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Pagon RA, Bird TD, Dolan CR, et al., editors. GeneReviews™ [Internet]. Seattle (WA): University of Washington, Seattle; 1993-.

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Hereditary Neuropathy with Liability to Pressure Palsies

Synonyms: HNPP, Hereditary Pressure Sensitive Neuropathy, Tomaculous Neuropathy

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Summary

Disease characteristics. Hereditary neuropathy with liability to pressure palsies (HNPP) is characterized by repeated focal pressure neuropathies such as carpal tunnel syndrome and peroneal palsy with foot drop. The first attack usually occurs in the second or third decade. Recovery from acute neuropathy is often complete; when recovery is not complete, the resulting disability is usually mild. Some affected individuals also have signs of a mild to moderate peripheral neuropathy.

Diagnosis/testing. The diagnosis of HNPP is established in an adult with recurrent focal compression neuropathies who has a family history consistent with autosomal dominant inheritance. *PMP22* is the only gene known to be associated with HNPP. A contiguous gene deletion of chromosome 17p11.2 that includes *PMP22* is present in approximately 80% of affected individuals; the remaining 20% have a mutation in *PMP22*. Testing is available in clinical laboratories.

Management. *Treatment of manifestations*: A wrist splint may alleviate carpal tunnel syndrome; ankle-foot orthoses (AFOs) may alleviate foot drop.

Prevention of primary manifestations: Protective pads at elbows or knees may prevent pressure and trauma to local nerves.

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

Other: Surgical decompression of nerves is not beneficial and may cause harm.

Genetic counseling. HNPP is inherited in an autosomal dominant manner. Each child of an affected individual is at a 50% risk of inheriting the mutation. Prenatal testing for pregnancies at increased risk is possible if the disease-causing mutation has been identified in the family; however, requests for prenatal testing for typically adult-onset conditions such as HNPP are not common.

Diagnosis

Clinical Diagnosis

The diagnosis of hereditary neuropathy with liability to pressure palsies (HNPP) is established in an adult with (1) recurrent focal compression neuropathies and (2) family history consistent with autosomal dominant inheritance.

Findings that support the diagnosis include the following:

- Mild polyneuropathy, with or without symptoms
- Evidence on physical examination of previous nerve palsy such as focal weakness, atrophy, or sensory loss
- Absent ankle reflexes (50%-80%)
- Diffusely reduced tendon reflexes (15%-30%)
- Mild to moderate pes cavus foot deformity (20%)

Electrophysiologic studies are usually abnormal:

- Prolongation of distal nerve conduction latencies (e.g., of the median nerve at the wrist) occurs in essentially all individuals whether symptomatic or asymptomatic.
- According to Mouton et al [1999], the key electrophysiologic diagnostic features are bilateral slowing of

sensory and motor nerve conduction at the carpal tunnel with at least one additional abnormal finding for motor conduction in one peroneal nerve. Infante et al [2001] emphasize the need to evaluate sensory conduction in the sural nerve and motor conduction in at least two nerves across usual entrapment sites, especially the ulnar nerve at the elbow. Li et al [2002] found evidence for prolonged distal motor latencies in the median and peroneal nerves but not ulnar or tibial nerves.

- Nerve conduction velocity (NCV) may be delayed at the site of compression.
- General motor NCVs are usually normal (>40 m/s); a few individuals have electrical evidence of a mild diffuse polyneuropathy.

Sural nerve biopsy often shows evidence of demyelination and "tomaculous" (focal, sausage-like enlargement of the nerve) change. Tomaculous change is not specific and has been noted occasionally in other neuropathies.

Molecular Genetic Testing

Gene. *PMP22* is the only gene in which mutation is known to cause HNPP.

Clinical testing

- **Deletion/duplication analysis.** A 1.5-Mb deletion at 17p11.2 (including *PMP22*) is detected in approximately 80% of individuals with HNPP. Methods to detect this specific deletion and novel deletions including *PMP22* are variable (Table 1, footnote 2). Selected published studies include:
  - Long polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) [Lorentzos et al 2003, Thiel et al 2003]
  - Southern blot analysis (pulse field gel electrophoresis) to detect large-scale *PMP22* deletions
  - Multiplex ligation-dependent probe amplification (MLPA)

    Note: In one study MPLA was used to detect smaller deletions [Sutton et al 2004].
  - Fluorescence in situ hybridization (FISH) [Mohammed & Shaffer 2003]
- **Sequence analysis.** Sequence analysis of *PMP22* detects point mutations and small deletions in approximately 20% of individuals with HNPP.

