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Headaches and polygenic scores

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Page e364

Polygenic risk scores are en vogue. This ubiquitous statistic quantifies disease liability for an individual by aggregating risk contributions from a large number of genetic variants into a single score. Recent publications have argued that risk models currently used in clinical settings for coronary artery disease can be improved by including polygenic risk scores.[1,2] Similarly, polygenic risk scores have shown promise in improving breast cancer risk prediction[3] and are already routinely used by direct-to-consumer genetic testing companies, such as 23andMe, to estimate disease risk. Now, in this issue of *Neurology® Genetics*, Kogelman et al.[4] find that the polygenic risk score for migraine, a common headache disorder that is thought to affect about 18% of the population[5] and estimated to be quite heritable (between 34% and 57%),[6] correlates with triptans treatment response when treating migraine. However, there is no reason for people having migraines to rush and get genotyped. First, the treatment response effect was found to be small (but significant). Second, although Kogelman et al. accounted for population structure in their statistical analysis, it is hard to rule out other sources of confounding. Third, it is very difficult to estimate population risk, or conditional risk, as the sample used in this study (and most other studies) is of course ascertained (nonrandom sample). Fourth, if in doubt about the treatment response, why not try the drug?

Even without a clear case for using genetic testing and polygenic scores when treating migraine, the work by Kogelman et al.[4] and others[7] provides a strong argument for more research on whether polygenic scores can predict treatment response and to what extent. This is of course not a new suggestion.[8] This is what pharmacogenomics is about—namely, studying the genetics of drug responses. Indeed, genetic testing for drug responses is already routinely used in clinical settings when prescribing specific drugs.[9] It is therefore not hard to imagine that polygenic scores, which can be viewed as a genetic test that includes more than 1 genetic variant, can improve drug response predictions. To illustrate this further, let us imagine a polygenic disease with 2 common subtypes for which the genetic architecture is different. If a drug is only effective in treating the first subtype, a polygenic prediction distinguishing between the 2 would of course also predict the drug response. How common such examples are in practice of course remains to be seen.

Toward a data-driven prediction approach

Risk prediction is common in clinical settings. For example, most pregnant women currently undergo an ultrasound to measure nuchal fold thickness, which (together with other risk factors) is used in many countries to screen for chromosomal abnormalities. Similarly, genetic variants, metabolites in blood, age, body mass index, and other individual-level data may tell a story for other diseases and disorders. The challenge is to identify what clinically relevant questions are we interested in answering, and which ones can we answer with the available data, including genetic data. As genetic data sets continue to grow rapidly, we expect them to become more relevant in clinical settings.

When considering applying polygenic scores in clinical settings, it is important that it rigorously validated in terms of accuracy and how useful it is.[10] First, the validation sample

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should be fully independent (from the training sample). Second, biases due to population structure or other confounders should be accounted for. Third, the validation sample must represent the population or subpopulation on which it will be applied and be large enough to report meaningful accuracies. Fourth, it is important that any proposed model is benchmarked against current practices and models currently used. This includes examining relative gains in prediction accuracy compared with currently used approaches. This is especially important if the aim is to use it in clinical settings. Finally, clinical relevance and value should be considered carefully, as genetic screening comes with a cost, both economical and sometimes a significant psychological cost that can easily outweigh benefits.

Author contributions

B.J. Vilhjálmsson/F. Privé: drafting/revising the manuscript.

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