The Pharmacogenetics of Cardiovascular Disease Therapy

Researchers at the Montreal Heart Institute used the Infinium® HumanOmni2.5Exome BeadChip to identify responder genotypes in a failed cholesterol drug trial.

Introduction

The success rate of late-stage clinical trials is estimated to be 25–50%[1]. Could a reason that so many drugs fail be that their efficacy varies across genetic profiles? That's what Marie-Pierre Dubé, PhD and her colleagues at the Montreal Health Institute (MHI) have set out to determine. As the director of the Beaulieu-Saucier Pharmacogenomics Centre at MHI, Dr. Dubé collaborates with pharmaceutical companies to look for the genetic determinants that modulate the efficacy and safety of cardiovascular therapeutics.

Dr. Dubé and her team, along with Jean-Claude Tardif, MD, focused their first study on dalcetrapib, a cholesterol-lowering drug candidate that failed to reduce cardiovascular adverse events in subjects who received it in Phase 3 clinical studies. The MHI team investigated the pharmacogenomics of subject response using the Infinium HumanOmni2.5Exome BeadChip. They analyze DNA samples collected as part of the dalcetrapib clinical trials program and identified the genotypes of responders and nonresponders[2].

iCommunity spoke with Dr. Dubé about her pharmacogenomics studies and how Illumina technologies are making them possible.

Q: What sparked your interest in pharmacogenomics?
Marie-Pierre Dubé (MPD): I became fascinated by the analytical aspect of genetics as an undergraduate student at McGill University and later focused my PhD studies on developing new statistical approaches to genetics. During my post doc in public health, I became more interested in population approaches and epidemiology. A subsequent job at a biotech company gave me experience working with extreme phenotypes for drug discovery. That has really defined my current interest in pharmacogenomics, the study of an individual's unique genetic response to medications.

Q: What are the genetics behind drug response?
MPD: There are 2 genomic aspects of drug response. One of them has to do with the pharmacodynamics, changes in efficacy related to drug target or phenotypic aspects. The other is pharmacokinetics, which has to do with how a drug is transformed, absorbed, metabolized, and excreted. Genetic variations in proteins directly or indirectly involved in any of those processes could modulate drug response.

Q: How has the field of pharmacogenomics changed over the past decade?
MPD: There was a lot of hype about pharmacogenomics 15 years ago and it's been slow to deliver on its promise. Pharmacogenomics was first used to identify genetic factors of adverse response, but there has been a major shift in the field recently. Today genetics is being seen more and more as a valuable tool to identify efficacy factors. We're now seeing drugs launched with companion diagnostics that were developed based on pharmacogenomic data. For example, we're seeing the integration of companion diagnostics for genotype-dependent therapeutics in treating breast and lung cancer.

Q: What recent technologies are making pharmacogenomics possible?
MPD: The genomic tools available today have really advanced the field of pharmacogenomics. Illumina has been a strong player in the field and its arrays and sequencing systems are enabling population approaches to genomics. In this case, those tools are enabling efficient analysis of data from very large clinical trials.

Q: What is dalcetrapib and what was it developed to treat?
MPD: Dalcetrapib is a cholesterylester transfer protein (CETP) inhibitor developed by Roche. It raises HDL cholesterol, which people sometimes refer to as 'good cholesterol.' A large body of epidemiological evidence supports the idea that higher HDL cholesterol is better for you; it prevents cardiovascular disease in general and myocardial infarction specifically. In May 2012, Roche ended its dal-OUTCOMES dalcetrapib clinical trial program because an interim analysis showed that it did not significantly reduce cardiovascular adverse events in the nearly 8000 people who received the drug, although it successfully increased HDL cholesterol by approximately 30%.

Dalcetrapib was the second CETP inhibitor to fail in clinical trials despite initial excitement that raising HDL-cholesterol levels would translate into a reduction in clinical cardiac events. This caused some in the cardiovascular disease community to believe that raising HDL was the wrong approach for reducing cardiovascular events.

Dr. Marie-Pierre Dubé is Director of the Beaulieu-Saucier Pharmacogenomics Centre at the Montreal Health Institute.

Q. What prompted you to focus on the pharmacogenomic of dalcetrapib?
MPD: We focused on the pharmacogenomics of dalcetrapib because we still believed that raising HDL was a good approach. We wondered whether there could be a genetic subgroup that would benefit from the drug and decided to reanalyze the data to look at the pharmacogenomics.

> "We worked with the HumanOmni2.5Exome BeadChip in the past and were pleased with its quality and fast turnaround time."

Q: What were the objectives of your pharmacogenomics analyses?
MPD: Our primary objective was to determine whether there was a group of subjects in the treatment arm that did benefit from dalcetrapib. The end point was a reduction in cardiovascular events, such as coronary heart disease death, resuscitated cardiac arrest, nonfatal MI, nonfatal stroke, and unstable angina, or revascularization while on treatment. The secondary objective was to identify if there were genetic factors that put certain subjects at risk of a recurrent cardiovascular event, regardless of the treatment arm in which they were enrolled.

