Bristol Genetics Laboratory is a UKAS accredited medical laboratory No.9307.

North Bristol NHS Trust

Inherited Peripheral Neuropathies

(Charcot-Marie-Tooth disease, HSAN and dHMN)

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Sample Required:
Adult: 3-4mls blood in EDTA
Paediatric: at least 1ml EDTA (preferably >2ml)
DNA: 1µg total (conc. >80ng/µl)

Samples should be accompanied by a FULLY completed request form (available as download at www.nbt.nhs.uk/genetics or from the laboratory).

Please include details of test, family history, address and POSTCODE, NHS number, referring clinician and unit/hospital.

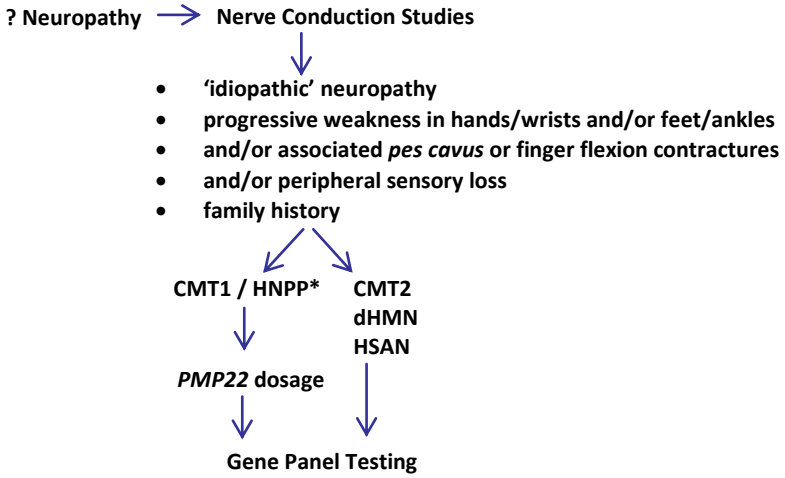
Consent and DNA Storage:
All genetic testing requires consent. **It is the responsibility of the referring clinician to ensure that appropriate consent has been obtained.**

This is a gene panel testing using next generation sequencing. Only genes associated with IPN are included, however the possibility of incidental findings cannot be completely excluded. Results obtained may have implications for the wider family. Results may include variants of unknown clinical significance requiring further family studies to determine their role in the patient's symptoms. The interpretation provided is based on the available information at the date of issue; it may change if further evidence becomes available.

DNA is stored from all patients unless consent for this is specifically denied. Stored samples may be used anonymously for quality assurance and development purposes for this disorder.

Clinical Background and Genetics

- The inherited peripheral neuropathies (IPN) are a clinically and genetically heterogeneous group of disorders with overall prevalence of 1 in 2,500.
- There are in excess of 50 genes associated with IPN which show high heterogeneity, as mutations in a single gene can cause different phenotypes, while the same phenotype can be caused by mutations in different genes.
- Clinical classification distinguishes between **CMT (HMSN)** with motor and sensory involvement; **Hereditary Sensory and Autonomic Neuropathies (HSAN)** with fewer motor features and **distal Hereditary Motor Neuropathy (dHMN**) with no sensory signs. Intermediate forms also exist.
- The diagram below presents the testing strategy using **Gene Panel Testing**: 56 genes associated with different types of inherited neuropathy are tested simultaneously (refer to Table 1).



*HNPP patients without *PMP22* dosage abnormality to be tested for *PMP22* gene point mutations only

Service offered

- Patients with **CMT1** and **HNPP** are initially tested for dosage abnormality of the *PMP22* gene (17p12) using MLPA (approximately 70% of CMT1 patients have the duplication and 84% of HNPP patients have the deletion). CMT1 patients without a dosage abnormality are subsequently tested with the gene panel assay.
- Patients with **CMT2, HSAN** and **dHMN** are directly tested with the gene panel assay.
- If gene panel testing is not required, sequential gene testing with Sanger sequencing is also available for 16 genes (details in page 4).

Referrals

- Diagnostic referrals are accepted from Consultant Neurologists, Consultant Paediatricians and Clinical Geneticists.
- It is **essential** that the referring Clinician provides the **clinical information** required in page 3 (UKGTN proforma or relevant clinical letter).

