CLASSIFICATION OF THE INHERITED PERIPHERAL NEUROPATHIES[a]

	PATHOLOGY	ONSET	GENE	CLINICAL AND THERAPEUTIC FEATURES
I. Charcot-Marie-Tooth (CMT) and Related Disorders				
1. CMT1 (demyelinating, dominantly inherited)				
*CMT1A**	demyelinating	c	PMP22 duplication	Early areflexia, distal weakness, sensory loss
*CMT1B**	demyelinating	c, a	Myelin protein P0 (MPZ)	Early areflexia, distal weakness, sensory loss
CMT1C	demyelinating	a	Lipopolysaccharide-induced TNF-α (LITAF)	
CMT1D, CMT4E	demyelinating	c, a	Transcription factor EGR2	May be severe and congenital
CMT1F, CMT2E	demyelinating, axonal	c, a	Neurofilament light subunit (NEFL) or PMP22 point mutation	
Congenital hypomyelination	demyelinating	c	Rho guanine exchange factor	Mild or asymptomatic
2. CMT2 (axonal, dominantly inherited)				
*CMT2A**	axonal	c, a	Kinesin KIF1Bβ motor protein	
CMT2A2 (alt)	axonal	c, a	Mitofusin (MFN2)	
CMT2B	axonal	a	GTP-binding protein RAB7	
CMT2C	axonal	c, a	TRPV4	Vocal cord, diaphragm paralysis
CMT2D	axonal	a	Glycyl t-RNA synthetase (GARS)	
CMT2F	axonal	c, a	Heat shock protein (BSPB1)	Slow, motor predominant
3. AR-CMT2—(recessively inherited axonopathy)				
AR-CMT2A	axonal		Nuclear membrane lamin (LMNA)	
4. CMT3 (Dejerine-Sottas disease)	demyelinating	inf	PMP22 most common; also P0, EGR2 (see above)	
5. CMT4 (recessively inherited myelin-axonopathy)				
CMT4A	demyelinating	c	Ganglioside-induced differentiation protein (GDAP1)	May be rapidly progressive
CMT4B	demyelinating	c	Myotubularin-related protein (MTMR2)	Focally folded myelin
CMT4B2	demyelinating	c, a	SET-binding factor (MTMR13))	
CMT4C	demyelinating	c	SHT3TC2	Early scoliosis
CMT4D	demyelinating	c	Schwann cell protein Nm-ycDRG1 (NDRG1)	Neuropathy + hearing loss
CMT4F	demyelinating	c	Nuclear membrane protein (periaxin; PRX)	Early onset, severe
6. *CMT1 X (X-linked demyelinating)**	demyelinating	c, a	GJB1	Similar to CMT1A
7. Recurrent brachial plexopathy (AD)	axonal	c, a	Unknown	Focal, painful brachial plexitis
8. *HNPP**	axonal	c	*PMP22* gene deletion	Focal entrapments, chronic neuropathy
II. Hereditary Sensory and Autonomic Neuropathy (HSAN)				
1. HSAN1 (AD)	axonal	a	Serine palmitoyl transferase	Small-fiber sensory and distal motor deficits
2. HSAN2 (AR)	axonal	inf	Novel neuronal protein	
3. HSAN3 (Riley-Day, AR)	axonal	inf	Kinase-associated protein (IKBKAP)	
4. HSAN4 (AR)	axonal	inf	TrkA/NGF receptor	Congenital SN with anhidrosis
5. HSAN5 (AR)	axonal	inf	Nerve growth factor-beta	Absent pain

CLASSIFICATION OF THE INHERITED PERIPHERAL NEUROPATHIES[a] (*CONTINUED*)