Genetic data had not been systematically collected from everyone in the trial, but about 6000 dal-OUTCOMES participants agreed to participate in a Roche research program where DNA samples were taken. These samples made it possible to perform genome-wide association studies (GWAS) to see if there was a genetic basis behind subject response to dalcetrapib. In performing the follow-on dalcetrapib study for Roche, we also were given subject data from dal-PLAQUE-2, an imaging trial to show whether dalcetrapib altered atherosclerosis as measured by carotid intima-media thickness (IMT). This provided supporting evidence to the GWAS results.

Q: Why did you choose the HumanOmni2.5Exome BeadChip for your analyses?
MPD: We worked with the HumanOmni2.5Exome BeadChip in the past and were pleased with its quality and fast turnaround time. We thought it offered great potential in answering our primary research question, because it includes markers from the HumanOmni2.5 and HumanExome BeadChips and therefore provides information on common, rare, and exonic SNP variants. We liked the fact that when we identified a GWAS hit in a region, we'd also had the exome data to determine if there was a coding variant that could be involved in the signal.

Q: What were the results of your study?
MPD: The data from GWAS with the HumanOmni2.5Exome BeadChip showed a strong association between the effects of dalcetrapib and *ADCY9* (adenylate cyclase 9) on chromosome 16, particularly for a specific genetic variant (rs1967309). We would never have discovered this gene using a candidate gene study.

ADCY9 was not the drug target; however, it's a gene that makes sense at the physiological level. When we stratified genotypes in the dalcetrapib arm of the dal-OUTCOMES trial, subjects that were homozygous for the rs1967309 AA allele had a 39% reduction in cardiovascular events or urgent coronary revascularization compared with placebo. In contrast, participants who were homozygous for the GG variation had a 27% increased risk of cardiovascular events or revascularization. We then evaluated samples from the dal-PLAQUE-2 study. Again, individuals homozygous for the protective AA allele showed a significant reduction in IMT when treated with dalcetrapib. In contrast, subjects with a wild-type genotype showed coronary atherosclerosis progression. Subjects with the protective genotype made up approximately 20% of the participants in the dal-OUTCOMES study. We were excited to identify a variant that could be a valuable biomarker.

Q: Have the results from this study triggered further clinical studies of dalcetrapib?
MPD: This fundamental genomics work will lead to a genetics-guided Phase 3 clinical study of dalcetrapib in subjects with the genetic profile associated with a positive response to dalcetrapib. A positive outcome in this Phase 3 clinical trial could result in a personalized cardiovascular therapy.

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Q: Could this pharmacogenomics approach be valuable in resuscitating other failed cardiovascular drug candidates?
MPD: I believe that the same approach can be used to analyze data retrospectively from other drugs that showed potential, but ultimately failed in clinical trials. AstraZeneca has recently entrusted our team with its cardiovascular and metabolic disease biobank. It has 80,000 samples and data from 99 clinical trials of 10 different drugs. We'll be analyzing those Phase 2 through Phase 4 clinical trial data with the new Infinium Multi-Ethnic Genotyping Array (MEGA), looking for differences in drug response across the populations. We'll also look at optimization of the subject profile, genotyping of the diseases in those populations, and metaanalyses across different clinical trial phases.

Q: Do you think pharmacogenomics will change the way drug trials are conducted?
MPD: I'm inspired by the success we had with dalcetrapib and with the potential that pharmacogenomics is finally offering. Pharmacogenomics relies on a combination of large clinical trial data and efficient genomic

approaches to identify variants and potential biomarkers. In the end, patients and clinicians need to recognize the value and the potential of pharmacogenomics information to improve health care. I think eventually people will want drug response information included in their medical records, so that attending physicians will know if they are allergic, sensitive, or nonresponders to certain drugs. But the only way to identify responders and nonresponders is through pharmacogenomic studies. I'm hoping that increasing numbers of people will participate in studies that support personalized medicine and precision management of therapeutics. It might be a slow process, but there is finally real hope for it to become a reality.

> "We'll be analyzing this Phase 2 through Phase 4 (dalcetrapib) clinical trial data with the new Infinium Multi-Ethnic Genotyping Array (MEGA), looking for differences in drug response across the populations."

References

1. Grainger D. Why Too Many Clinical Trials Fail – And A Simple Solution That Could Increase Returns On Pharma R&D. *Forbes.* January 29, 2015. www.forbes.com/sites/davidgrainger/2015/01/29/why-too-many-clinical-trials-fail-and-a-simple-solution-that-could-increase-returns-on-pharma-rd/. Accessed July 8, 2015.
2. Tardif JC, Rhéaume E, Lemieux Perreault LP, et al. Pharmacogenomic determinants of the cardiovascular effects of dalcetrapib. *Circ Cardiovasc Genet.* 2015;8(2):372–382.

Learn more about the Illumina products mentioned in this article:

- HumanOmni2.5Exome BeadChip, www.illumina.com/products/humanomni25exome-8.html.
- Infinitum Multi-Ethnic Genotyping Array (MEGA), www.genomeweb.com/microarrays-multiplexing/illumina-collaborators-design-multi-ethnic-genotyping-array-empower-gwas
- HumanOmni2.5 Beadchip, www.illumina.com/products/humanomni25-8_beadchip_kits.html.
- HumanExome BeadChip, www.illumina.com/products/infinium_humanexome_beadchip_kit.html.

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 Pub. No. 1070-2015-001 Current as of 12 May 2017

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