Quality

- BGL participates in the appropriate GenQA schemes for this service.

Target reporting Time (calendar days)

- MLPA (17p12 dosage analysis) 42 days
- Gene panel testing 84 days
- Sanger sequencing 42 days (see page 4)

For more information, including test costs, please contact the laboratory.

Clinical Advice:

If clinical discussion is required, we would recommend contact with Dr Andrew Norman, Consultant Clinical Geneticist at St Michael's Hospital, Bristol, Andrew.Norman@UHBristol.nhs.uk

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TABLE 1 Inherited Peripheral Neuropathies - Gene Panel Genetic Testing

GENE	OMIM	Locus	CMT1	CMT2	HMN	HS(A)N	OMIM	Inheritance
AARS	601065	16q22		CMT 2N			613287	AD
ARHGEF10	608136	8p23	Slowed NCV; hypomyelination				608236	AD
ATL1	606439	14q11-q21				HSN 1D	613708	AD
ATP7A	300011	Xq12-q13			dSMAX3		300489	XL
BAG3	603883	10q26.11	myopathy; myofibrillar, BAG-3 related				612954	AD
BSCL2	606158	11q12.3			HMN 5		600794	AD
CCT5	610150	5p15.2				HSN with spastic paraplegia	256840	AR
CTDP1	604927	18q23	CCFDN: Congenital cataracts, facial dysmorphism, neuropathy				604168	AR
DCTN1	601143	2p13.1			HMN 7B		607641	AD
DNM2	602378	19p13.2		CMT DI B/ CMT 2M			606482	AD
DYNC1H1	600112	14q32.31		CMT 2O	SMA-LED		614228 / 158600	AD
EGR2	129010	10q21.1-q22.1	CMT 1D/CMT 4E CHN/ DSS				607678 / 605253 / 145900	AD / AR
FAM134B	613114	5p15.1				HSAN 2B	613115	AR
FGD4	611104	12p11.21	CMT 4H				609311	AR
FIG4	609390	6q21	CMT 4J				611228	AR
GAN	605379	16q23.2	Giant Axonal Neuropathy 1				256850	AR
GARS	600287	21q22.11		CMT 2D	HMN 5		601472 / 600794	AD
GDAP1	606598	8q21	CMTA RI/CMT 4A	CMT 2H/ CMT 2K			608340 / 214400 607706 / 607831	AR / AR AR / AD
GJB1	304040	Xq13.1	CMT X1				302800	XL
HOXD10	142984	2q31.1	HMSN with Congenital vertical talus				192950	AD
HSPB1	602195	7q11		CMT 2F	HMN 2B		606595 / 608634	AD
HSPB3	604624	5q11.2			HMN 2C		613376	AD
HSPB8	608014	12q24		CMT 2L	HMN 2A		608673 / 158590	AD
IGHMBP2	600502	11q13.3		CMT 2S	HMN 6		604320 / 616155	AR
IKBKAP	603722	9q31.3				HSAN 3	223900	AR
KARS	601421	16q23.1	CMT RI B				613641	AR
KIF1B	605995	1p36.22		CMT 2A1			118210	AD
LITAF	603795	16p13.3-p12	CMT 1C				601098	AD
LMNA	150330	1q22		CMT 2B1			605588	AR
LRSAM1	610933	9q33.3		CMT 2P			614436	AD / AR
MED25	610197	19q33.13		CMT 2B2			605589	AR
MFN2	608507	1p35-36		CMT 2A2 /HMSN6			609260 / 601152	AD
MPZ	159440	1q22	CMT 1B/CHN/ CMT DI D	CMT 2I/ CMT 2J			118220 / 605253 / 607791 607677 / 607736	AD
MTMR2	603557	11q21	CMT 4B1				601382	AR
NDRG1	605262	8q24.22	CMT 4D				601455	AR
NEFL	162280	8p21	CMT 1F	CMT 2E			607734 / 607684	AD
NGF	162030	1p13.2				HSAN 5, absence of pain	608654	AR
NTRK1	191315	1q23.1				HSAN 4; anhidrosis, insensitivity to pain	256800	AR
PLEKHG5	611101	1p36.31	CMT RIC		dSMA 4		615376 / 611067	AR
PMP22	601097	17p12	CMT 1A/ HNPP/ CMT 1E/DSS				118220 / 162500 118300 / 145900	AD / AD AD / AR
PRPS1	311850	Xq22.3	CMT X5				311070	XL D/ R
PRX	605725	19q13.1-q13.2	CMT 4F/ DSS				145900	AR
RAB7A	602298	3q21.3		CMT 2B		HSN	600882	AD
REEP1	609139	2p11.2			HMN5B		614751	AD
SBF2	607697	11p15.4	CMT 4B2				604563	AR
SCN9A	603415	2q24.3	Absence of pain / extreme pain / small fiber neuropathy				243000 / 167400 / 133020	AR / AD / AD
SEPT9	604061	17q25.2-q25.3	Hereditary neuralgic amyotrophy, HNS, HNA & symorphic features				162100	AD
SH3TC2	608206	5q32	CMT 4C/ MNMN				601596 / 613353	AR / AD
SLC12A6	604878	15q14	PN with agenesis of the corpus callosum				218000	AR
SOX10	602229	22q13.1	PCWH syndrome				609136	AD
SPTLC1	605712	9q22.1-q22.3				HSAN 1A	162400	AD
SPTLC2	605713	14q24.3				HSAN 1C	613640	AD
TDP1	607198	14q32.11	Spinocerebellar ataxia, with axonal neuropathy				607250	AR
TRPV4	605427	12q24.1		CMT 2C			606071	AD
WNK1	605232	12p13.33				HSAN 2A	201300	AR
YARS	603623	1p13.1	CMT DI C				608323	AD