	PATHOLOGY	ONSET	GENE	CLINICAL AND THERAPEUTIC FEATURES
III. Familial Amyloid Polyneuropathies (AD)				
1. Type 1—Portuguese	axonal	a	Transthyretin	Liver transplant may be beneficial
2. Type 2—Indiana/Swiss	axonal	a	Transthyretin	Liver transplant may be beneficial
3. Type 3—Van Allen	axonal	a	Apolipoprotein A1	
4. Type 4—Finnish	axonal	a	Gelsolin	Lax skin and "blood-hound" face; corticospinal, posterior column deficits
IV. Hereditary Disorders of Lipid Metabolism Causing Neuropathy (AR)				
1. Metachromatic leukodystrophy	demyelinating	inf-a	Arylsulfatase A and B	
2. Krabbe disease	demyelinating, axonal	inf-a	β-galactosidase	Early bone marrow transplant may be beneficial
3. Fabry disease	axonal	c	α-galactosidase	Heat-induced pain, macular rash
4. Adrenomyeloneuropathy (XR/XD)	demyelinating, axonal	inf-a	ABCD1 transporter	Early bone marrow transplant may be beneficial
5. Refsum disease	demyelinating	inf-a	Phytanoyl-αCoA-hydroxylase	Dietary restriction may ameliorate the disease
6. Tangier disease	axonal	a	ABC1	Small-fiber neuropathy, facial weakness, very low HDL
7. Bassen-Kornzweig	axonal	c	MTP	Acanthocytosis, cerebellar ataxia
V. Miscellaneous Inherited Neuropathies				
1. Giant axonal neuropathy (AR)	axonal	c	Gigaxonin	
2. Porphyria (AR)	axonal	c, a	Porphobilinogen deaminase	May respond to hematin, glucose
3. "Mitochondrial" neuropathies (NARP)	axonal			Retinitis pigmentosa
4. Severe PNS, CNS demyelination (AD)	demyelinating	inf, c	Myelin transcription factor SOX10	CNS, PNS hypomyelination

[a]*Italicized* types with an asterisk are the most common in practice. CMT1A accounts for approximately 40 percent of cases with an identifiable mutation; CMT1B and HNPP approximately 6 percent each, and CMT1X approximately 6 percent of affected males.
a, adult onset; c, childhood onset; inf, infantile onset.

★ Most commonly tested

Charcot-Marie-Tooth

- Heterogenous group of disorders caused by mutations in genes expressed in myelin, gap junctions, or axonal structures of peripheral nerve
- Age of onset, mode of inheritance, gene affected, and even clinical characteristics are highly variable depending on type of CMT
- Clinical characteristics can be variable, but generally include at least: Distal weakness and atrophy, foot drop, pes cavus (high arches), mild or no sensory symptoms

Charcot Marie Tooth

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40% of all CMT

(70-80% of CMT1)

CMT1A (Demyelinating)

- Autosomal dominant - PMP22 gene **duplication** - Demyelinating
- **Pathophysiology:** Peripheral Myelin Protein overproduction and over-insertion into myelin sheath over time.
- 'Onion Bulb' pathology on nerve biopsy due to demyelination / remyelination cycles from Schwann cells as an aberrant response for the pathological demyelination.
- **Onset:** Ages 1 - 20

CMT2A

- Autosomal dominant - MFN2 mutation - Axonal
- **Onset:** Ages 10 - 30
- **Clinical features:**
  - Frequent sprained ankles, difficulty keeping up with peers
  - Distal calf muscle atrophy, “stork legs”
  - More prominent sensory loss

CMT2A

- **Exam findings:**
  - Areflexia, pes cavus, distal weakness, atrophy of distal musculature
  - Loss of vibration, proprioception

- **Prognosis:** Difficulty with ambulation, but rarely lose ability to ambulate. Normal life expectancy.

CMT1X

- **Clinical features:**
  - Similar to CMT1
  - Toe walking, difficulty running
  - Tremor, hand weakness, sensorineural deafness
  - Transient CNS manifestations: Limb weakness, hemiparesis, dysarthria, dysphagia, ataxia
  - MRI abnormalities: ADEM-like lesions predominantly in posterior brain or splenium of corpus callosum
- **Prognosis:** Remain ambulatory

- **Exam findings:**
  - Loss of achilles reflex, others preserved
  - Pes cavus, distal weakness, atrophy of distal musculature
  - Loss of vibration, proprioception