Table 1. Summary of Molecular Genetic Testing Used in HNPP

Gene Symbol	Test Method	Mutations Detected	Mutation Detection Frequency by Test Method [1]	Test Availability
PMP22	Deletion / duplication analysis [2]	1.5-Mb deletion including *PMP22*	~80%	Clinical Testing
	Sequence analysis [3]	Point mutations and small deletions	~20%	

Test Availability refers to availability in the GeneTests™ Laboratory Directory. *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.

1. The ability of the test method used to detect a mutation that is present in the indicated gene.

2. Testing that identifies deletions/duplications not readily detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA; included in the variety of methods that may be used are: quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment. See CMA.

3. Small intragenic deletions/insertions, missense, nonsense, and splice site mutations.

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

Testing Strategy

To confirm/establish the diagnosis in a proband requires detection of a *PMP22* mutation using molecular genetic testing. If the *PMP22* deletion test is normal in a person with the typical HNPP phenotype, the next step is *PMP22* sequence analysis.

Predictive testing for at-risk asymptomatic adult family members requires prior identification of the disease-causing mutations in the family.

Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the disease-causing mutation in the family.

Note: It is the policy of *GeneReviews* to include in *GeneReviews*™ chapters any clinical uses of testing available from laboratories listed in the GeneTests™ Laboratory Directory; inclusion does not necessarily reflect the endorsement of such uses by the author(s), editor(s), or reviewer(s).

Genetically Related (Allelic) Disorders

The other phenotypes associated with alterations of *PMP22* are Charcot-Marie-Tooth neuropathy type 1A (CMT1A) and Charcot-Marie-Tooth neuropathy type 1E (CMT1E) (see CMT Overview).

Clinical Description

Natural History

Hereditary neuropathy with liability to pressure palsies (HNPP) is characterized by recurrent sensory and motor neuropathy in a single nerve beginning in adolescence or young adulthood. The most common presenting symptom of HNPP is the acute onset of a non-painful focal sensory and motor neuropathy in a single nerve (mononeuropathy) [Pareyson et al 1996, Kumar et al 2002, Li et al 2004]. Some individuals experience transient sensory phenomena without weakness. History of actual physical compression of the nerve may or may not be present.

Occasional episodes have been reported during pregnancy, perhaps related to physiologic changes such as soft tissue swelling and edema. The nerve palsies often recur over a period of many years, but some individuals have a single episode and some individuals who have a disease-causing mutation are asymptomatic.

The first attack is usually in the second or third decade (mean age: 37 years), although the age range extends from two to 70 years. Radial nerve palsy has been reported in a two-year-old with HNPP [Hardon et al 2002] and peroneal nerve palsies have been reported shortly after birth [Goikhman et al 2003].

Males and females are equally affected.

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

- The peroneal nerve at the fibular head causing foot drop
- The ulnar nerve at the elbow, causing hypothenar and interossei muscle weakness and atrophy with sensory loss over the lateral aspect of the hand
- The 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]
- The brachial plexus and radial nerve, causing transient sensory symptoms and hand pain [Marriott et al 2002].

Full recovery over a period of days to months occurs in approximately 50% of episodes. Incomplete recovery is fairly common, but the remaining symptoms are rarely severe. Poor recovery correlates with a history of prolonged focal compression of the nerve [Koike et al 2005].

Symptomatic individuals have the frustration and disability associated with recurrent pressure palsies, although the degree of handicap in performing activities of daily living is usually not severe.

In addition to the typical presentation of HNPP, Mouton et al [1999] described five other phenotypes:

- Recurrent positional short-term sensory symptoms
- Progressive mononeuropathy
- CMT-like polyneuropathy
- Chronic sensory polyneuropathy
- Chronic inflammatory demyelinating polyneuropathy-like disorder [Korn-Lubetzki et al 2002]

Note: Some individuals may be asymptomatic.

