy with compression of the superficial peroneal nerve at the fibular head, and ulnar nerve compression at the elbow.

\* HNPP is not a common cause of isolated idiopathic carpal tunnel syndrome [Stockton et al 2001, Sander et al 2005].

**Diabetes mellitus.** Persons with an underlying polyneuropathy, such as those with diabetes mellitus, are at increased risk for compression neuropathies.

**Vasculitic neuropathy.** Although affected persons present with acute and multifocal onset that may mimic HNPP, progression of the findings and lack of recovery without treatment suggest this diagnosis.

**Chronic inflammatory demyelinating polyneuropathy (CIDP).** Multifocal neuropathies such as multifocal acquired demyelinating sensory and motor (MADSAM) neuropathy or Lewis and Sumner syndrome should be considered in the differential diagnosis, as these entities are treatable [Shah et al 2015]. Moreover, individuals whose findings overlap both CIDP and HNPP have been reported, suggesting that recurrent demyelination could be a trigger for an autoimmune reaction [Vrinten et al 2016].

## Hereditary Disorders

**Hereditary peripheral neuropathies** should be considered in the differential diagnosis of HNPP, including [CMT hereditary neuropathy](#) and multisystem disorders in which peripheral motor neuropathy may be a presenting feature (i.e., before multisystem involvement is appreciated) and/or one manifestation in a complex neurologic disorder (see [CMT Overview](#), [Table 1. Other Hereditary Neuropathies](#)).

**Hereditary neuralgic amyotrophy (OMIM 162100).** HNPP sometimes involves the brachial plexus, thus overlapping with hereditary neuralgic amyotrophy, a distinct disorder associated with heterozygous pathogenic variants in *SEPTIN9* (formerly *SEPT9*). Stögbauer et al [2000] compare the clinical features of this disorder and HNPP.



## Management

### Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with hereditary neuropathy with liability to pressure palsies (HNPP), the evaluations summarized in Table 2 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

**Table 2.** Recommended Evaluations Following Initial Diagnosis in Individuals with HNPP

System/Concern	Evaluation	Comment
<b>Neurologic</b>	Neurologic eval	To evaluate for pain & determine: <ul style="list-style-type: none"> <li>• Extent of weakness &amp; atrophy, <i>pes cavus</i>, gait stability, &amp; sensory loss</li> <li>• If there are assoc manifestations (e.g., focal atrophy or sensory loss in less common sites of entrapment)</li> <li>• If affected person &amp;/or a family member has had episodes of acute transient nerve palsy</li> </ul>
<b>Musculoskeletal</b>	Orthopedics / physical medicine & rehab / PT/OT evaluation	To incl assessment of: <ul style="list-style-type: none"> <li>• Gross motor &amp; fine motor skills &amp; need for PT (to improve gross motor skills) &amp;/or OT (to improve fine motor skills)</li> <li>• Feet for evidence of <i>pes cavus</i> &amp; need for AFOs, specialized shoes</li> <li>• Mobility, ADL, &amp; need for adaptive devices</li> <li>• Need for handicapped parking</li> </ul>
<b>Genetic counseling</b>	By genetics professionals <sup>1</sup>	To inform affected persons & families re nature, MOI, & implications of HNPP to facilitate medical & personal decision making
<b>Family support &amp; resources</b>		Assess need for: <ul style="list-style-type: none"> <li>• Community resources &amp; support/advocacy organizations (e.g., <a href="#">Parent to Parent</a>);</li> <li>• Social work involvement for parental support.</li> </ul>

ADL = activities of daily living; AFO = ankle-foot orthosis; MOI = mode of inheritance; OT = occupational therapy; PT = physical therapy

1. Medical geneticist, certified genetic counselor, or certified advanced genetic nurse

### Treatment of Manifestations

No specific treatment for the underlying genetic or biochemical defect exists, and no special diet or vitamin regimen is known to alter the natural course of HNPP.

Treatment is symptomatic and involves the following.

#### Neuropathy

- Occupational therapy and physical therapy may be needed to address issues with fine motor and gross motor skills, including activities of daily living.
- Transient bracing, such as with a wrist splint or ankle-foot orthosis (AFO), may be useful. Special shoes, including those with good ankle support, may be needed.
- Some individuals with residual foot drop may permanently use an AFO.
- Protective pads at elbows or knees may prevent pressure and trauma to local nerves.