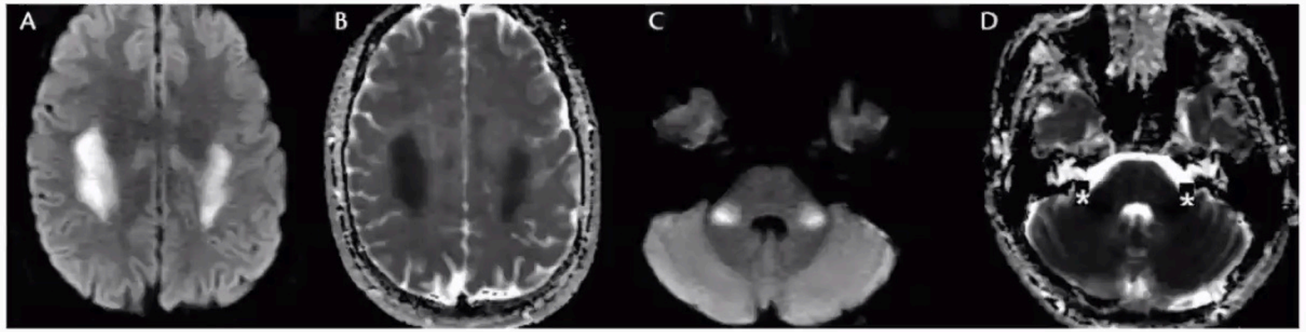


Figure 3. Brain MRI at 17 years of age. Diffusion-weighted image sequence (A, C) and apparent diffusion coefficient (B, D) showing restricted diffusion in the centrum semiovale (A, B) and the cerebellar peduncles (C, D).

Hereditary Neuropathy with liability to Pressure Palsy (HNPP)

- Autosomal dominant - PMP22 gene **deletion** - Demyelinating
- **Pathophysiology:** Peripheral Myelin Protein overproduction and over-insertion into myelin sheath over time.
- **Onset:** Ages 5 - 30
- **Clinical features:**
  - Episodic, isolated nerve palsies in area prone to compression (ulnar elbow, median wrist, peroneal at fibular head, radial at spiral groove)
  - When severe, may mimic CIDP
- **Treatment:** Minimization of nerve compression (protective splints, pads)

Hereditary Sensory and Autonomic Neuroapthy (HSAN)

II. Hereditary Sensory and Autonomic Neuropathy (HSAN)				
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4. HSAN4 (AR)	axonal	inf	TrkA/NGF receptor	Congenital SN with anhidrosis
5. HSAN5 (AR)	axonal	inf	Nerve growth factor-beta	Absent pain

- Generally more rare than CMT / HNPP
- This group includes hereditary neuropathies with a predominantly loss of large myelinated and unmyelinated fibers.

HSAN1

- Autosomal dominant - SPTLC1 gene mutation* - Axonal
- Progressive degeneration of dorsal root ganglion and motor neurons
- **Onset:** Ages 12-70, mean is 29 years old
- **Diagnosis:** EMG + genetic testing (panel)
- **Clinical features:**
  - Onset of sharp brief leg pains, followed by worsening sensory and motor symptoms, foot ulcers
  - Most frequent presenting feature: sensory loss in feet.
  - Prominent sensory loss develops
  - Variable involvement of autonomic and motor symptoms
- **Exam findings:**
  - Areflexia, pes cavus, distal weakness, atrophy of distal musculature
- **Prognosis:** Complete loss of sensation in limbs, face is spared. Often require distal amputations for ulcers/bone necrosis. No treatment available.

Hereditary Disorders of Lipid Metabolism

IV. Hereditary Disorders of Lipid Metabolism Causing Neuropathy (AR)					
1.	Metachromatic leukodystrophy	demyelinating	inf-a	Arylsulfatase A and B	
2.	Krabbe disease	demyelinating, axonal	inf-a	β-galactosidase	Early bone marrow transplant may be beneficial
3.	Fabry disease	axonal	c	α-galactosidase	Heat-induced pain, macular rash
4.	Adrenomyeloneuropathy (XR/XD)	demyelinating, axonal	inf-a	ABCD1 transporter	Early bone marrow transplant may be beneficial
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7.	Bassen-Kornzweig	axonal	c	MTP	Acanthocytosis, cerebellar ataxia

Hereditary Disorders of Lipid Metabolism

Metachromatic Leukodystrophy

- Pathophysiology: Absence of enzyme **Sulfatase, autosomal recessive (Arylsulfatase A and B)**
- **Age of onset:** Typically in first 3 years of life (juvenile/adult forms exist, less common)
- **Clinical features:** Difficulty walking progressing over months to inability walk or talk.
- **Prognosis:** Rare survival beyond childhood.

