Inherited Peripheral Neuropathies
(Charcot Marie Tooth disease, HSAN and dHMN)

Contact details:
Bristol Genetics Laboratory
Pathology Sciences
Southmead Hospital
Bristol, BS10 5NB
Enquiries: 0117 323 6271
FAX: 0117 323 5572

Head of department:
Eileen Roberts FRCPath

Consultant Lead for Molecular Genetics:
Maggie Williams FRCPath

Service Lead:
Thalia Antoniadi PhD, FRCPath
Thalia.Antoniadi@nbt.nhs.uk

Sample Required:
Adult: 5mls blood in EDTA
Paediatric: at least 1ml EDTA (preferably >2ml)

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.

DNA is stored from all patients unless consent for this is specifically denied.

Stored samples may be used for quality assurance purposes and may be used anonymously for the development of new tests for the disorder in question.

Clinical Background and Genetics

• The hereditary neuropathies are a clinically and genetically heterogeneous group of disorders with overall prevalence of 1 in 2,500.
• This disease is characterised clinically by distal muscle wasting and weakness, distal sensory loss, reduced tendon reflexes, hypoflexia, variable amount of foot deformity and neurophysiological changes.
• Clinical classifications distinguish 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.
• Neurophysiological classification divides CMT into type 1 (median or ulnar motor conduction velocity <38m/s), demyelinating, and type 2 (MCV >38m/s), axonal, while an intermediate form is increasingly recognised.
• Hereditary neuropathy with liability to pressure palsies (HNPP) is genetically related to CMT1 and is also considered under the genetic neuropathies.
• There are in excess of 30 genes associated with inherited peripheral neuropathies, while 75% of the causative genes are still unknown. There is overlap between the various clinical groups, mutations in a single gene can cause different phenotypes, and the same phenotype can be caused by mutations in different genes.

Service offered

Level 1
• CMT type 1 or HNPP: Testing for dosage abnormality of PMP22 gene at 17p11.2 using MLPA (Approximately 70% of CMT1 patients have the duplication and 84% of HNPP patients have the deletion).
• CMT type 2: Full screen of MFN2 gene by direct sequence analysis is recommended (20-30% CMT2 patients have a MFN2 mutation).

Level 2
Screening of specific genes as appropriate. Please refer to the flow diagram on page 2 for suggested testing strategies, and page 3 for specific clinical criteria.

Referrals
• Diagnostic referrals are welcomed from Consultant Neurologists, Consultant Paediatricians and Clinical Geneticists. Predictive familial referrals are accepted only from Clinical Genetics.
• Screening tests for the rare HMSN genes EGR2, PRX, NEFL, LITAF, RAB7A, BSCL2, HSPB1, HSPB8, DYN1CH1, GAPD1 and TRPV4 are only available to Genetics and Neurology specialists and when clinical criteria are met. Please refer to the specific UKGTN testing criteria table on page 3.
• Please ensure that clinical details, family history, neurophysiology data and previous genetic test results are provided on the referral form.

Quality
• BGL participates in the external quality assurance EMQN sequencing QA schemes (since the pilot scheme was introduced in 2002) and UKNEQAS Unclassified Variant interpretation scheme (pilot scheme introduced in 2012).

Target reporting Time and Indicative Cost (2012/2013)

Level 1: MLPA (17p11.2 dosage analysis) 20 days £172
Level 2: Gene screen by sequence analysis 40 days £see over cost varies according to gene, please refer to table, page 2
Familial: Sequence analysis for known mutation 10 days £190
### Inherited Peripheral Neuropathies
(Charcot Marie Tooth disease, HSAN and dHMN)