UKGTN Testing Criteria

Approved name and symbol of disease/condition(s):	OMIM number(s)
Charcot-Marie-Tooth Hereditary Neuropathy	see Table 1
Hereditary Motor Neuropathy	
Hereditary Sensory Autonomic Neuropathy	

Approved name and symbol of gene(s):	OMIM number(s)
see Table 1	see Table 1

Patient name:	**Date of birth:**
Patient postcode:	**NHS number:**
Name of referrer:	
Title/Position:	**Lab ID:**

Minimum Criteria required for testing to be appropriate as stated in the Gene Dossier:		Tick as appropriate	
		YES	**NO**
'Idiopathic' peripheral neuropathy diagnosed by:			
	1. Clinical presentation with progressive weakness in hands/wrists and/or feet/ankles and/or associated *pes cavus* or finger flexion contractures and/or peripheral sensory loss		
AND	2. Supportive nerve conduction test result (defining type I or II according to NCV)		
AND	3. Absence of other non-genetic causes (alcohol, B12 defy, diabetes, trauma)		
	4. No associated CNS involvement		

…giving a suggested diagnosis as one of:

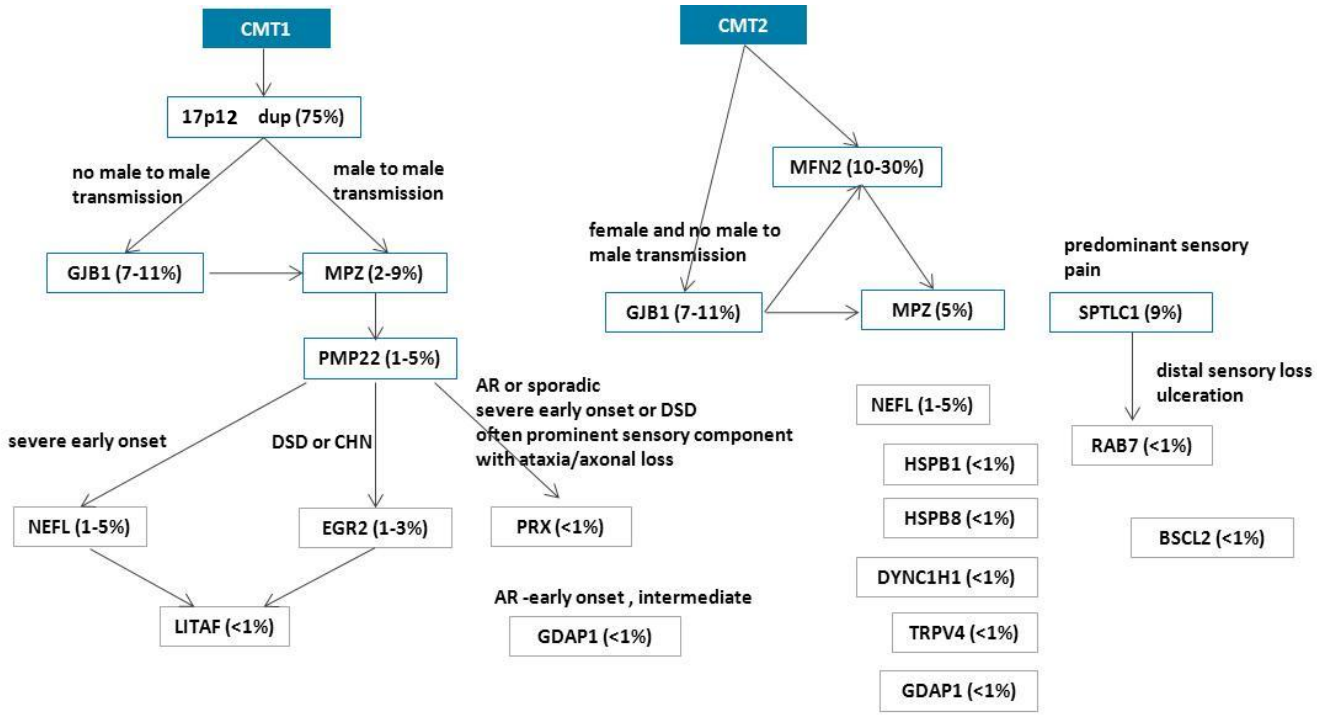
		Autosomal Dominant	Autosomal Recessive	X-Linked
	Demyelinating Neuropathy			
OR	Axonal Neuropathy			
OR	Motor Neuropathy			
OR	Sensory Neuropathy			

Clinical details:

Family history:

If the patient does not fulfil the clinical criteria and you still feel that testing should be performed, please contact the laboratory to discuss

Sequential testing and details of HMSN services available at Bristol Genetics Laboratory



