

## CLINICAL UTILITY GENE CARD

# Clinical utility gene card for: HMSN/HNPP HMSN types 1, 2, 3, 6 (CMT1,2,4, DSN, CHN, GAN, CCFDN, HNA); HNPP

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### 1. DISEASE CHARACTERISTICS

#### 1.1 Name of the disease (synonyms)

Hereditary motor and sensory neuropathy types 1, 2, 3, 6, X (HMSN1, HMSN2, HMSN3, HMSN6, HMSN X1);  
Charcot–Marie–Tooth neuropathy type 1, 2, 4, X1 (CMT1, CMT2, CMT4, CMTX1);  
Dejerine–Sottas neuropathy (DSN);  
Congenital hypomyelinating neuropathy (CHN);  
Giant axon neuropathy 1 (GAN1);  
Congenital cataracts, facial dysmorphism and neuropathy syndrome (CCFDN);  
Hereditary neuralgic amyotrophy (HNA);  
Hereditary neuropathy with liability to pressure palsies (HNPP).

For current stage of knowledge see reference 1.

#### 1.2 OMIM# of the disease

118220, 118210, 118200, 609260, 162500, 145900, 302800 607677, 605253, 256850, 162100, 601455, 608323 and 607736.

#### 1.3 Name of the analysed genes or DNA/chromosome segments

PMP22, MPZ, GJB1 (CX32), MFN2, EGR2, SIMPLE, NEFL, DNMT2, RAB7, SH3TC2, GDAPI, GARS, PRX, LMNA, BSCL2, CTDPI, FIG4, MTMR2, SBF2/MTMR13, FGD4, NDRG1, YARS, AlaRS and SEPT9. Current stage of knowledge, annual revision recommended.

#### 1.4 OMIM# of the gene(s)

601097, 159440, 304040, 608507, 129010, 603795, 162280, 602378, 602298, 608206, 606598, 600287, 605725, 150330, 606158, 604927, 609390, 603557, 607697, 605379, 611104, and 604061. Current state of knowledge, annual revision recommended.

#### 1.5 Mutational spectrum

30–50% CMT1A duplication/HNPP deletion in chromosome region 17p11.2 (PMP22).

Remaining patients: private and recurrent mutations in any of the above-mentioned and newly identified genes (see reference 2).

#### 1.6 Analytical methods

MLPA, Multiplex Amplicon Quantification (MAQ) ([http://www.vibgeneticservicefacility.be/tech/MAQ\\_Application\\_Note\\_1.1.pdf](http://www.vibgeneticservicefacility.be/tech/MAQ_Application_Note_1.1.pdf)),

microsatellite analysis, qPCR, Southern blot, FISH for PMP22 duplication/deletion screening, PFGE, dHPLC, high-resolution melting, restriction analysis, direct sequencing (current state of knowledge).

#### 1.7 Analytical validation

Participation on proficiency tests. For detection of the CMT1A duplication/HNPP deletion two methods are used, and the results of which verify each other. The results of the molecular genetic diagnostics are unambiguously evaluated, as a rule.

#### 1.8 Estimated frequency of the disease (incidence at birth ('birth prevalence') or population prevalence)

Prevalence in the general population 10–40 per 100 000, in Finland 1:2500.

#### 1.9 If applicable, prevalence in the ethnic group of investigated person

Not applicable in general. For ethnic subgroups like Roma and eg CCFDN (CTDPI gene) data not yet available.

#### 1.10 Diagnostic setting

	Yes	No
A. (Differential) diagnostics	<input checked="" type="checkbox"/>	<input type="checkbox"/>
B. Predictive testing	<input checked="" type="checkbox"/>	<input type="checkbox"/>
C. Risk assessment in relatives	<input checked="" type="checkbox"/>	<input type="checkbox"/>
D. Prenatal	<input checked="" type="checkbox"/>	<input type="checkbox"/>

#### Comment:

A prenatal test is rarely requested.

### 2. TEST CHARACTERISTICS

Genotype or disease	A: true positives		C: false negative	
	B: false positives		D: true negative	
	Present	Absent		
Test				
Positive	A	B	Sensitivity:	A/(A+C)
			Specificity:	D/(D+B)
Negative	C	D	Positive predictive value:	A/(A+B)
			Negative predictive value:	D/(C+D)

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**2.1 Analytical sensitivity****(proportion of positive tests if the genotype is present)**

Almost 100%.

**2.2 Analytical specificity****(proportion of negative tests if the genotype is not present)**

Almost 100%.

**2.3 Clinical sensitivity****(proportion of positive tests if the disease is present)**

The clinical sensitivity can be dependent on variable factors such as age or family history. In such cases a general statement should be given, even if a quantification can only be made case by case.

Duplication/deletion PMP22: about 50%.

Mutation in PMP22: about 1%.

Mutation/deletion GJB1: up to 10% (depending in clinical manifestation and family history).

Mutation MFN2: about 20%, deletion/duplication not yet described.

Mutation MPZ: about 5%, deletion/duplication not yet described.

Mutation SH3TC2: about 20% of autosomal recessive HMSN.

Mutation other genes: &lt; 1–5% each.