#### Suggested Testing Strategy and details of HMSN Services available at Bristol Genetics Laboratory

<table>
<thead>
<tr>
<th>Gene</th>
<th>OMIM</th>
<th>Method</th>
<th>Indicative Cost 2012/13 (NHS)</th>
<th>Phenotypes</th>
<th>Inheritance pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>17p11.2 dup/del</td>
<td>601097</td>
<td>MLPA</td>
<td>£172</td>
<td>CMT1/HNPP</td>
<td>Autosomal Dominant (AD) or sporadic</td>
</tr>
<tr>
<td>PMP22</td>
<td>601097</td>
<td>Sequencing</td>
<td>£309</td>
<td>CMT1A, Dejerine Sottas disease (DSD) congenital hypomyelinating neuropathy (CHN), HNPP</td>
<td>AD</td>
</tr>
<tr>
<td>MPZ</td>
<td>159440</td>
<td>Sequencing</td>
<td>£358</td>
<td>CMT1B, DSD, CHN, CMT2</td>
<td>AD</td>
</tr>
<tr>
<td>GJB1 (Cx32)</td>
<td>304040</td>
<td>Sequencing</td>
<td>£210</td>
<td>X-Linked CMT males CMT1 (+/- patchy MCVs); females CMT2</td>
<td>AD or sporadic, 20% AD families</td>
</tr>
<tr>
<td>MFN2</td>
<td>608507</td>
<td>Sequencing</td>
<td>£745</td>
<td>CMT2 / progressive optic atrophy</td>
<td>X-linked dominant/recessive</td>
</tr>
<tr>
<td>EGR2</td>
<td>129010</td>
<td>Sequencing</td>
<td>£358</td>
<td>CMT1/DSD/CHN</td>
<td>AD</td>
</tr>
<tr>
<td>NEFL</td>
<td>162280</td>
<td>Sequencing</td>
<td>£387</td>
<td>CMT2 but can present as CMT1 with slow MCVs and early onset severe disease</td>
<td>CMT2 AD, CMT1 sporadic or AD</td>
</tr>
<tr>
<td>Periaxin</td>
<td>605725</td>
<td>Sequencing</td>
<td>£561</td>
<td>CMT1 or DSDI, often prominent sensory component /locally folded myelin</td>
<td>Autosomal Recessive (AR) or sporadic</td>
</tr>
<tr>
<td>SPTLC1 (exons 5, 6 &amp; 11)</td>
<td>605712</td>
<td>Sequencing</td>
<td>£184</td>
<td>Hereditary sensory neuropathy type, no autonomic involvement/pain/sensory complications</td>
<td>AD</td>
</tr>
<tr>
<td>RAB7A</td>
<td>602296</td>
<td>Sequencing</td>
<td>£358</td>
<td>Distal muscle weakness, wasting and sensory loss, often with ulceration.</td>
<td>AD</td>
</tr>
<tr>
<td>LITAF</td>
<td>603795</td>
<td>Sequencing</td>
<td>£242</td>
<td>CMT1C</td>
<td>AD or sporadic</td>
</tr>
<tr>
<td>BSCL2 (exon 3)</td>
<td>606156</td>
<td>Sequencing</td>
<td>£178</td>
<td>Distal Hereditary Motor Neuropathy (dHMN), CMT2</td>
<td>AD or sporadic</td>
</tr>
<tr>
<td>HSPB1</td>
<td>602195</td>
<td>Sequencing</td>
<td>£242</td>
<td>dHMN, CMT2</td>
<td>AD or sporadic</td>
</tr>
<tr>
<td>HSPB8</td>
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<td>Sequencing</td>
<td>£242</td>
<td>dHMN, CMT2</td>
<td>AD or sporadic</td>
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<tr>
<td>DYNC1H1 (exons 5-14)</td>
<td>600112</td>
<td>Sequencing</td>
<td>£561</td>
<td>Atypical CMT2</td>
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<tr>
<td>GDAP1</td>
<td>606598</td>
<td>Sequencing</td>
<td>£387</td>
<td>CMT2/CMT4</td>
<td>AD, AR</td>
</tr>
<tr>
<td>TRPV4</td>
<td>605427</td>
<td>Sequencing</td>
<td>£745</td>
<td>CMT2/ distal SMA</td>
<td>AD</td>
</tr>
</tbody>
</table>

### Useful references
- Classification and diagnosis of the inherited neuropathies. MM Reilly Ann Indian Acad Neurol 2009 12: 80-88
- Inherited Peripheral Neuropathy Mutation Database: http://www.molgen.ua.ac.be/CMTmutations

