Scientist spotlight

Mining the multiethnic Brazilian population for genetic risk factors in cardiovascular disease and Sars-CoV-2 exposure

Introduction

Predictive genomics holds the power of turning genetic data from populations into predictions of disease risk or drug response for people. Population genomics studies are already beginning to yield insights that may provide new treatment options and more positive clinical outcomes in the future. As understanding of how individual genotypes impact our susceptibility and response to disease and treatment grows, so do discoveries that reveal important differences based on geography and ethnicity. With the Applied Biosystems™ Axiom™ Precision Medicine Research Array, Axiom™ Precision Medicine Diversity Array (PMDA), Axiom™ Asia Precision Medicine Research Array (Asia PMRA), and Axiom™ SARS-CoV-2 Research Array researchers can assess human disease-associated variants genome-wide across a wide range of ancestral groups.

We spoke to Alexandre Pereira, a Principal Investigator at the Laboratory of Genetics and Molecular Cardiology at Sao Paulo University Heart Institute to learn more about his research using population-based predictive genomics to build understanding of unique determinants of cardiovascular disease, as well as responses to SARS-CoV-2 exposure, in the Brazilian population.

The Sao Paolo University Laboratory of Genetics and Molecular Cardiology provides complete infrastructure for research and development (R&D) in genetics and molecular cardiology funded by Brazilian federal and state development agencies. The Laboratory integrates bottom-up and top-down approaches to identify genetic determinants associated with cardiovascular diseases and to develop novel therapeutic approaches for cardiac repair.

Alexandre Pereira, MD, PhD, São Paulo University Heart Institute; Leader of Human Genetics, Laboratory of Genetics and Molecular Cardiology; Head of Genetics Outpatient Clinic

Thermo Fisher Scientific: Why did you choose microarrays, and specifically Axiom arrays, for your large-scale genome-wide association studies (GWASs)?

Alexandre Pereira (AP): We have been using microarrays for years. It was the first technology that could be used at scale for

genotyping. We in the Brazilian genetics research community are leveraging epidemiological studies with hundreds of thousands, or even millions, of samples. In Brazil, cost is important because most labs can't afford to employ large-scale next-generation sequencing (NGS) systems. The ease of bioinformatics analysis with microarrays is also valuable for labs with constrained resources and lack of extensive bioinformatics capabilities. Microarrays enable us, as a core lab, to provide large-scale genotyping data at affordable pricing.

Many years ago, we worked with Affymetrix (now part of Thermo Fisher Scientific) to develop a customized array to establish a Brazilian human genome biobank. More recently, we started using the Axiom arrays as they evolved to include more comprehensive markers for diverse populations. Now we use the Axiom PMRA and Axiom Human Genotyping SARS-CoV-2 Research Array. The quality is very robust and the data is very consistent. Different labs can compare data across multiple studies.

Thermo Fisher Scientific: What is the importance of predictive genomics in your work?

AP: We are studying the environmental and genetic predictors of a key modulator of LDL cholesterol levels in serum, PCSK9. Inhibiting PCSK9 is an established therapy to treat hypercholesterolemia. Gain-of-function mutations in the PCSK9 gene can cause familial hypercholesterolemia and increased risk of developing cardiovascular disease. Conversely, loss-of-function mutations are associated with low LDL cholesterol and reduced cardiovascular risk.

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Alexandre Pereira, MD, PhD

We used the Axiom PMRA to genotype multi-ethnic DNA samples from the ELSA-Brasil study. The study contributes clinical phenotype information and genomic DNA from about 15,000 people regarding the development and progression of chronic diseases including cardiovascular disease. Leveraging the biobank made our study financially feasible.

In a recent study using the Axiom PMRA, we identified PCSK9 loci that were different in Brazilians from European descent than Brazilians from African descent. Ultimately, understanding environmental and genetic predictors of PCSK9 levels in different ethnic populations may help to identify new targets for cardiovascular disease treatment and contribute to better assessment of the benefits and risks of PCSK9 inhibition as a long-term therapy. Many biobanks are doing this and we believe the Brazilian population can significantly contribute to this enterprise.

Thermo Fisher Scientific: How will your work impact health care in Brazil?

AP: Cardiovascular disease is the number one cause of death in Brazil. It has a similar impact on healthcare as in the United States, but in Brazil hypertension seems to have a larger relative importance whereas in the United States it is obesity. We want to understand both genetic and social determinants of cardiovascular disease in Brazil.

Race is an important factor. Brazil has one of the most admixed populations in the world, with strong European, African, and Native American origin populations. Earlier population genotyping studies only included North American and Northern European white populations. Those were the populations that were most accessible at the time, and consistency was important to establish the technology for the early studies. As GWASs are revealing differences across ethnicities, it is becoming more important to include diverse populations in genomics studies. In Brazil, cardiovascular disease risk is very population specific. Polygenic risk scoring will be different for varying populations across the country. The Axiom arrays cover a wide range of ancestral population groups, so now we can begin to incorporate a wider range of ethnicities across Brazil in our studies.

During the COVID-19 pandemic, in addition to our work in cardiovascular disease we are also participating in a large GWAS of SARS-CoV-2-infected people in Sao Paulo. Brazil is one of the countries that has been hardest hit by the SARS-CoV-2 pandemic. Twenty months after the start of the spread, about 13% of deaths worldwide were in Brazil. The study is investigating genetic associations with the wide range of individual responses to exposure to the virus within the Brazilian population.

Using the Axiom PMRA array and the Axiom SARS-CoV-2 Research Array, we have identified a new genome-wide locus that is associated with COVID-19 hospitalization in the Brazilian population and might play a role in regulating immune responses to SARS-CoV-2 infection

Thermo Fisher Scientific: What challenges do you face as a genotyping core lab?

AP: We do all the non-commercial genotyping for Brazil. The challenges are huge. We need to support many investigators whose data we will also leverage in our own studies. Having the right infrastructure is essential for population-scale sample sizes. We're at the stage of building infrastructure that will encompass polygenic risk scoring, biological determinants, and other factors to support studies on the scale of ELSI and ELSA.

However, funding for life science research and development in Brazil has dropped over the past five years. The entire research ecosystem is stressed. It's very important to me to keep the population genomics research infrastructure that we have built over the last few decades.

Thermo Fisher Scientific: What do you most appreciate about working with Thermo Fisher Scientific?

AP: The technical support we get is amazing. We have a very experienced technician in our lab and Thermo Fisher Scientific experts are always in contact with her. We only have one instrument so if it isn't running, we would have to stop providing microarray genotyping services. Getting fast and reliable troubleshooting is a must. Thermo Fisher Scientific also helps us when our collaborators ask for help with analysis. This is very important because not all research groups who want to harness genetic information from their studies have the needed bioinformatics resources.

Thermo Fisher Scientific: What excites you most about the future of genomics for health care in Brazil?

AP: With the capabilities of microarrays, looking at genetic determinants for heterogeneous populations will definitely allow us to find new things. This new biology might point to new disease mechanisms or new therapeutics and, as has happened for other populations, may help research and therapeutic development worldwide.

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