**Pain.** Since pain is known as a common complication, clinicians should assess for pain and treat with analgesic medications according to the level of neuropathic pain. Medications could range from common topical analgesics to more systemic neuropathic treatment (including pregabalin, carbamazepine, and duloxetine). Orthosis (e.g., a foot pad or heel insert or an AFO) could help to improve pain during the recovery phase.

**Other.** Because spontaneous recovery is common and because there is no systematic controlled study of surgical intervention, the benefits of a surgical approach are controversial.

## Surveillance

**Table 3.** Recommended Surveillance for Individuals with HNPP

System/Concern	Evaluation	Frequency
<b>Neurologic</b>	Screening neurologic exam focused on muscle atrophy, strength, & sensory loss	Annually
	Eval for neuropathic pain	
<b>Musculoskeletal</b>	PT (gross motor skills) & ADL	
	OT (fine motor skills) & ADL	
<b>Foot examination</b>	For pressure sores or poorly fitting footwear	Annually by physician; at more frequent intervals by affected person

ADL = activities of daily living; OT = occupational therapy; PT = physical therapy

## Agents/Circumstances to Avoid

Activities that are risk factors for pressure palsies include the following [Cruz-Martinez et al 2000, Marriott et al 2002]:

- Prolonged sitting with legs crossed
- Prolonged leaning on elbows
- Occupations requiring repetitive movements of the wrist
- Rapid weight loss
- Wearing a heavy backpack on shoulders

Particular care must be taken in positioning during surgery (particularly knee surgery) to avoid nerve compression [Kramer et al 2016].

Vincristine, commonly used in the chemotherapy of lymphoma, has been reported to exacerbate HNPP, as other potential neurotoxic chemotherapy or agents [Kalfakis et al 2002].

Medications that are toxic or potentially toxic to persons with CMT comprise a spectrum of risk ranging from definite high risk to negligible risk. See the Charcot-Marie-Tooth Association [website](#) (pdf) for an up-to-date list.

## Evaluation of Relatives at Risk

Asymptomatic relatives at risk may wish to clarify their genetic status by undergoing molecular genetic testing for the *PMP22* pathogenic variant identified in an affected family member in order to be advised about agents and circumstances to avoid.

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



## Therapies Under Investigation

Search [ClinicalTrials.gov](https://clinicaltrials.gov) in the US and [EU Clinical Trials Register](https://european-clinical-trials-register.eu) in Europe 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.

## Genetic Counseling

*Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of 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; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.*

## Mode of Inheritance

Hereditary neuropathy with liability to pressure palsies (HNPP) is inherited in an autosomal dominant manner.

## Risk to Family Members

### Parents of a proband

- Approximately 6% to 23% of individuals diagnosed with HNPP have an asymptomatic affected parent [van Paassen et al 2014].
  - Approximately 20% of individuals diagnosed with HNPP have the disorder as the result of a *de novo* *PMP22* pathogenic variant [Infante et al 2001].
  - Molecular genetic testing is recommended for the parents of a proband with an apparent *de novo* pathogenic variant.
  - If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or germline mosaicism in a parent.\* Though theoretically possible, no instances of a proband inheriting a pathogenic variant from a parent with germline mosaicism have been reported.
- \* Misattributed parentage can also be explored as an alternative explanation for an apparent *de novo* pathogenic variant.

**Sibs of a proband.** The risk to the sibs of the proband depends on the clinical/genetic status of the proband's parents.

- If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibs is 50%; however, intrafamilial variability is considerable [van Paassen et al 2014].
- If the proband has a known HNPP-related pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be 1% because of the theoretic possibility of parental germline mosaicism [Rahbari et al 2016].
- If the parents have not been tested for the *PMP22* pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for HNPP because of the possibility of reduced penetrance in a heterozygous parent or the theoretic possibility of parental germline mosaicism.

**Offspring of a proband.** Each child of an individual with HNPP has a 50% chance of inheriting the *PMP22* pathogenic variant.

**Other family members.** The risk to other family members depends on the genetic status of the proband's parents: if a parent has the *PMP22* pathogenic variant, the parent's family members may be at risk.

## Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and avoidance of certain agents and circumstances.

### Predictive testing (i.e., testing of asymptomatic at-risk individuals)

- Predictive testing for at-risk relatives is possible once the HNPP-related pathogenic variant has been identified in an affected family member.
- Potential consequences of such testing (including, but not limited to, socioeconomic changes and the need for long-term follow up and evaluation arrangements for individuals with a positive test result) as well as the capabilities and limitations of predictive testing should be discussed in the context of formal genetic counseling prior to testing.

