Polygenic Risk Scores Could Become Useful Tools in the Physician's Toolbox

Researchers perform large genome-wide association studies with the Global Screening Array to identify disease-associated DNA risk loci and develop PRSs for clinical validation.

Introduction

In an era where genetic testing is becoming more affordable, preventative and personalized medicine approaches are slowly nearing reality. Genetic tests for monogenic diseases, such as cystic fibrosis or Huntington's disease, that are caused by a single mutation have been in use for over a decade. However, researchers are still in the early stages of developing genetic risk assays for complex diseases, which are caused by thousands of DNA code variants (risk loci) that act together with environmental factors. Complex diseases are far more common in the population and vary greatly, from heart disease and cancer, to depression, amyotrophic lateral sclerosis (ALS), and glaucoma.

Using array technologies to perform genome-wide association studies (GWAS), researchers are searching for gene mutations associated with complex disease. At the University of Queensland, the Infinium™ Global Screening Array (GSA) is being used to identify complex disease–associated DNA risk loci to generate polygenic risk scores (PRSs). In addition to their potential in preventive medicine, PRSs might also be effective tools contributing to disease diagnosis and informing personalized medical treatments.

iCommunity spoke with several researchers at the University of Queensland and the QIMR Berghofer Medical Research Institute in Brisbane, Australia. Naomi Wray, PhD, is a Professor of Psychiatric and Quantitative Genetics at the University of Queensland studying the genetics of psychiatric and neurological disorders. She also co-leads the Program in Complex Trait Genomics (PCTG), which studies the genetic basis of common, complex diseases and traits. Peter Visscher, PhD, is a Professor of Quantitative Genetics at the University of Queensland studying the genetic basis of complex traits and disease and co-leads PCTG. Stuart MacGregor, PhD, is the head of the Statistical Genetics Laboratory at the Queensland Institute studying the genetic basis of disease in glaucoma. David Evans, PhD, is a Professor of Statistical Genetics at the University of Queensland Diamantina Institute using GWAS and other statistical techniques to map complex genetic traits.

Their varied backgrounds contribute to a multifaceted effort to decipher the causes of complex disease and understand how PRSs could enable clinicians to predict, diagnose, and treat patients in the future.

Q: How much of a role does genetics play in complex diseases compared with other factors?

Naomi Wray (NW): While common complex diseases are influenced by genetics, some are more heritable than others. We can measure the heritability, or relative contribution of genetic factors to a disease liability, by first comparing the incidence of disease in relatives of those with and without the disease.

Peter Visscher (PV): We know from family and twin studies that one- to two-thirds of individual differences between people are due to genetic factors and the rest are due to environmental risk factors.

Stuart MacGregor (SM): The role of genetics depends on the complex disease in question. My lab focuses on glaucoma. There are essentially no environmental factors associated with the disease. In fact, glaucoma is one of the most heritable human diseases. A small proportion of cases carry rare high-penetrance mutations, allowing genetic testing in some families. For the majority of glaucoma cases, however, we've shown there is a major contribution of common risk loci that individually have a small effect, but collectively play a major role in determining a person's risk.

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Q: What are some of the non-genetic factors that contribute to complex disease?
NW: Lifetime stress and childhood trauma are environmental factors associated with psychiatric disorders. Environmental toxins might be risk factors for neurological diseases.

David Evans (DE): Diet and vitamin D are environmental factors that could affect whether someone gets osteoporosis.

PV: Non-genetic risk factors for cancer include whether you smoke or not, while age is a risk factor for late-onset dementia. For most environmental risk factors, we can only quantify the variation that they contribute in total. We haven't yet managed to pin down the percentage variation that each individual environmental risk factor contributes.

> "A PRS represents the genomic profile of an individual based on all the known risk loci for that disease."

Q: How are genes associated with complex disease identified?
NW: We've known for a long time that complex diseases have a genetic component. It's only in the last 10 years that we've had the array technology to measure the DNA code of a person at hundreds of thousands of places genome wide.

DE: In order to identify genes associated with complex diseases, we perform GWAS. These are large-scale genetic studies using samples from potentially hundreds of thousands of individuals with and without the disease. With GWAS, we can compare the genomes of individuals with the disease against healthy controls to see if the frequency of genetic variants differs between the two groups.

NW: We need thousands of samples because we're assessing so many locations in the DNA. This enables us to better separate the true signals from the background noise.

SM: In our glaucoma research, we study common and rare variants to understand who is at higher risk of developing glaucoma. We performed the first GWAS study on 600 blinding glaucoma cases using Infinium Omni 1M arrays ~10 years ago. We progressed to larger studies with > 3000 subjects (using the OmniExpress and Infinium Core arrays) to link genotype with phenotype, identifying 13 variants. Our most recent work includes the GSA and has identified many more loci.