Other findings reported in a few individuals:

- Motor brachial paralysis [Kumar et al 2002, Makela et al 2006]
- Proximal muscle atrophy and severe respiratory insufficiency [Asahina et al 2000]
- CNS white matter lesions that are usually asymptomatic [Dackovic et al 2001, Sanahuja et al 2005, Tackenberg et al 2006]
- Hypoglossal nerve paralysis of the tongue, including after carotid endarterectomy [Corwin & Girardet 2003, Winter & Juel 2003]
- Rapid onset and progression of neuropathy early in military physical training [Horowitz et al 2004]

- Scapuloperoneal syndrome [Verma 2005]

Genotype-Phenotype Correlations

Persons with the *PMP22* frameshift mutation (p.Arg95GlyfsX128) have a typical HNPP phenotype but are also more likely to have an associated clinically evident motor/sensory neuropathy mimicking Charcot-Marie-Tooth Neuropathy Type 1 (CMT1) [Lenssen et al 1998]. Other point mutations in *PMP22* with a similar phenotype have been described [Bellone et al 2006, Li et al 2007, Muglia et al 2007, Moszyńska et al 2009].

Shy et al [2006] described an HNPP phenotype associated with the p.Thr118Met mutation in *PMP22*.

Al-Thihli et al [2008] reported a severely affected child with a two abnormal *PMP22* alleles: a *PMP22* deletion inherited from the mother and deletion of exons 2 and 3 of *PMP22* inherited from the father.

Penetrance

Many individuals with the *PMP22* 1.5-Mb deletion have few (or no) symptoms and go undiagnosed. The penetrance is not known.

Anticipation

Anticipation has not been described.

Nomenclature

Hereditary neuropathy with liability to pressure palsies was previously referred to as tomaculous neuropathy, recurrent pressure-sensitive neuropathy, and tulip-bulb digger's palsy or potato-grubbing palsy [Koehler 2003].

Prevalence

The prevalence of HNPP is unknown; it is estimated at two to five cases per 100,000 population. The actual prevalence may be higher because of under-diagnosis.

Meretoja et al [1997] found the prevalence in Finland to be 16:100,000.

Differential Diagnosis

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

Pressure palsies are most commonly the result of environmentally acquired physical compression of peripheral nerves. The most common are the 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. 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).

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

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

The proportion of individuals with a single episode of compression neuropathy who have a 17p11 deletion or *PMP22* point mutation is not known. However, because some individuals with HNPP may have no family history of neuropathy, a single episode of nerve compression, or a *de novo* mutation, some authors have advocated molecular genetic testing of individuals with a negative family history who have compression neuropathy. A more selective approach is to test only those individuals with either:

- More than one episode of compression neuropathy,
- One episode of compression neuropathy and an unexplained polyneuropathy, or
- One episode of compression neuropathy and a family history of neuropathy.

HNPP sometimes involves the brachial plexus, thus overlapping with hereditary neuralgic amyotrophy, a distinct disorder that maps to 17q. Stogbauer et al [2000] contrast the clinical features of HNPP and hereditary neuralgic amyotrophy.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with hereditary neuropathy with liability to pressure palsies (HNPP), the following evaluations are recommended:

- History of focal nerve symptoms
- Family history
- Neurologic examination
- Electromyography / nerve conduction velocity (EMG/NCV)

Treatment of Manifestations

Transient bracing, such as with a wrist splint or ankle-foot orthosis (AFO), may be useful. Some individuals with residual foot drop may permanently use an AFO.

Prevention of Primary Manifestations

Protective pads at elbows or knees may prevent pressure and trauma to local nerves.

Prevention of Secondary Complications

Bracing of weak muscles, such as ankle-foot-orthosis for foot drop, may prevent injury.

Agents/Circumstances to Avoid

Risk factors for pressure palsies (and thus activities to avoid) include prolonged sitting with legs crossed, occupations requiring repetitive movements of the wrist, prolonged leaning on elbows, and rapid weight loss [Cruz-Martinez et al 2000, Marriott et al 2002].

Vincristine, commonly used in the chemotherapy of lymphoma, has been reported to exacerbate HNPP [Kalfakis et al 2002].