### Predictive testing in minors (i.e., testing of asymptomatic at-risk individuals younger than age 18 years)

- For asymptomatic minors at risk for adult-onset conditions for which early treatment would have no beneficial effect on disease morbidity and mortality, predictive genetic testing is considered inappropriate, primarily because it negates the autonomy of the child with no compelling benefit. Further, concern exists regarding the potential unhealthy adverse effects that such information may have on family dynamics, the risk of discrimination and stigmatization in the future, and the anxiety that such information may cause.
- For more information, see the National Society of Genetic Counselors [position statement](#) on genetic testing of minors for adult-onset conditions and the American Academy of Pediatrics and American College of Medical Genetics and Genomics [policy statement](#): ethical and policy issues in genetic testing and screening of children.

In a family with an established diagnosis of HNPP, it is appropriate to consider testing of symptomatic individuals regardless of age.

### Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy. Similarly, decisions about testing to determine the genetic status of at-risk asymptomatic family members are best made 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 or at risk.

## Prenatal Testing and Preimplantation Genetic Testing

Once the *PMP22* pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for HNPP are possible. Note: Age of onset, severity, type of manifestations, and rate of progression cannot be predicted on the basis of prenatal genetic test results.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

## Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click [here](#).

- Hereditary Neuropathy Foundation**  
**Phone:** 855-435-7268 (toll-free); 212-722-8396  
**Fax:** 917-591-2758  
**Email:** [info@hnf-cure.org](mailto:info@hnf-cure.org)  
[www.hnf-cure.org](http://www.hnf-cure.org)
- National Library of Medicine Genetics Home Reference**  
[Hereditary neuropathy with liability to pressure palsies](#)
- Charcot-Marie-Tooth Association (CMTA)**  
**Phone:** 800-606-2682 (toll-free); 610-427-2971  
**Email:** [info@cmtausa.org](mailto:info@cmtausa.org)  
[www.cmtausa.org](http://www.cmtausa.org)
- European Charcot-Marie-Tooth Consortium**  
 Department of Molecular Genetics  
 University of Antwerp  
 Antwerp Antwerpen B-2610  
 Belgium  
**Fax:** 03 2651002  
**Email:** [gisele.smeyers@ua.ac.be](mailto:gisele.smeyers@ua.ac.be)

## 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.** Hereditary Neuropathy with Liability to Pressure Palsies: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
<a href="#">PMP22</a>	17p12	Peripheral myelin protein 22	<a href="#">IPN Mutations, PMP22</a> <a href="#">PMP22 homepage - Leiden Muscular Dystrophy pages</a>	<a href="#">PMP22</a>	<a href="#">PMP22</a>

Data are compiled from the following standard references: gene from [HGNC](#); chromosome locus from [OMIM](#); protein from [UniProt](#). For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click [here](#).

**Table B.** OMIM Entries for Hereditary Neuropathy with Liability to Pressure Palsies ([View All in OMIM](#))

<a href="#">162500</a>	NEUROPATHY, HEREDITARY, WITH LIABILITY TO PRESSURE PALSIES; HNPP
<a href="#">601097</a>	PERIPHERAL MYELIN PROTEIN 22; PMP22

## Molecular Pathogenesis

HNPP is associated with decreased mRNA message for *PMP22* and decreased peripheral myelin protein 22 in peripheral nerve. Guo et al [2014] have shown that *PMP22* deficiency disrupts myelin junctions, resulting in impaired propagation of nerve action potentials.

### Mechanism of disease causation. Loss of function

The HNPP recurrent 1.5-Mb deletion is a submicroscopic DNA rearrangement. Although many genes are deleted, only *PMP22*, appears to be dosage sensitive, resulting in a haploinsufficiency phenotype. The proof for this concept is provided by the identification of *PMP22* frameshift pathogenic variants that presumably result in null alleles in some individuals with HNPP [Stögbauer et al 2000, van de Wetering et al 2002, Kleopa et al 2004, Li et al 2013].

***PMP22*-specific laboratory technical considerations.** The most common pathogenic variant, present in 80% of affected individuals, is the recurrent 1.5-Mb submicroscopic DNA deletion at 17p11.2 that includes *PMP22*. This is the reciprocal of the 1.5-Mb duplication that occurs in Charcot-Marie-Tooth neuropathy type 1A (see [CMT Overview](#)); both of these rearrangements result from unequal crossing over following misalignment of flanking repeat sequences at this chromosomal location.