Q: What is a PRS?
NW: A PRS represents the genomic profile of an individual based on all the known risk loci for that disease. Every one of us carries risk loci for every common disease. It's when we carry a high number of these risk loci that we have a higher chance to be affected by that disease sometime in our life.

To determine a PRS, we use the risk alleles identified in a GWAS. In the person whose risk we want to assess, we count how many risk alleles they have. In fact, we usually weight the count by the effect size estimated in the GWAS, recognizing that some alleles have a greater risk effect than others. Each person is likely to carry their own unique combination of risk alleles. A PRS can be viewed like a biomarker, just like a cholesterol test is a biomarker for heart disease.

Q: How could PRSs provide predictive information?
NW: There is a recognized need to provide earlier diagnosis for psychiatric and neurological diseases. For example, in neurological diseases, diagnosis can take several months while tests are conducted to exclude alternative diagnoses. In the context of psychiatric disorders, young people present in a prodromal phase, the period between the appearance of initial symptoms and the development of more diagnostically specific ones. PRSs of psychiatric disorders might help contribute to clinical decision making. These are important questions that need further research.

PV: PRSs are already being used in select cases, such as differentiating between Type I and Type II diabetes. In the future, PRSs could be useful in getting people who are at risk for developing a specific disease to change their lifestyle. Preventing disease is significantly more cost-effective than treating it.

SM: Glaucoma is a slow disease that develops over many years. People often don't realize they have it until it's too late and irreversible blindness has occurred. Using PRSs we hope to identify people who are at the highest risk for developing glaucoma. We've found that people in the top 10% of glaucoma PRSs get the disease 10 years earlier than those in the bottom 10%. It's important that we identify these people before disease onset. Although we have effective treatments to lower intraocular pressure (such as eye drops and surgery), these treatments need to be applied early in the disease to be effective.

> "With GWAS, we can compare the genomes of individuals with the disease against healthy controls to see if the frequency of genetic variants differs between the two groups."

Q: How could PRSs help doctors treat patients?
PV: I believe that PRSs will be used in several ways within a clinical setting in the next 10–20 years. In addition to being used as predictive medicine tools, PRSs will contribute as first-line diagnostic tools at the primary point of care, just as cholesterol tests and X-rays are used today.

NW: I can see a day when someone arrives at a clinic presenting certain symptoms, and a PRS algorithm will be applied to their stored genetic data. I can also see GWAS being conducted to

compare subjects who have responded well to a therapeutic and those who haven't. The data from those studies could tell us the PRS profiles of which drugs should be given to which patients.

SM: We have initial indications that PRSs can predict the loss of ganglion cells, which are cells in the eye that carry visual information to the brain. Even after accounting for traditional risk factors, we found that PRS data are more predictive than clinical factors as to whether a person is likely to need glaucoma surgery to lower intraocular pressure. PRSs also show promise in predicting the people who are at greatest risk of developing a more advanced or blinding form of the disease. These examples show how PRSs could be used to make clinical decisions that improve outcomes.

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Q: How can PRSs help your respective diseases of interest?

NW: I am involved in the Genetics of Depression study, an Australia-wide GWAS led by my colleague, Professor Nick Martin at the QIMR Berghofer Medical Research Institute. Depression is a particularly heterogeneous disorder. We are grateful that 15,000 Australians who have suffered depression provided DNA samples and completed detailed online questionnaires that asked about lifetime environmental risk factors, such as stressful life events and childhood trauma, and about antidepressants that did and didn't work. Many people suffering from depression will cycle through different antidepressants until they find the one that works for them. We're performing GWAS with the GSA to obtain the DNA variant data to unravel that story. We hope that this study will give us a better understanding of the genetic risk loci associated with major depression and response to treatment. In the long run it might be possible to develop PRSs to inform antidepressant choice.

DE: We're investigating how useful PRSs could be in predicting osteoporosis and fractures. The largest known risk factor is bone mineral density, which is a very heritable trait. If we could tell someone ahead of time that they're at a high risk of developing osteoporosis, then there are certain things that person could do to mitigate the risk of disease in the future, such as engaging in weight-bearing exercises and, perhaps, dietary supplementations and modifications.

SM: One model for screening glaucoma is for people to obtain PRS screens early in life, with those at high risk screened regularly at the ophthalmologist. Those with normal risk could be screened again in their 40s or 50s. The data might indicate that they'll get glaucoma in 5-10 years, giving their optometrist or ophthalmologist time to determine the best treatment options. Or they'll receive good news and be told that they have the eyes of a 50 year-old when they're 65.

Q: How will PRSs transfer across different populations?

SM: The PRSs that researchers have computed so far were predominantly in individuals of European descent. In our studies, we've found that the common variants for glaucoma are mostly shared across populations. There's good overlap in these glaucoma loci among Asian and European populations[1-3]. We also tested a PRS for glaucoma in a population with South Indian ancestry and the PRS works almost as well as it does in Europeans, which is exciting. It's an open question whether PRSs will transfer across populations more broadly.

