Lessons from London
Michael E Shy

Mutations in more than 50 genes cause the inherited peripheral neuropathies known as Charcot-Marie-Tooth (CMT) disease, distal hereditary motor neuropathies or hereditary sensory and autonomic neuropathies. How to diagnose these disorders is a challenge for clinicians and patients. Murphy et al have provided a simple, rational approach to this challenge in their very nice article published in last month’s issue of the Journal of Neurology, Neurosurgery and Psychiatry. Not only were they able to evaluate over 900 patients they had personally seen in their primary inherited neuropathy clinic but also study results of more than 1000 other patients in whom a diagnosis is currently possible. There is no reason that most practicing neurologists should not focus on these same four genes.3

Nerve conduction velocities in the CMT1 range were not identified in any of the London patients with CMT2A and no patient with CMT1A had nerve conduction velocities in the CMT2 range. Male to male transmission of course excluded a diagnosis of CMT1X and the presence of intermediate conduction velocities made a diagnosis of CMT1B or CMT1X more likely. Thus even within these four genes there are simple steps that can be taken to identify the most likely candidate gene for genetic testing. If the focus is maintained on these four genes there is no reason that most practicing neurologists should not be able to diagnose most patients in whom a diagnosis is currently possible.

A second lesson concerns approaches to take for those patients who do not have mutations within the four common genes. Murphy’s data suggests that these are the patients that one should consider referring to a specialised CMT centre such as the

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(CMT1A) or mutations in three other genes; MPZ (CMT1B), GJB1 (CMT1X) or MFN2 (CMT2A). If no mutation was detected with these four genes there was less than a three per cent chance of making a molecular diagnosis. This was true of course only for patients with autosomal dominant or X linked CMT although as the authors point out, many of these patients may present without a family history. For patients with clear autosomal recessive (AR) CMT the authors found that CMT4C, caused by mutations in SH3TC2 was the most likely cause, at least if the neuropathy was demyelinating. AR CMT can be much more common in non-European or non-North American populations; the results of this study should be interpreted with this in mind. Murphy et al also demonstrated that the chances of making a molecular diagnosis in their population was significantly higher in patients referred to their inherited neuropathy clinic as compared with patients whose DNA samples had been sent to the diagnostic lab alone. Specifically, a genetic diagnosis was made in 63% of patients evaluated in the London CMT clinic as opposed to only 37% of patients not seen in the clinic; these differences occurred in patients with CMT1, CMT2 and ICMT. There are several lessons that come out of the study.

one that exists in the National Hospital in London. The likelihood that any particular gene is causing the neuropathy is low, at best <5% and often <1%. Those working in CMT centres are likely to be familiar with specific features that make particular forms of CMT more likely such as hand predominance in patients with CMT2D (mutations in GARS). Centres are also likely to have specialists including neuro-pathologists with specific peripheral nerve training who are able to perform and interpret nerve biopsies on selected patients such as MTMR2 (CMT4B1) or MTMR13 (CMT4B2) that are associated with characteristic myelin misfolding on EM sections. Perhaps most importantly, with characteristic myelin misfolding on MTMR13 (CMT4B2) that are associated patients such as training who are able to perform and all patients with CMT (63% in Murphy CMT . Using our current methods we will still account for most patients with technologies however it is virtually certain able costs. Even with these emerging on DNA samples at increasingly reason-
other forms of NGS. Comprehensive which the whole genome can be evaluated
diagnose inherited neuropathies. Genetic
testing for CMT is entering a new era in
which the whole genome can be evaluated
by novel techniques such as high-density
genotyping, high-density microarrays and
other forms of NGS. Comprehensive exome sequencing can now be performed
on DNA samples at increasingly reason-
able costs. Even with these emerging
techologies however it is virtually certain
that the same four genes cited by Murphy
will still account for most patients with
CMT. Using our current methods we
already can diagnose almost two thirds of
all patients with CMT (63% in Murphy
et al) including 80% of patients with
CMT1. Patients with novel forms of CMT
diagnosed with NGS are likely to be those
with CMT2 where about two-thirds of
patients can still not be diagnosed. It is
unlikely that the novel forms will have
a single predominant cause, such as in
CMT1A. It is more likely that there will be
multiple rare genetic causes for the
remaining patients with CMT2. Thus it
would behove diagnostic labs that
perform NGS to focus initially on PMP22,
MPZ, GJB1 and MFN2 and only if they
prove uninformative to look at additional
candidates. This is all the more the case
since mutations that alter the coding
sequence in three of the four (PMP22,
MPZ, and GJB1) almost invariably cause
neuropathy and only rarely act as benign
polymorphisms. Thousands of non-

non-synonymous variants that alter the amino
acid sequence of proteins occur in all
individuals and it can be challenging to
determine if any of these cause CMT by
exome sequencing or other NGS
approaches. To interpret results from
NGS DNA from multiple family members
often needs to be analysed and even then
extensive filtering and interpretation of
the data needs to be performed before
a particular mutation can be declared
disease causing. It would seem prudent to
focus on the four common genes before
such analysis is undertaken.

A final lesson from Murphy relates
to CMT centres. A danger of
determining the natural histories of the
patient populations is to consider the
cases as separate entities. In reality,
at least two things are the same in
all cases.

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