**Table 4.** Notable *PMP22* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000304.4 NP_000295.1	c.281dupG	p.Arg95Glnfs128	Recurrent variant; possible genotype-phenotype correlation [Lenssen et al 1998]
	c.289delT	p.Tyr97ThrfsTer14	See footnote 1 [Yurrebaso et al 2014].
	c.353C>T	p.Thr118Met	Conflicting interpretations of pathogenicity [van Paassen et al 2014] <sup>2</sup>

Variants listed in the table have been provided by the author. *GeneReviews* staff have not independently verified the classification of variants.

*GeneReviews* follows the standard naming conventions of the Human Genome Variation Society ([varnomen.hgvs.org](http://varnomen.hgvs.org)). See [Quick Reference](#) for an explanation of nomenclature.

1. Associated with painful neuropathy without recurrent nerve palsies in one family [Yurrebaso et al 2014]

2. Reported as a benign polymorphism, as an autosomal recessive inherited variant, or as an autosomal dominant variant with the HNPP phenotype. Detailed in National Center for Biotechnology Information, ClinVar ([VCV000008431.12](https://www.ncbi.nlm.nih.gov/clinvar/variant/PMP22/353C>T)) (accessed 9-27-22).

## Chapter Notes

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## References

### Published Guidelines / Consensus Statements

Committee on Bioethics, Committee on Genetics, and American College of Medical Genetics and Genomics Social, Ethical, Legal Issues Committee. Ethical and policy issues in genetic testing and screening of children. Available [online](#). 2013. Accessed 11-1-23.

National Society of Genetic Counselors. Position statement on genetic testing of minors for adult-onset conditions. Available [online](#). 2018. Accessed 11-1-23.

### Literature Cited

- Abe A, Nakamura K, Kato M, Numakura C, Honma T, Seiwa C, Shirahata E, Itoh A, Kishikawa Y, Hayasaka K. Compound heterozygous PMP22 deletion mutations causing severe Charcot-Marie-Tooth disease type 1. *J Hum Genet*. 2010;55:771–3. PubMed PMID: 20739940.
- Al-Thihli K, Rudkin T, Carson N, Poulin C, Melançon S, Der Kaloustian VM. Compound heterozygous deletions of PMP22 causing severe Charcot-Marie-Tooth disease of the Dejerine-Sottas disease phenotype. *Am J Med Genet A*. 2008;146A:2412–6. PubMed PMID: 18698610.
- Barroso FA, Leiguarda R, Nogués MA. Hereditary neuropathy with liability to pressure palsies manifesting by recurrent neuropathic pain. *J Clin Neuromuscul Dis*. 2006;8:26–30.
- Bayrak AO, Bayrak IK, Battaloglu E, Ozes B, Yildiz O, Onar MK. Ultrasonographic findings in hereditary neuropathy with liability to pressure palsies. *Neurol Res*. 2015;37:106–11. PubMed PMID: 25005138.
- Beales D, Fary R, Little C, Nambiar S, Sveinall H, Leng Y, Tampin B, Mitchell T. Characterisation of pain in people with hereditary neuropathy with liability to pressure palsy. *J Neurol*. 2017;264:2464–71. PubMed PMID: 29079893.