> "Our goal is for PRSs to become an effective tool for glaucoma screening, enabling earlier treatment paradigms that slow disease progression and allow people to see their loved ones, participate in activities, and lead fuller lives."

Q: What are the next steps in transitioning PRSs from the research setting into the clinic?

NW: It will be exciting to see how PRSs transition into the clinic in the next few years. We'll concentrate first on the diseases where PRSs have demonstrated a high utility in a research setting. We might need to conduct clinical trials to evaluate PRSs properly in each individual disease. We tend to lump common diseases together and that's not the correct way forward. These diseases have different genetic architectures, different contributions of genetics to their etiology, and different numbers of risk loci, and different intervention strategies.

DE: I think four things need to happen to move PRSs from the research setting into the clinic successfully. First, we'll need to do a better job of constructing PRSs to enhance their use in clinical situations. For example, how do we handle the question of linkage disequilibrium between variants? How do we include family and environmental information in the risk score? Second, we'll need to validate PRSs. Most PRSs have been derived from large case control studies, so we'll need to validate them in independent clinical populations. Third, we will need the infrastructure to perform PRS assays routinely in our health systems. Finally, we'll need to educate clinicians so they are able to interpret the reports correctly so that they can treat patients accordingly.

SM: We've already built a model for predicting glaucoma risk with PRSs and are working to improve it. We're using larger training sets of GWAS data, testing different statistical models to

incorporate the information more effectively. We hope to apply these in randomized trials to validate the approaches and determine practical application of PRS data in glaucoma. Our goal is for PRSs to become effective tools for glaucoma screening, enabling earlier treatment paradigms that slow disease progression and allow people to see their loved ones, participate in activities, and lead fuller lives.

> "The precision of PRSs will depend on how heritable a trait or disease is. Its accuracy will depend on the GWAS sample size used to identify disease-associated genetic variants. "

Q: What are the important considerations for researchers conducting PRS studies?

PV: If you were to create PRSs for traits that haven't been done before, the first thing would be to extract as much information as possible from the GWAS data using the best analytical approaches and algorithms. The second is to validate them in completely independent samples. And the third consideration is to determine whether these PRSs will have utility. Could the data change the course or treatment of a patient's disease?

SM: It's important to keep in mind that even if a disease is highly heritable, environmental factors might play a role. You will need to map enough genes using large-scale GWAS to identify risk factors so your risk prediction is accurate. Ultimately, the heritability of the trait places a limit on the predictive accuracy of the test.

PV: The precision of PRSs will depend on how heritable a trait or disease is. Its accuracy will depend on the GWAS sample size used to identify disease-associated genetic variants. GWAS of hundreds of thousands or millions of samples are necessary to ensure PRS accuracy.

NW: Complex diseases are common in our society, costing a significant amount of money to diagnose and treat. Even a small improvement in the health economics of a few of these diseases would make a significant impact in the long run. But it will be important for researchers not to overpromise what PRSs can deliver, the value may be small for an individual but large combined across the population.

Q: How will new genetic technologies impact PRS research and clinical medicine in the future?

NW: Advances in disease research during the last 10 years were driven by advances in technology, such as sequencing and arrays. I think the technologies developed in the next 10 years will be equally disruptive.

I believe the limiting factor in the development of PRSs as clinical tools will be people. Up until now, we've conducted our studies on historically collected cohorts of cases and controls. We have very little clinical symptom information. If everyone contributed DNA together with their medical records, it would help advance science and ultimately health care, as we would be able to better relate genetic features to clinical symptoms. We're trying to change that in our Genetics of Depression study, but data for research needs to be collected routinely as part of the health care system.

PV: GWAS has been tremendously successful. They've only been used for a decade and have led to numerous discoveries. In the future, I think GWAS using SNP arrays will be replaced by whole-genome sequencing (WGS). WGS captures all genetic variants that exist in a population, not just common variants, but at the moment array technology is more affordable.

PV: I believe that the value of PRSs is limited purely by what we actually measure. The more GWAS that we perform and the more PRSs we produce, the more PRSs will be used in the future for prevention, diagnosis, and precision medicine.

SM: I think it will become routine for people to have their PRSs computed for a range of diseases shortly after they are born. People will literally have their PRSs at their fingertips. It will enable them to modify their lifestyles if, or when, necessary, and inform their PRS screening frequency and treatment decisions.

Learn more about PRSs from leading researchers:

PRS video, www.illumina.com/company/video-hub/3HjHSRjwiQk.html

Learn more about the product mentioned in this article:

Global Screening Array, www.illumina.com/products/by-type/microarray-kits/infinium-global-screening.html

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