In summary, this study provides valuable evidence that sphenopalatine ganglion stimulation benefits patients with chronic cluster headache. Like most good studies, it raises new questions in addition to providing answers. Patients badly need more treatment options, and hopefully this therapy will be available in the near future, although the sponsor of this study has gone out of business because of financial issues, which could delay further developments.

Werner J Becker
University of Calgary, Calgary, AB, Canada; and Chronic Pain Centre, Richmond Road Diagnostic and Treatment Centre, Calgary, AB T2T 5C7, Canada
wbecker@ucalgary.ca

I have served on medical advisory boards and received speaker's honoraria from Allergan, Novartis, and Weber and Weber.

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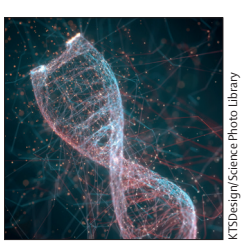
Challenges in disentangling the genetic background of Parkinson's disease

For more than two decades, it has been acknowledged that Parkinson's disease is genetically heterogeneous, and that large-scale studies are required to identify relevant genetic variants with small to modest effects.[1] The meta-analysis of genome-wide association studies (GWAS) of non-monogenic Parkinson's disease, reported by Mike Nalls and colleagues[2] in *The Lancet Neurology*, is the most comprehensive study to date on the genetic background of this complex disease. Clearly exemplifying the merits of large-scale aggregation of data, this work also illustrates some of the challenges in disentangling the genetic background of complex diseases.

The first challenge relates to the use of the results from GWAS for explaining heritability and informing genetic testing. Nalls and colleagues have identified 90 independent variants with promising functional associations; however, a large proportion of the heritability is still unexplained. This reduces the hope for the use of broad genetic testing in the near future, beyond the few Parkinson's disease genes that unequivocally have a causal role when mutated. To identify even more relevant variants, at least two avenues could be taken. The obvious method is to increase sample sizes even further to detect variants with yet smaller effects. However, the novel loci identified by Nalls and colleagues increased the odds for Parkinson's disease by as little as 1·05,[2] and to detect even smaller changes in risk, sample sizes of more than half a million individuals would be required. Another potentially promising method is to make use of the heterogeneity of Parkinson's disease and investigate subgroups defined by features such as age at onset and motor and other clinical characteristics,[3] as different phenotypic groups might have different genetic causes.[4] Given that, even within pedigrees, clinical features can differ to a relevant extent across carriers of the same familial mutation, selecting phenotypes that might be indicative of the cause will be an essential but difficult step. On a related note, extending the focus to less investigated ethnic groups is not only ethically mandatory, but also a promising lead to identify more underlying disease variants.

A second challenge of modern GWAS relates to the knowledge they provide on functionality and causality in complex diseases such as Parkinson's disease. GWAS originally set out to solve some of the problems of previous genetic epidemiological studies—such as difficulties in recruitment of families in linkage studies and risk of false-positive results in candidate association studies. However, one drawback of association studies compared with linkage studies is that an association can be caused also by other confounding factors, making it more difficult to show causality of the genetic loci. Indeed, the original hope that using single nucleotide polymorphisms as markers would directly identify the culprit via direct association has only seldom been fulfilled.[5] For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instance, most of the 90 variants identified by Nalls and colleagues[2] are either in introns or intergenic regions.

Thus, a meta-analysis of GWAS is just the starting point, requiring further functional analyses; Nalls and colleagues[2] went to great efforts to gain insight into the functionality of the identified variants by using tissue-specific expression, methylation, rare variants, and non-genetic risk factors. Importantly, use of additional data and statistical tests raises the probability of false positive results. Because the statistical tests are not independent from one another, adequate adjustment for multiple testing is not straightforward. Caution is thus needed when interpreting findings considered to be significant. Particular caution is required for results from Mendelian randomisation studies, which contribute substantially to the work by Nalls and colleagues.[2] In general, accounting for the number of tests requires knowledge of how many hypotheses are being tested, but this number can be established only if the non-genetic risk factors that are investigated are defined a priori. However, when selective reporting of findings occurs, the denominator of tested hypotheses is unknown, thus making it impossible to evaluate the significance of a finding.

Nalls and colleagues provide the most complete picture of the genetic background of Parkinson's disease to date. Although direct practical consequences cannot be drawn from their findings yet, they have provided the groundwork for future studies, which is likely to yield exciting results soon. Tackling the general challenges, as described above, will be a task for the broader scientific community.

Inke R König
Institut für Medizinische Biometrie und Statistik, Universität zu Lübeck, Universitätsklinikum Schleswig-Holstein, Campus Lübeck, 23562 Lübeck, Germany
inke.koenig@imbs.uni-luebeck.de

I declare no competing interests.

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Serum neurofilament light chain as a preclinical marker of neurodegeneration


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To date, most clinical trials of disease-modifying drugs for neurodegenerative diseases, namely Alzheimer's disease, have been unsuccessful, mainly due to the inclusion of patients with too advanced disease.[1] One explanation is that, once the pathophysiological process overcomes the clinical threshold, the excessive neuronal loss could make the therapeutic intervention ineffective. Besides the overarching need for a timely diagnosis, the possibility of detecting neurodegeneration before the appearance of clinical symptoms is captivating.

Genetic forms of neurodegenerative diseases represent a unique model for studying the presymptomatic phases of these disorders, since they allow for a better understanding of biomarker dynamics at the stages before clinical manifestations. In *The Lancet Neurology*, Emma L van der Ende and colleagues[2] report their investigation of the longitudinal trajectories of serum neurofilament light chain (NfL), a sensitive and reliable biomarker of neuronal damage,[3] in a large international multicentre cohort of individuals carrying different genetic mutations for frontotemporal dementia (namely mutations in GRN, C9orf72, or MAPT) and their healthy first-degree relatives who were followed up for about 2 years. The authors looked at the differences in serum NfL concentration over time between presymptomatic carriers who did not develop frontotemporal dementia during follow-up (n=140), presymptomatic carriers who developed the disease during follow-up (ie, converters; n=9), symptomatic carriers (n=59), and healthy non-carriers (n=127). Changes in NfL were correlated with longitudinal imaging and clinical parameters, after adjustment for age, sex, and study site.

At baseline, healthy participants had the lowest serum NfL concentration, followed by presymptomatic mutation carriers, converters, and symptomatic carriers, which highlights NfL as a marker of disease intensity. During