Evaluation of Relatives at Risk

Relatives at risk may wish to clarify their genetic status by undergoing molecular genetic testing; if found to have the *PMP22* mutation identified in an affected family member, they can choose to avoid the aforementioned agents and circumstances.

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

Controversy exists as to whether surgical decompression of nerves is of benefit. Because spontaneous recovery is common and because no systematic controlled study of surgical intervention has been done, this decision must be made on an individual basis, taking into consideration knowledge of the natural history of the disease. There is a developing consensus that surgical repair of carpal tunnel syndrome is of little benefit to individuals with HNPP and that transposition of the ulnar nerve at the elbow may actually produce poor results [Lazar et al 2007].

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.

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.

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

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

Risk to Family Members

Parents of a proband

- Approximately 80% of individuals with HNPP have inherited the disease-causing mutation from an affected parent.
- Approximately 20% of affected individuals have a *de novo* mutation [Infante et al 2001].
- It is appropriate to evaluate the parents of an individual with HNPP to determine if either parent has clinical findings of HNPP.

Note: Although 80% of individuals diagnosed with HNPP have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members [Beydoun et al 2008].

Sibs of a proband

- The risk depends on the genetic status of the proband's parents.
- If a parent 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 the disease-causing mutation found in the proband cannot be detected in the DNA of either parent, the risk to sibs is low but greater than that of the general population because of the possibility of germline mosaicism.
- Although no instances of germline mosaicism have been reported, it remains a possibility.

Offspring of a proband. Each child of an individual with HNPP has a 50% chance of inheriting the mutation.

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

Testing of at-risk asymptomatic adults. Testing of at-risk asymptomatic adults for HNPP is available using the techniques described in Molecular Genetic Testing. Such testing is not useful in predicting age of onset, severity, type of symptoms, or rate of progression in asymptomatic individuals. When testing at-risk individuals for HNPP, an affected family member should be tested first to confirm the diagnosis in the family and identify the mutation.

Testing for the disease-causing mutation in the absence of definite symptoms of the disease is predictive testing. At-risk asymptomatic adult family members may seek testing in order to make personal decisions regarding reproduction, financial matters, and career planning. Others may have different motivations including simply the "need to know." Testing of asymptomatic at-risk adult family members usually involves pre-test interviews in which the motives for requesting the test, the individual's knowledge of HNPP, the possible impact of positive and negative test results, and neurologic status are assessed. Those seeking testing should be counseled about possible problems that they may encounter with regard to health, life, and disability insurance coverage, employment and educational discrimination, and changes in social and family interaction. Other issues to consider are implications for the at-risk status of other family members. Informed consent should be procured and records kept confidential. Individuals with a positive test result need arrangements for long-term follow-up and evaluations.

Testing of asymptomatic at-risk individuals during childhood. Consensus holds that individuals younger than age 18 years who are at risk for adult-onset disorders should not have testing in the absence of symptoms. The principal arguments against such testing are that it removes the individual's choice to know or not know this information, it raises the possibility of stigmatization within the family and in other social settings, and it could have serious educational and career implications.

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 (i.e., 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. 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.

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. See Testing for a list of laboratories offering DNA banking.

Prenatal 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 to 18 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.

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

Requests for prenatal testing for typically adult-onset conditions such as HNPP are not common. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

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

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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, Inc.**

  1751 2nd Avenue

  Suite 103

  New York NY 10128

  Phone: 877-463-1287 (toll-free); 212-722-8396

  Email: info@hnf-cure.org

  www.hnf-cure.org
- **National Library of Medicine Genetics Home Reference**

  Hereditary neuropathy with liability to pressure palsies
- **Charcot-Marie-Tooth Association (CMTA)**

  2700 Chestnut Street

  Chester PA 19013-4867

  Phone: 800-606-2682 (toll-free); 610-499-9264

  Fax: 610-499-9267

  Email: info@charcot-marie-tooth.org

  www.charcot-marie-tooth.org
- **European Charcot-Marie-Tooth Consortium**

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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 Symbol	Chromosomal Locus	Protein Name	Locus Specific	HGMD
PMP22	17p12	Peripheral myelin protein 22	IPN Mutations, PMP22 PMP22 homepage - Leiden Muscular Dystrophy pages	PMP22

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) to which links are provided, click here.