Hereditary Disorders of Lipid Metabolism

Fabry

- Pathophysiology: Absence of enzyme **alpha-galactosidase A, x-linked. Glycolipid accumulation in peripheral nerve results.**
- **Age of onset:** Typically in childhood/adolescence
- **Clinical features:** Starts with burning, lancing pains. Temperature change leads to pain crisis, unique to Fabry.

  Skin: presence of numerous dark red macules and papules (angiokeratomas), up to 2 mm in diameter, over the trunk and limbs, most closely clustered over the thighs and lower trunk
- **Prognosis:** Rare survival beyond childhood.





Familial Amyloidosis

- *amyloid* is a descriptive term for any of the proteins that are deposited in filamentous beta-pleated sheets; it can be derived from a number of precursor protein sources.
- Peripheral neuropathy is one of the most common manifestations of amyloidosis (acquired or hereditary)
- The most common form of neuropathy is associated with the familial form from an abnormal serum protein transthyretin (TTR)

III. Familial Amyloid Polyneuropathies (AD)				
1. Type 1—Portuguese	axonal	a	Transthyretin	Liver transplant may be beneficial
2. Type 2—Indiana/Swiss	axonal	a	Transthyretin	Liver transplant may be beneficial
3. Type 3—Van Allen	axonal	a	Apolipoprotein A1	
4. Type 4—Finnish	axonal	a	Gelsolin	Lax skin and "blood-hound" face; corti-cospinal, posterior column deficits

Familial Amyloidosis

Treatment:

- Patisiran, vutrisiran, and inotersen are approved by the US Food and Drug Administration (FDA) for treatment of polyneuropathy caused by hereditary transthyretin-related amyloidosis (hATTR) in adults, and tafamidis is approved for transthyretin-mediated amyloid cardiomyopathy (ATTR-CM).

Familial Amyloidosis

Portuguese / Andrade type:

- Age of onset: 25-35 years
- TTR gene mutation
- Clinical features:
  - Onset of numbness, paresthesias in the feet
  - Mild weakness early in course
  - Pain and temperature more affected than other modalities
  - Autonomic: Loss of pupillary light reflexes, miosis, anhidrosis, orthostatic hypotension, GI dysfunction, erectile dysfunction
  - Late: Cranial nerve findings
- Non-CNS: Cardiomegaly, AV block, hepatomegaly, vitreous opacities (blindness), nephrotic syndrome
- Prognosis: Typically progressive and fatal within 10-15 years
- Labs: SPEP/UPEP w/ Immunofixation, TTR quantification
- Diagnosis: Biopsy with Congo Red staining, can be affected organ or more commonly bone marrow or abdominal fat pad.

Sample Case

- Patient is a 53 year old woman who presents for evaluation of hand and feet weakness. She describes 10+ years of progressive weakness noticed in hands and feet on both sides. She denies any significant sensory changes such as numbness or tingling.

- Examination shows high arches and hammer toes bilaterally. She has 2/5 ankle dorsiflexion bilaterally, 4/5 finger abduction. Sensation is intact to light touch throughout, there is reduced sensation to vibration, proprioception in the feet. Reflexes are absent throughout. EMG/NCS was performed.

Sample Case

- **Impression:** This is an abnormal study which shows a bilateral, symmetric, length-dependent, sensory-motor, demyelinating polyneuropathy. In this clinical context, this is consistent with a hereditary sensory-motor polyneuropathy such as Charcot-Marie-Tooth disease (CMT).