#### Phenotypes and Inheritance pattern
- **Mild** (70-90%): CMT1, 2, X-linked, proximal involvement, rapid progression
- **Moderate** (10-20%): CMT2, X-linked, distal involvement, slowly progressive
- **Severe** (10%): CMT1, X-linked, dejerine sottas disease (DSD), congenital hypomyelinating neuropathy (CHN), HNPP
- **Proximal** (5%): X-linked, proximal involvement

### Details and Prices Correct at Date of Printing Only.

Information document No.32 Version 24  page 2 of 3
Active date of this version: 15.01.2013

Details and prices correct at date of printing only.
Approved by: Thalia Antoniadi

Exceptional healthcare, personally delivered
UKGTN testing criteria for screening rare genes; this form is not required for the common genes.

Please complete as applicable and return to the laboratory with any additional information available.

<table>
<thead>
<tr>
<th>Referrer</th>
<th>Date of birth</th>
<th>NHS No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consultant Clinical Geneticist</td>
<td>Consultant Neurologist</td>
<td>Consultant Paediatric Neurologist</td>
</tr>
</tbody>
</table>

**UKGTN Testing criteria for EGR2**

- CMT1 or DSS (HMSNIII) presentation; severe early childhood onset degenerative distal demyelinating motor and sensory peripheral neuropathy
  - **tick**
- Or CMT1 or DSS with very slow NCV and peripheral nerve hypertrophy /onion bulbs
- Or CHN diagnosed (congenital hypomyelinating neuropathy) with hypotonia, delayed motor milestones, and absent myelination on biopsy
  - **And** Isolated case or pedigree suggestive of autosomal dominant or autosomal recessive inheritance
  - **And** Exclusion of common forms of CMT1, CHN or DSD (GJB1, MPZ, PMP22)

**UKGTN Testing criteria for NEFL**

- CMT1 of early childhood onset and severe; isolated case or pedigree suggestive for autosomal dominant inheritance
  - **And** Exclusion of common forms of CMT1 (MPZ, GJB1, PMP22)
- Or CMT2 with autosomal dominant inheritance
  - **And** Exclusion of common forms of CMT2 (MFN2, MPZ)

**UKGTN Testing criteria for PERIAXIN**

- CMT1 or DSS (HMSNIII) presentation; Severe early childhood onset, degenerative distal demyelinating motor and sensory peripheral neuropathy.
- Or diagnosed DSS (with very slow NCV, and peripheral nerve hypertrophy /onion bulbs), often with prominent sensory component with ataxia and severe axonal loss
  - **And** Isolated case or pedigree suggestive of autosomal recessive inheritance
  - **And** Exclusion of common forms of CMT1/DSS (GJB1, MPZ, PMP22)

**UKGTN Testing criteria for LITAF**

- CMT1 phenotype with median nerve MCV under or equal to 38m/sec; sensory impairment
  - **And** Isolated case or pedigree suggestive for autosomal dominant inheritance
  - **And** Negative molecular diagnosis of CMT1A, CMT1B, CMTX1, ie absence of a mutation in PMP22, GJB1, MPZ, EGR2 or NEFL especially when patients present median NCVs between 16 and 33 m/s

**UKGTN Testing criteria for Autosomal Dominant Distal Hereditary Motor Neuropathy (BSCL2, HSPB1, HSPB8)**

- Distal muscle weakness /wasting (affecting hand muscles and/or gait difficulty) attributable to motor neuropathy without sensory element
  - **And** Electrophysiology (nerve conduction +/-EMG) shows pure motor nerve involvement, and no sensory involvement and Normal nerve conduction velocity (ie. axonal, rather than demyelination)
  - **And** Onset from 1st decade up to 5th decade of life
  - **And** Family History/ Pedigree suggestive for or compatible with autosomal dominant inheritance or new dominant mutation

**UKGTN Testing criteria for RAB7A**

- Axonal neuropathy with prominent distal sensory loss and autonomic disturbances (NCV may be mildly slowed) and onset in first to fifth decade of life, with pedigree compatible with autosomal dominant inheritance.
  - **And** History of painless injuries and chronic skin ulceration of hands and feet in at least one affected family member.
  - **And** Exclusion of mutations in SPTLC1.