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

162500	NEUROPATHY, HEREDITARY, WITH LIABILITY TO PRESSURE PALSIES; HNPP
601097	PERIPHERAL MYELIN PROTEIN 22; PMP22

Normal allelic variants. *PMP22* spans approximately 5 kb and has four exons.

Pathologic allelic variants. The molecular defect present in 80% of affected individuals is a 1.5-Mb 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 CMT1). These rearrangements are the result of unequal crossing over following misalignment of flanking repeat sequences at this chromosomal location. HNPP is likely to be the result of a gene dosage effect.

Approximately 20% of families with HNPP have a variety of *PMP22* point mutations that produce frameshifts, premature termination of translation, or other abnormalities [Young et al 1997, Lenssen et al 1998, Stogbauer et al 2000, van de Wetering et al 2002, Kleopa et al 2004]. The clinical and molecular aspects of other point mutations associated with the HNPP phenotype are reviewed by Stogbauer et al [2000] and van de Wetering et al [2002]. These include mutations resulting in frameshifts, premature termination translation, 5' splice-site mutation, and a mutation affecting the junction of the extracellular loop and the first transmembrane domain of *PMP22*. Additionally, Meuleman et al [2001] have reported a 3' splice-site mutation, preceding coding exon 3, resulting in a mild HNPP phenotype. The p.Arg95GlyfsX128 mutation not only results in a frameshift at residue 95 but also creates a new translation termination site, thereby adding 61 more amino acids to the length of the protein. See Table 2.

Table 2. Selected *PMP22* Pathologic Allelic Variants

DNA Nucleotide Change	Protein Amino Acid Change (Alias [1])	Reference Sequences
c.281_282insG	p.Arg95GlyfsX128 [2] (Gly94fs)	NM_000304.2 NP_000295.1
c.353C>T	p.Thr118Met [2]	

See Quick Reference for an explanation of nomenclature. GeneReviews follows the standard naming conventions of the Human Genome Variation Society (www.hgvs.org).

1. Variant designation that does not conform to current naming conventions

2. See Genotype-Phenotype Correlations.

Normal gene product. Peripheral myelin protein 22 is a 160-amino acid protein that is present in compact myelin and has four transmembrane domains.

Abnormal gene product. HNPP is associated with decreased mRNA message for *PMP22* and decreased peripheral myelin protein 22 in peripheral nerve [Gabriel et al 1997, Schenone et al 1997a, Schenone et al 1997b].

References

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

Published Guidelines/Policy Statements

1. American Society of Human Genetics and American College of Medical Genetics. Points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents. Available online. 1995. Accessed 10-8-12.
2. National Society of Genetic Counselors. Resolution on prenatal and childhood testing for adult-onset disorders. Available online. 1995. Accessed 10-8-12.

