

Practical guidelines for molecular testing in Charcot-Marie-Tooth disease

Disease definition : Charcot-Marie-Tooth (CMT) hereditary neuropathy refers to a clinically and genetically very heterogeneous group of neurological disorders characterized by chronic and progressive hereditary motor and/or sensory neuropathy (HMSN).

Frequency : CMT is the most common genetic cause of peripheral neuropathy, with an estimated prevalence of 1 on 3,000 – 5,000.

Main clinical symptoms : CMT patients typically have a progressive peripheral polyneuropathy characterised by distal muscle weakness and atrophy, depressed tendon reflexes, high-arched feet, and distal sensory loss. The only associated symptom is moderate sensory loss.

Inheritance : CMT can be inherited in an autosomal dominant autosomal recessive or X-linked manner, but most patients (80 %) have an autosomal dominant type.

Clinical diagnosis : Nerve conduction velocity (NCV) is reduced.

Clinical classification : CMT can be subdivided on clinical grounds or mode of inheritance in several types:

- **CMT1 :** a demyelinating type with severely reduced nerve conduction velocity (< 30 m/s; normal: 40-45 m/s). CMT1 is the most frequent type of CMT present in nearly 50 % of the patients.
- **CMT2 :** an axonal, non-demyelinating type with nerve conduction velocities within the normal or mildly abnormal range (35-40 m/s). After CMT1 this is the most frequent type present in nearly 30 % of CMT patients.
- **Intermediate CMT :** a rare type of CMT with combined myelinopathy and axonopathy and nerve conduction velocities intermediate between those of CMT1 and CMT2.
- **CMT4 :** a rare axonal or demyelinating type with autosomal recessive inheritance.
- **CMTX1 :** an X-linked dominant type with severe (males) or moderate (females) features, present in 15 % of CMT patients.
- **HNPP :** Hereditary neuropathy with liability to pressure palsies (HNPP) is characterized by repeated and temporary isolated nerve palsies caused by

trivial compression or trauma. The symptoms are carpal tunnel syndrome or peroneal palsy with foot drop.

- **Dejerine-Sottas disease** : a severe demyelinating type with early-onset. As it is demyelinating it can be classified also as CMT1; some cases showing autosomal recessive inheritance can also be classified as CMT4.

Molecular testing

- **CMT1** : in more than 80% of patients with CMT1 a mutation is found in the PMP22, MPZ, or the GJB1 gene, with the duplication of the PMP22 gene representing 70 % and the MPZ gene 5-10 % of all CMT1 cases. Mutations in the GJB1 gene are found in the majority of X-linked CMT1. The remaining cases are due to mutations in the LITAF, EGR2, or NEFL gene.
- **CMT2** : at least 10 genes are responsible for CMT2. Only the MFN2 gene represents a significant proportion of cases (10-20 %) and should be analysed. Testing for all other genes is not recommended at present.
- **Intermediate CMT** : can be caused by autosomal dominant mutations in the DNM2 or YARS genes. As only a few mutations have been identified in these genes, testing is not recommended at present.
- **CMT4** : autosomal recessive CMT can be caused by at least 7 different genes. Only the GDAP1 gene represents a significant proportion of cases (4-20 %) and should be analysed. Testing for all other genes is not recommended at present.
- **CMTX1** : as 90 % of X-linked CMT is encountered for by mutations in the GJB1 gene encoding connexin 32, only the GJB1 gene should be tested.
- **HNPP** : as all cases are caused by autosomal dominant mutations in the PMP22 gene, this gene should be analysed : 80 % is due to a common deletion of the PMP22 gene, whereas 20 % is due to various PMP22 intragenic mutations.
- **Dejerine-Sottas disease** : this disease can be caused by at least 4 different genes. As it is very severe with early-onset we recommend sequential testing of the 4 genes involved PMP22, MPZ, EGR2 and PRX.

References

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Databases

<http://www.molgen.ua.ac.be/CMTMutations/Home/IPN.cfm>

Table 1. Different types of CMT with the relative proportion of the respective disease gene, the size of the gene, a price indication, and a test advise.

Type	Feature	Gene	Protein	Relative gene contribution	Number of Exons (AA)	Price Indication (Euro)	Advise
CMT1	Demyelinating	PMP22	Peripheral myelin protein 22	70-80 %	1 mutation: duplication	250	Test 1
		MPZ	Myelin protein zero, P0	5-10 %	6 exons (250 AA)	500	Test 2
		GJB1 (Gap junction beta-1)	Connexin 32	Unknown	2 exons (283 AA)	400	Test 3
		LITAF	Lipopolysaccharide-induced tumor necrosis factor-alpha factor	Low	4 exons (161 AA)	400	No test advised
		EGR2	Early growth response protein 2	Low	2 exons (476 AA)	700	No test advised
		NEFL	Neurofilament light polypeptide	Low	6 exons (400 AA)	600	No test advised
		PMP22	Peripheral myelin protein 22	Low	5 exons (160 AA)	600	No test advised
CMT2	Axonal	MFN2	Mitofusin 2	10- 20 %	19 exons (758 AA)	800	Only test advised
		GDAP1, GARS, GJB1, HSPB1, KIF1B, LMNA, MPZ, NEFL, RAB7	Various	Unknown	Various	Various	No test advised
Intermediate CMT	Intermediate demyelinating-axonal	DNM2, YARS	Various	Unknown	Various		No test advised
CMT4	Recessive	GDAP1	Ganglioside-induced differentiation-associated protein 1	4-20 %	6 exons (358 AA)	800	Only test advised
		EGR2, MTMR2, NDRG1, PRX, SBF2, SH3TC2	Various	Unknown	Various	Various	No test advised
CMTX	X-linked	GJB1 (Gap junction beta-1)	Connexin 32	90 %	2 exons (283 AA)	400	Only test advised
HNPP	Hereditary neuropathy with liability to pressure palsies	PMP22	Peripheral myelin protein 22	80 %	1 mutation: deletion	250	Test 1
		PMP22	Peripheral myelin protein 22	20 %	5 exons (160 AA)	600	Test 2
Dejerine-Sottas	Early-onset demyelinating	MPZ	Myelin protein zero, P0	Unknown	6 exons (250 AA)	500	Test 1
		PMP22	Peripheral myelin protein 22	Unknown	5 exons (160 AA)	600	Test 2
		EGR2	Early growth response protein 2	Unknown	2 exons (476 AA)	700	Test 3
		PRX	Periaxin	Unknown	7 exons (1461 AA)	1100	Test 4

Figure 1. Suggested molecular testing in different CMT types