17p12 dup/del	601097	MLPA	CMT1/HNPP	Autosomal Dominant (AD) or sporadic
PMP22	601097	Sequencing	CMT1A, Dejerine Sottas disease (DSD) congenital hypomyelinating neuropathy (CHN), HNPP	AD
MPZ	159440	Sequencing	CMT1B, DSD, CHN, CMT2	AD
GJB1 (Cx32)	304040	Sequencing	X-Linked CMT males CMT1 (+/- patchy MCVs); females CMT2	X-linked dominant/recessive
MFN2	608507	Sequencing	CMT2 / progressive /optic atrophy	AD or sporadic 20% AD families
EGR2	129010	Sequencing	CMT1/DSD/CHN	CMT1: AD CMT1/DSD/CHN: AR
NEFL	162280	Sequencing	CMT2 but can present as CMT1with slow MCVs and early onset severe disease	CMT2 AD CMT1 sporadic or AD
PRX (Periaxin)	605725	Sequencing	CMT1 or DSD/ often prominent sensory component /focally folded myelin	Autosomal Recessive (AR) or sporadic
SPTLC1 (exons 5,6 & 11)	605712	Sequencing	Hereditary sensory neuropathy type, no autonomic involvement/pain/sensory complications	AD
RAB7A	602298	Sequencing	Distal muscle weakness, wasting and sensory loss, often with ulceration.	AD
LITAF	603795	Sequencing	CMT1C	AD or sporadic
BSCL2 (exon 3)	606158	Sequencing	Distal Hereditary Motor Neuropathy (dHMN), CMT2	AD or sporadic
HSPB1	602195	Sequencing	dHMN, CMT2	AD or sporadic
HSPB8	608014	Sequencing	dHMN, CMT2	AD or sporadic
DYNC1H1 (exons 5-14)	600112	Sequencing	Atypical CMT2	AD
GDAP1	606598	Sequencing	CMT2/CMT4	AD, AR
TRPV4	605427	Sequencing	CMT2/ distal SMA	AD

For further details regarding clinical requirements please contact the laboratory

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