Literature Cited

1. 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: 18698610]
2. Asahina M, Kuwabara S, Hattori T, Asahina M, Katayama K. Respiratory insufficiency in a patient with hereditary neuropathy with liability to pressure palsy. J Neurol Neurosurg Psychiatry. 2000;68:110–1. [PMC free article: PMC1760634] [PubMed: 10671122]
3. 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. [PMC free article: PMC2077485] [PubMed: 16199442]
4. Beydoun SR, Sykes SN, Ganguly G, Lee TS. Hereditary neuropathy with liability to pressure palsies: description of seven patients without known family history. Acta Neurol Scand. 2008;117:266–72. [PubMed: 17922888]
5. Corwin HM, Girardet RE. Hereditary neuropathy with liability to pressure palsies mimicking hypoglossal nerve injuries. Neurology. 2003;61:1457–8. [PubMed: 14638986]
6. Cruz-Martinez A, Arpa J, Palau F. Peroneal neuropathy after weight loss. J Peripher Nerv Syst. 2000;5:101–5. [PubMed: 10905469]
7. Dackovic J, Rakocevic-Stojanovic V, Pavlovic S, Zamurovic N, Dragasevic N, Romac S, Apostolski S. Hereditary neuropathy with liability to pressure palsies associated with central nervous system myelin lesions. Eur J Neurol. 2001;8:689–92. [PubMed: 11784354]
8. 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: 12827539]
9. Gabriel JM, Erne B, Pareyson D, Sghirlanzoni A, Taroni F, Steck AJ. Gene dosage effects in hereditary peripheral neuropathy. Expression of peripheral myelin protein 22 in Charcot-Marie-Tooth disease type 1A and hereditary neuropathy with liability to pressure palsies nerve biopsies. Neurology. 1997;49:1635–40. [PubMed: 9409359]
10. Goikhman I, Meer J, Zelnik N. Hereditary neuropathy with liability to pressure palsies in infancy. Pediatr Neurol. 2003;28:307–9. [PubMed: 12849887]
11. Hardon WJ, van Alfen N, Zwarts MJ, Rotteveel JJ. Hereditary neuropathy with liability to pressure palsies in a toddler. Neurology. 2002;59:2008. [PubMed: 12499508]
12. 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. [PMC free article: PMC1738805] [PubMed: 15489403]
13. 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: 11494267]
14. 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: 12427913]
15. 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: 15205993]
16. Koehler PJ. Hereditary neuropathy with liability to pressure palsies: the first publication (1947). Neurology. 2003;60:1211–3. [PubMed: 12682341]
17. 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. [PMC free article: PMC1739771] [PubMed: 16024889]
18. Korn-Lubetzki I, Argov Z, Raas-Rothschild A, Wirguin I, Steiner I. Family with inflammatory demyelinating polyneuropathy and the HNPP 17p12 deletion. Am J Med Genet. 2002;113:275–8. [PubMed: 12439896]
19. 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: 19078663]
20. Lazar CC, Auquit-Auckbur I, Milliez PY. Hereditary neuropathy with liability to pressure palsies (HNPP) in hand surgery: reminds and warn against a usually unrecognised disease. Ann Chir Plast Esthet. 2007;52:606–8. [PubMed: 17030391]

21. Lenssen 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: 9712007]
22. 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: 17620487]
23. 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: 14755484]
24. Li J, Krajewski K, Shy ME, Lewis RA. Hereditary neuropathy with liability to pressure palsy: the electrophysiology fits the name. Neurology. 2002;58:1769–73. [PubMed: 12084875]
25. Lorentzos P, Kaiser T, Kennerson ML, Nicholson GA. A rapid and definitive test for Charcot-Marie-Tooth 1A and hereditary neuropathy with liability to pressure palsies using multiplexed real-time PCR. Genet Test. 2003;7:135–8. [PubMed: 12885335]
26. Makela JP, Ramstad R, Mattila V, Pihlajamaki H. Brachial plexus lesions after backpack carriage in young adults. Clin Orthop Relat Res. 2006;452:205–9. [PubMed: 16906084]
27. 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. [PMC free article: PMC1724562] [PubMed: 12453844]
28. Meretoja P, Silander K, Kalimo H, Aula P, Meretoja A, Savontaus ML. Epidemiology of hereditary neuropathy with liability to pressure palsies (HNPP) in south western Finland. Neuromuscul Disord. 1997;7:529–32. [PubMed: 9447611]
29. Meuleman J, Pou-Serradell A, Lofgren A, Ceuterick C, Martin JJ, Timmerman V, Van Broeckhoven C, De Jonghe P. A novel 3'-splice site mutation in peripheral myelin protein 22 causing hereditary neuropathy with liability to pressure palsies. Neuromuscul Disord. 2001;11:400–3. [PubMed: 11369192]
30. Mohammed MS, Shaffer LG. Fluorescence in situ hybridization (FISH) for identifying the genomic rearrangements associated with three myelinopathies. Charcot-Marie-Tooth disease, hereditary neuropathy with liability to pressure palsies, and Pelizaeus-Merzbacher disease. Methods Mol Biol. 2003;217:219–38. [PubMed: 12491936]
31. 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: 19830275]
32. Mouton P, Tardieu S, Gouider R, Birouk N, Maisonobe T, Dubourg O, Brice A, LeGuern E, Bouche P. Spectrum of clinical and electrophysiologic features in HNPP patients with the 17p11.2 deletion. Neurology. 1999;52:1440–6. [PubMed: 10227632]
33. 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: 17707409]
34. Pareyson D, Scaioli V, Taroni F, Botti S, Lorenzetti D, Solari A, Ciano C, Sghirlanzoni A. Phenotypic heterogeneity in hereditary neuropathy with liability to pressure palsies associated with chromosome 17p11.2-12 deletion. Neurology. 1996;46:1133–7. [PubMed: 8780105]
35. Sanahuja J, Franco E, Rojas-Garcia R, Gallardo E, Combarros O, Begue R, Granes P, Illa I. Central nervous system involvement in hereditary neuropathy with liability to pressure palsies: description of a large family with this association. Arch Neurol. 2005;62:1911–4. [PubMed: 16344349]
36. 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: 16344182]
37. Schenone A, Nobbio L, Caponnetto C, Abbruzzese M, Mandich P, Bellone E, Ajmar F, Gherardi G, Windebank AJ, Mancardi G. Correlation between PMP-22 messenger RNA expression and phenotype in hereditary neuropathy with liability to pressure palsies. Ann Neurol. 1997a;42:866–72. [PubMed: 9403478]
38. Schenone A, Nobbio L, Mandich P, Bellone E, Abbruzzese M, Aymar F, Mancardi GL, Windebank AJ. Underexpression of messenger RNA for peripheral myelin protein 22 in hereditary neuropathy with liability to pressure palsies. Neurology. 1997b;48:445–9. [PubMed: 9040736]
39. Shy ME, Scavina MT, Clark A, Krajewski KM, Li J, Kamholz J, Kolodny E, Szigeti K, Fischer RA, Saifi GM, Scherer SS, Lupski JR. T118M PMP22 mutation causes partial loss of function and HNPP-like neuropathy. Ann Neurol. 2006;59:358–64. [PubMed: 16437560]
40. 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: 11594922]
41. Stogbauer F, Young P, Kuhlenbaumer G, De Jonghe P, Timmerman V. Hereditary recurrent focal neuropathies: clinical and molecular features. Neurology. 2000;54:546–51. [PubMed: 10680781]
42. Sutton IJ, Mocroft AP, Lindley VH, Barber RM, Bryon RJ, Winer JB, MacDonald F. Application of multiplex ligation-dependent probe analysis to define a small deletion encompassing PMP22 exons 4 and 5 in