**2.4 Clinical specificity****(proportion of negative tests if the disease is not present)**

The clinical specificity can be dependent on variable factors such as age or family history. In such cases a general statement should be given, even if a quantification can only be made case by case.

Almost 100%.

**2.5 Positive clinical predictive value****(lifetime risk to develop the disease if the test is positive)**

The penetrance in verified mutation carriers is almost 100%, according to the literature; because of the wide clinical variability, clinically mildly affected persons may not be diagnosed or they died from other causes in the preclinical stage.

**2.6 Negative clinical predictive value****(probability not to develop the disease if the test is negative)**

Assume an increased risk based on family history for a non-affected person. Allelic and locus heterogeneity may need to be considered.

Index case in that family had been tested:

Almost 100%.

Index case in that family had not been tested:

About 86% (detection rate of mutations). As a rule, however, such an approach is not recommended.

**3. CLINICAL UTILITY****3.1 (Differential) diagnosis: the tested person is clinically affected**

(To be answered if in 1.10 'A' was marked)

**3.1.1 Can a diagnosis be made other than through a genetic test?**

No	<input type="checkbox"/>	(continue with 3.1.4)
Yes	<input checked="" type="checkbox"/>	
	<input checked="" type="checkbox"/>	Clinically
	<input type="checkbox"/>	Imaging
	<input type="checkbox"/>	Endoscopy
	<input type="checkbox"/>	Biochemistry
	<input checked="" type="checkbox"/>	Electrophysiology
	<input type="checkbox"/>	Other (please describe) <i>family history</i>

3.1.2 Describe the burden of alternative diagnostic methods to the patient NCV/EMG: acceptable.

Nerve biopsy: may be a strain.

3.1.3 How is the cost effectiveness of alternative diagnostic methods to be judged? Recommended diagnostic procedure:

- (1) Clinical and electrophysiological diagnostics for delineating the type of CMT (demyelinating, axonal, or intermediate).
- (2) Search for mutations, to verify diagnosis or subtype of disease, differential diagnosis for Friedreich's ataxia, Roussy–Levy syndrome, carpal tunnel syndrome.
- (3) First step of molecular genetics: duplication/deletion screening in chromosome region 17p11.2 (PMP22 gene) in demyelinating types 1, 3, and HNPP. Mutation analysis in MFN2 in axonal CMT2.
- (4) Economic viability of search for mutations in the other genes can only be assessed individually, in the context of general clinical situation, diagnostic problem, mode of inheritance, ethnic origin, additional symptoms (deafness, pupillary anomalies, scoliosis, visual impairment, cataract, curly hair, etc) and psychological suffering of patients/relatives.

3.1.4 Will disease management be influenced by the result of a genetic test?

**3.2 Predictive setting: the tested person is clinically unaffected but**No Yes 

Therapy (please describe) Avoidance of unnecessary therapy with undefined diagnosis, eg amputation of limbs. Future therapeutical approaches will be mutation specific, hence knowledge of the disease-causing variant is crucial for inclusion of a patient in these upcoming procedures.

Prognosis (please describe) Not in general, but for selected subtypes possible.

Management (please describe) Prophylactic physical/orthopaedic therapy if required, recommendations for avoidance of specific neurotoxic substances, choice of occupation.

**carries an increased risk based on family history**

(To be answered if in 1.10 'B' was marked)

3.2.1 Will the result of a genetic test influence lifestyle and prevention? Yes.

If the test result is positive (please describe):

See 3.3.1, prophylactic physical therapeutic/orthopaedic interventions if required and additional recommendations depending on the subtype.

If the test result is negative (please describe):

Positive influence on choice of occupation and family planning; psychological relief.

3.2.2 Which options in view of lifestyle and prevention does a person at-risk have if no genetic test has been done (please describe)? Choice of occupation depending on risk of disease, avoidance of neurotoxic compounds, avoiding obesity.

**3.3 Genetic risk assessment in family members of a diseased person**

(To be answered if in 1.10 'C' was marked)

3.3.1 Does the result of a genetic test resolve the genetic situation in that family? Yes.

3.3.2 *Can a genetic test in the index patient save genetic or other tests in family members?* Yes, because specific diagnostics is possible in relatives, else an unspecific differential diagnostic scheme would be applied in symptomatic patients.

3.3.3 *Does a positive genetic test result in the index patient enable a predictive test in a family member?* Yes.

### 3.4 Prenatal diagnosis

(To be answered if in 1.10 'D' was marked)

3.4.1 *Does a positive genetic test result in the index patient enable a prenatal diagnostic?* Yes, but is rarely requested.

## 4. IF APPLICABLE, FURTHER CONSEQUENCES OF TESTING

Please assume that the result of a genetic test has no immediate medical consequences. Is there any evidence that a genetic test is nevertheless useful for the patient or his/her relatives? (Please describe).

Verification of the diagnosis is for many patients a value in itself, irrespective of medical benefits: it gives the disease a name and often explains their cause.

Demonstration of a genetic cause eliminates the feeling of guilt and 'own faults' (exogenous poisons, 'incorrect conduct'), which may be relieving.

Knowledge of the individual mutation may enable in the future the access to therapies that are presently in developmental stage. Effects of neurotoxic compounds, eg chemotherapeutic agents for treatment of cancer, can be ameliorated or avoided.

### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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