- Bellone E, Balestra P, Ribizzi G, Schenone A, Zocchi G, Di Maria E, Ajmar F, Mandich P. An abnormal mRNA produced by a novel PMP22 splice site mutation associated with HNPP. *J Neurol Neurosurg Psychiatry*. 2006;77:538–40. PubMed PMID: 16199442.
- Chanson JB, Echaniz-Laguna A, Blanc F, Lacour A, Ballonzoli L, Kremer S, Namer IJ, Lannes B, Tranchant C, Vermersch P, de Seze J. Central nervous system abnormalities in patients with PMP22 gene mutations: a prospective study. *J Neurol Neurosurg Psychiatry*. 2013;84:392–7. PubMed PMID: 23243264.
- Chrestian N, McMillan H, Poulin C, Campbell C, Vajsar J. hereditary neuropathy with liability to pressure palsy in childhood: case series and literature update. *Neuromusc Disord*. 2015;25:693–8. PubMed PMID: 26189194.
- Cortese A, Piccolo G, Lozza A, Schreiber A, Callegari I, Moglia A, Alfonsi E, Pareyson D. Laryngeal and phrenic nerve involvement in a patient with hereditary neuropathy with liability to pressure palsies (HNPP). *Neuromuscul Disord*. 2016;26:455–8. PubMed PMID: 27241821.
- Corwin HM, Girardet RE. Hereditary neuropathy with liability to pressure palsies mimicking hypoglossal nerve injuries. *Neurology*. 2003;61:1457–8.
- Cruz-Martinez A, Arpa J, Palau F. Peroneal neuropathy after weight loss. *J Peripher Nerv Syst*. 2000;5:101–5. PubMed PMID: 10905469.
- Del Colle R, Fabrizi GM, Turazzini M, Cavallaro T, Silvestri M, Rizzuto N. Hereditary neuropathy with liability to pressure palsies: electrophysiological and genetic study of a family with carpal tunnel syndrome as only clinical manifestation. *Neurol Sci*. 2003;24:57–60. PubMed PMID: 12827539.
- Dubourg O, Mouton P, Brice A, Leguern E, Bouche P. Guidelines for diagnosis of hereditary neuropathy with liability to pressure palsies. *Neuromuscul Disord*. 2000;10:206–8. PubMed PMID: 10734269.
- Gouider R, LeGuern E, Gugenheim M, Tardieu S, Maisonobe T, Léger JM, Vallat JM, Agid Y, Bouche P, Brice A. Clinical, electrophysiologic, and molecular correlations in 13 families with hereditary neuropathy with liability to pressure palsies and a chromosome 17p11.2 deletion. *Neurology*. 1995;45:2018–23. PubMed PMID: 7501152.
- Guo J, Wang L, Zhang Y, Wu J, Arpag S, Hu B, Imhof BA, Tian X, Carter BD, Suter U, Li J. Abnormal junctions and permeability of myelin in PMP22-deficient nerves. *Ann Neurol*. 2014;75:255–65. PubMed PMID: 24339129.
- Horowitz SH, Spollen LE, Yu W. Hereditary neuropathy with liability to pressure palsy: fulminant development with axonal loss during military training. *J Neurol Neurosurg Psychiatry*. 2004;75:1629–31. PubMed PMID: 15489403.
- Infante J, Garcia A, Combarros O, Mateo JI, Berciano J, Sedano MJ, Gutierrez-Rivas EJ, Palau F. Diagnostic strategy for familial and sporadic cases of neuropathy associated with 17p11.2 deletion. *Muscle Nerve*. 2001;24:1149–55. PubMed PMID: 11494267.
- Kalfakis N, Panas M, Karadima G, Floroskufi P, Kokolakis N, Vassilopoulos D. Hereditary neuropathy with liability to pressure palsies emerging during vincristine treatment. *Neurology*. 2002;59:1470–1. PubMed PMID: 12427913.
- Karadima G, Koutsis G, Raftopoulou M, Karletidi KM, Zmbelis T, Karandreas N, Panas M. Mutational analysis of Greek patients with suspected hereditary neuropathy with liability to pressure palsies (HNPP): a 15-year experience. *J Peripher Nerv Syst*. 2015;20:79–85. PubMed PMID: 26110377.
- Kim K-E. Characteristic features of hereditary neuropathy with liability to pressure palsy (HNPP) presenting with brachial plexopathy in soldiers. *J Neurol Sci*. 2014;346:174–7. PubMed PMID: 25175852.
- Kleopa KA, Georgiou DM, Nicolaou P, Koutsou P, Papathanasiou E, Kyriakides T, Christodoulou K. A novel PMP22 mutation Ser22Phe in a family with hereditary neuropathy with liability to pressure palsies and CMT1A phenotypes. *Neurogenetics*. 2004;5:171–5. PubMed PMID: 15205993.