  Clinical comments: Based on the above findings and suspicion for a hereditary neuropathy, genetic testing was ordered today (and later returned positive for CMT1A)

- Note the seemingly severe motor and sensory findings (no response) on several simulations in many nerves, in stark contrast to the relatively mild clinical presentation.

- Note the uniformly reduced conduction velocities

Sample Case

Sensory Nerve Results

Site	Onset Lat (ms)	Latency (Peak) (ms)	Norm	Amplitude (O-P) (µV)	Norm	Distance (mm)	Velocity (m/s)	Norm	Temp °C
Left Median Sensory									
Wrist-Dig II	*NR	*NR	< 3.6	*NR	> 15	130	*NR	> 50	35
Left Radial Sensory									
Forearm-Wrist	*NR	*NR	< 2.7	*NR	> 14	100	*NR	-	33.6
Left Sural Sensory									
Calf-Lat Mall	*NR	*NR	< 4.6	*NR	> 4	140	*NR	> 40	33
Lower Leg-Lat Mall	*NR	*NR	-	*NR	-	70	*NR	-	32.3
Right Sural Sensory									
Calf-Lat Mall	*NR	*NR	< 4.6	*NR	> 4	140	*NR	> 40	32.7
Lower Leg-Lat Mall	*NR	*NR	-	*NR	-	70	*NR	-	31.9
Left Ulnar Sensory									
Wrist-Dig V	*NR	*NR	< 3.1	*NR	> 10	110	*NR	> 50	34.5

Electromyography

Side	Muscle	IA	Fib	PSW	Fasc	Other	Poly	Amp	Dur	Rate	Pattern	Effort
Left	Tib Anterior	*Incr	*2+	*2+	0	CRD	*Rare	Nml	*Incr	*Incr	*Reduced	Nml
Left	Gastroc LH	*Incr	*1+	*1+	0		None	*Gr Incr	*Incr	*Incr	*Reduced	Nml
Left	Vastus Lat	Nml	0	0	0		None	*Gr Incr	*Incr	*Incr	*Reduced	Nml
Left	FDI	*Incr	*2+	*2+	0		None	*Incr	*Incr	*Incr	*Reduced	Nml
Left	Deltoid	*Incr	0	0	0	CRD	None	Nml	*Sl Incr	Nml	Nml	Nml

Sample Case

Nerve Conduction Studies

Motor Nerve Results

	Latency		Amplitude		Rel Amp	Neg. Dur	Distance	Lat Diff	Velocity		Temp
Site	(ms)	Norm	(mV)	Norm	(%)	(ms)	(mm)	(ms)	(m/s)	Norm	°C
Left Median (APB) Motor											
Wrist	***10.7**	< 4.0	***1.64**	> 6.0		8.3	70				33.2
Elbow	18.6	-	1.60	-	-2.4	11.9	202	7.9	***26**	> 50	33.1
Left Peroneal (EDB) Motor											
Ankle	*NR	< 6.0	*NR	> 2.5		*NR	90				32
Right Peroneal (EDB) Motor											
Ankle	*NR	< 6.0	*NR	> 2.5		*NR	90				31.6
Left Peroneal (TA) Motor											
Fib Head	*NR	< 4.5	*NR	> 3.0		*NR					30.2
Right Peroneal (TA) Motor											
Fib Head	***7.1**	< 4.5	***0.59**	> 3.0		-					29
Pop Fossa	*NR	-	*NR	-	*NR	*NR	-	*NR	*NR	-	28.1
Left Tibial (AHB) Motor											
Ankle	*NR	< 5.0	*NR	> 4.0		*NR	90				29.2
Right Tibial (AHB) Motor											
Ankle	*NR	< 5.0	*NR	> 4.0		*NR	90				27.3
Left Ulnar (ADM) Motor											
Wrist	***5.6**	< 3.1	***2.5**	> 7.0		7.7	70				26.8
Bel Elbow	12.0	-	2.6	-	4.0	11.8	185	6.4	***29**	> 50	26.6
Abv Elbow	15.6	-	2.1	-	-19.2	13.1	116	3.6	***32**	> 50	26.5