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Lessons from London

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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*.¹ 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 whose DNA samples had been sent to the National Hospital for genetic testing. To briefly summarise their results, 600 of the 900 patients (66%) they had personally evaluated had a primary, nonsyndromic genetic neuropathy (425 CMT, 46 hereditary neuropathy with liability to pressure palsies, 61 hereditary motor neuropathies, 69 hereditary sensory and autonomic neuropathies). The 425 patients with CMT consisted of 240 patients with CMT1 (56%), 115 with CMT2 (27%) and 62 with CMT associated with intermediately slowed nerve conductions (ICMT). Ninety-two per cent of those patients with CMT and a genetic diagnosis had either a duplication of Peripheral Myelin Protein - *PMP22* (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;² 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.

The primary lesson is that in the absence of an AR pedigree genetic testing should focus on *PMP22*, *MPZ*, *GJB1* and *MFN2*, at least for patients in European or North American populations. The results in the current issue of *Journal of Neurology, Neurosurgery and Psychiatry* are not unique to London. Similar findings have been reported in USA,³ France⁴ and Northern England.⁵ There is no reason to order testing for any other form of nonsyndromic CMT until these genes have been excluded unless there is a clear AR inheritance pattern. For those practicing in the USA there is absolutely no basis for ordering

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large panels that sequence 15 genes or more and cost approximately \$20 000. There are no reasons to order demyelinating or axonal ‘panels’ that also cost thousands of dollars. There are clear algorithms to follow to guide testing including the straightforward algorithm provided by Murphy *et al.* Another has recently been published by our group with emphasis 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 one that exists in the National Hospital in London. The likelihood that any particular gene is causing the neuropathy is low, at best <3% 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*).⁶ Centres are also likely to have specialists including neuropathologists 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.⁷ Perhaps most importantly, investigators that are trying to identify molecular mechanisms of demyelination or axonal loss typically work in specialized CMT centres. It is only by evaluating patients with rare forms of CMT that they are truly able to identify these mechanisms.

It will be important to consider results from the Murphy paper as we begin to use next-generation sequencing (NGS) to 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 reasonable costs. Even with these emerging technologies 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*¹) 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 nonsynonymous 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.⁸ 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 again to when to consider referring patients to CMT centres. A danger of deciding whether to refer is that it can foster an ‘us versus them’ philosophy. The truth is that the best way to provide real service to patients with inherited neuropathies is to develop a true collaboration between individual caregivers and specialised centres. One of the beauties of the inherited neuropathies is that patients have known genetic causes of their disease. Because the cause is known, researchers can focus on identifying molecular mechanisms of demyelination, axonal degeneration or abnormalities in glial-axonal interactions. However researchers cannot identify mechanisms without having access to patients. Determining the natural histories of the common forms of CMT or whether modifier genes can alter the phenotype of frequent forms cannot be performed without the referral of large numbers of patients. Therapies cannot be developed and placed back in the hands of individual clinicians without this research. The development of rational therapies for patients with inherited neuropathies depends on ongoing partnerships between individual clinicians and CMT centres such as the excellent centre in London.

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