- Koehler PJ. Hereditary neuropathy with liability to pressure palsies: the first publication (1947). *Neurology*. 2003;60:1211–3. PubMed PMID: 12682341.
- Koehler PJ, Baas F. Hereditary neuropathy with liability to pressure palsies. Diagnosis in the first family (1947) confirmed. *J Peripher Nerv Syst*. 2012;17:412–3. PubMed PMID: 23279343.
- Koike H, Hirayama M, Yamamoto M, Ito H, Hattori N, Umehara F, Arimura K, Ikeda S, Ando Y, Nakazato M, Kaji R, Hayasaka K, Nakagawa M, Sakoda S, Matsumura K, Onodera O, Baba M, Yasuda H, Saito T, Kira J, Nakashima K, Oka N, Sobue G. Age associated axonal features in HNPP with 17p11.2 deletion in Japan. *J Neurol Neurosurg Psychiatry*. 2005;76:1109–14. PubMed PMID: 16024889.
- Kramer M, Ly A, Li J. Phenotype HNPP (hereditary neuropathy with liability to pressure palsies) induced by medical procedures. *Am J Orthop (Belle Mead NJ)*. 2016;45:E27–8. PubMed PMID: 26761923.
- Kumar N, Muley S, Pakiam A, Parry GJ. Phenotypic variability leads to under-recognition of HNPP. *J Clin Neuromuscul Dis*. 2002;3:106–12. PubMed PMID: 19078663.
- Lenzen PP, Gabreels-Festen AA, Valentijn LJ, Jongen PJ, van Beersum SE, van Engelen BG, van Wensen PJ, Bolhuis PA, Gabreels FJ, Mariman EC. Hereditary neuropathy with liability to pressure palsies. Phenotypic differences between patients with the common deletion and a PMP22 frame shift mutation. *Brain*. 1998;121:1451–8. PubMed PMID: 9712007.
- Li J, Ghandour K, Radovanovic D, Shy RR, Krajewski KM, Shy ME, Nicholson GA. Stoichiometric alteration of PMP22 protein determines the phenotype of hereditary neuropathy with liability to pressure palsies. *Arch Neurol*. 2007;64:974–8. PubMed PMID: 17620487.
- Li J, Krajewski K, Lewis RA, Shy ME. Loss-of-function phenotype of hereditary neuropathy with liability to pressure palsies. *Muscle Nerve*. 2004;29:205–10. PubMed PMID: 14755484.
- Li J, Parker B, Martyn C, Natarajan C, Guo J. The PMP22 gene and its related diseases. *Mol Neurobiol*. 2013;47:673–98. PubMed PMID: 23224996.
- Manganelli F, Pisciotta C, Dubbioso R, et al. Electrophysiological comparison between males and females in HNPP. *Neurol Sci*. 2013;34:1429–32. PubMed PMID: 23207550.
- Marriott M, Macdonell R, McCrory P. Flail arms in a parachutist: an unusual presentation of hereditary neuropathy with liability to pressure palsies. *Br J Sports Med*. 2002;36:465–6. PubMed PMID: 12453844.
- Moszyńska I, Kabzińska D, Sinkiewicz-Darol E, Kochański A. A newly identified Thr99fsX110 mutation in the PMP22 gene associated with an atypical phenotype of the hereditary neuropathy with liability to pressure palsies. *Acta Biochim Pol*. 2009;56:627–30. PubMed PMID: 19830275.
- Muglia M, Patitucci A, Rizzi R, Ungaro C, Conforti FL, Gabriele AL, Magariello A, Mazzei R, Motti L, Sabadini R, Sprovieri T, Marcello N, Quattrone A. A novel point mutation in PMP22 gene in an Italian family with hereditary neuropathy with liability to pressure palsies. *J Neurol Sci*. 2007;263:194–7. PubMed PMID: 17707409.
- Novakova L, Sussova J. Unusual form of hereditary neuropathy with liability to pressure palsies. *Clin Neurophysiol*. 2012;123:e41.
- Padua L, Coraci D, Lucchetta M, Paolasso I, Pazzaglia C, Granata G, Cacciavillani M, Luigetti M, Manganelli F, Pisciotta C, Piscoquito G, Pareyson D, Briani C. Different nerve ultrasound patterns in Charcot-Marie-Tooth and hereditary neuropathy with liability to pressure palsies. *Muscle Nerve*. 2018;57:E18–23. PubMed PMID: 28802056.
- Poloni TE, Merlo IM, Alfonsi E, Marinou-Aktipi K, Botti S, Arrigo A, Taroni F, Ceroni M. Facial nerve is liable to pressure palsy. *Neurology*. 1998;51:320–2. PubMed PMID: 9674839.
- Rahbari R, Wuster A, Lindsay SJ, Hardwick RJ, Alexandrov LB, Turki SA, Dominiczak A, Morris A, Porteous D, Smith B, Stratton MR, Hurles ME, et al. Timing, rates and spectra of human germline mutation. *Nat Genet*. 2016;48:126–33. PubMed PMID: 26656846.