hereditary neuropathy with liability to pressure palsies. Neuromuscul Disord. 2004;14:804–9. [PubMed: 15564036]

43. Tackenberg B, Moller JC, Rindock H, Bien S, Sommer N, Oertel WH, Rosenow F, Schepelmann K, Hamer HM, Bandmann O. CNS involvement in hereditary neuropathy with pressure palsies (HNPP). Neurology. 2006;67:2250–2. [PubMed: 17190957]
44. Thiel CT, Kraus C, Rauch A, Ekici AB, Rautenstrauss B, Reis A. A new quantitative PCR multiplex assay for rapid analysis of chromosome 17p11.2-12 duplications and deletions leading to HMSN/HNPP. Eur J Hum Genet. 2003;11:170–8. [PubMed: 12634865]
45. 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: 12207933]
46. Verma A. Neuropathic scapuloperoneal syndrome (Davidenkow's syndrome) with chromosome 17p11.2 deletion. Muscle Nerve. 2005;32:668–71. [PubMed: 16007675]
47. Winter WC, Juel VC. Hypoglossal neuropathy in hereditary neuropathy with liability to pressure palsy. Neurology. 2003;61:1154–5. [PubMed: 14581692]
48. Young P, Wiebusch H, Stogbauer F, Ringelstein B, Assmann G, Funke H. A novel frameshift mutation in PMP22 accounts for hereditary neuropathy with liability to pressure palsies. Neurology. 1997;48:450–2. [PubMed: 9040737]

Suggested Reading

1. Chance PF. Inherited focal, episodic neuropathies: hereditary neuropathy with liability to pressure palsies and hereditary neuralgic amyotrophy. Neuromolecular Med. 2006;8:159–74. [PubMed: 16775374]
2. Lupski JR, Garcia CA. Charcot-Marie-Tooth peripheral neuropathies and related disorders. In: Scriver CR, Beaudet AL, Sly WS, Valle D, Vogelstein B, eds. *The Metabolic and Molecular Bases of Inherited Disease (OMMBID).* New York, NY: McGraw-Hill. Chap 227. Available online. Accessed 10-08-12.

Chapter Notes

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