Highlighting the past and future of inherited peripheral neuropathies

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Inherited peripheral neuropathies (IPN) are among the most common inherited conditions in Neurology and are still largely not treatable. It is thus of great medical and public interest to understand IPN aetiologies more fully and enable the rational development of therapeutics. Similar to other inherited neurological disorders, the diagnostic gap is still substantial for IPN with an estimated 50% of patients not being genetically resolved after state-of-the-art genetic work-up. Families without a molecular diagnosis often face an extended diagnostic odyssey. In their *JNNP* paper, Parmar *et al* provide a timely and comprehensive review of the current state of IPN genetic diagnostics and also suggest six key research strategies to reduce the diagnostic gap.[1] This review meticulously lists 73 genes identified since 2012. Importantly, 30 of these genes cause multiple phenotypes and IPN is only one of several medical symptoms. Taking into account this overlap of classic disease entities widens the circle of genes to consider and appreciates the fact that IPN can be caused by every known Mendelian trait, by risk or incomplete penetrance genes, and by nearly any known disease-causing molecular genetic mechanism. Some genetic variant classes may indeed be difficult or impossible to detect by current standard testing methods. Examples include complex structural variants, translocations and regions of high homology. Fortunately, the recent maturation of long-read genome technologies is beginning to catalogue the vast extent of structural variation in the non-coding genome, at the population level. This review and perspective paper convinces the reader of the extraordinary opportunities ahead for the genetics of rare diseases. This optimism is also evidenced by much improved data-sharing expectations, data analysis tools and available public data resources. The review acknowledges the exceptional role of the allele frequency database gnomAD and that the GENESIS database, which houses the majority of the Inherited Neuropathy Consortium data, has contributed to at least one-third of all IPN gene discoveries in this time frame. The wealth of quality data and studies in the IPN field allowed for an impressive illustration of key arguments with impactful examples. This includes the possibly surprising fact, that already several repeat expansion loci are known to cause IPN, such as the *RFC1* gene, which constitutes a common cause for sensory neuropathy. Further, examples like the SORD gene demonstrate how genetic findings in a difficult-to-resolve gene–pseudogene homology region have led to a multicentre clinical trial within less than 24 months. Finally, known IPN genes contain thousands of variants of uncertain significance (VUS) that are difficult to classify according to pathogenicity. This constitutes a major detriment for IPN genetic diagnostics. In fact, as more IPN genes are discovered and ultimately tested in patients, the genomic space of interest grows and the number of VUS inevitable increases substantially. Parmar *et al* discuss this topic thoughtfully and suggest strategies for improvement, including new high-throughput functional approaches such as multiplex assays of variant effect (MAVE). Resolving VUS are highlighted as a major opportunity to arrive at a more definite diagnosis for many current patients. In summary, this work will serve the interested reader well as an encyclopaedic reference for this topic.

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