- Rajabally YA, Adams D, Latour P, Attarian S. Hereditary and inflammatory neuropathies: a review of reported associations, mimics and misdiagnoses. *J Neurol Neurosurg Psychiatry*. 2016;87:1051–60. PubMed PMID: 27010614.
- Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015;17:405–24. PubMed PMID: 25741868.
- Robert-Varvat F, Jousserand G, Bouhour F, Vial C, Cintas P, Echaniz-Laguna A, Delmont E, Clavelou P, Chauplannaz G, Jomir L, Pereon Y, Leonard-Louis S, Manel V, Antoine JC, Lacour A, Camdessanche JP. Hereditary neuropathy with liability to pressure palsy in patients under 30 years old: neurophysiological data and proposed electrodiagnostic criteria. *Muscle Nerve*. 2018;57:217–21. PubMed PMID: 28407266.
- Sander MD, Abbasi D, Ferguson AL, Steyers CM, Wang K, Morcuende JA. The prevalence of hereditary neuropathy with liability to pressure palsies in patients with multiple surgically treated entrapment neuropathies. *J Hand Surg Am*. 2005;30:1236–41. PubMed PMID: 16344182.
- Shah A, Rison RA, Beydoun SR. Chronic inflammatory demyelinating polyneuropathy manifesting as neuropathy with liability to pressure palsies: a case report. *J Clin Neuromuscul Dis*. 2015;17:78–83. PubMed PMID: 26583495.
- Stockton DW, Meade RA, Netscher DT, Epstein MJ, Shenaq SM, Shaffer LG, Lupski JR. Hereditary neuropathy with liability to pressure palsies is not a major cause of idiopathic carpal tunnel syndrome. *Arch Neurol*. 2001;58:1635–7. PubMed PMID: 11594922.
- Stögbauer F, Young P, Kuhlenbäumer G, De Jonghe P, Timmerman V. Hereditary recurrent focal neuropathies: clinical and molecular features. *Neurology*. 2000;54:546–51. PubMed PMID: 10680781.
- Taioli F, Cabrini I, Cavallaro T, Acler M, Fabrizi GM. Inherited demyelinating neuropathies with micromutations of peripheral myelin protein 22 gene. *Brain*. 2011;134:608–17. PubMed PMID: 21252112.
- Tohge R, Shinoto Y, Takahashi M. Case of hereditary neuropathy with liability to pressure palsies presenting progressive muscular atrophy with lower motor neuron degeneration in the spinal cord and the brainstem. *Neurol Clin Neurosci*. 2016;4:19–21.
- Topakian R, Wimmer S, Pischinger B, Pichler R. Hereditary neuropathy with liability to pressure palsies presenting with sciatic neuropathy. *BMJ Case Rep*. 2014;2014:bcr2014206883.
- van de Wetering RA, Gabreels-Festen AA, Timmerman V, Padberg GM, Gabreels FJ, Mariman EC. Hereditary neuropathy with liability to pressure palsies with a small deletion interrupting the PMP22 gene. *Neuromuscul Disord*. 2002;12:651–5. PubMed PMID: 12207933.
- van Paassen BW, van der Kooij AJ, van Spaendonck-Zwarts KY, Verhamme C, Baas F, de Visser M. PMP22 related neuropathies: Charcot-Marie-Tooth disease type 1A and hereditary neuropathy with liability to pressure palsies. *Orphanet J Rare Dis*. 2014;9:38. PubMed PMID: 24646194.
- Vrinten C, Gu X, Weinreich SS, Schipper MH, Wessels J, Ferrari M, Hoijsink H, Verschuuren J. An n-of-one RCT for intravenous immunoglobulin G for inflammation in hereditary neuropathy with liability to pressure palsy (HNPP). *J Neurol Neurosurg Psychiatry*. 2016;87:790–1. PubMed PMID: 26187721.
- Winter WC, Juel VC. Hypoglossal neuropathy in hereditary neuropathy with liability to pressure palsy. *Neurology*. 2003;61:1154–5. PubMed PMID: 14581692.
- Yurrebaso I, Casado OL, Barcena J, Perez de Nanclares G, Aguirre U. Clinical, electrophysiological and magnetic resonance findings in a family with hereditary neuropathy with liability to pressure palsies caused by a novel PMP22 mutation. *Neuromuscul Disord*. 2014;24:56–62. PubMed PMID: 24239057.

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