Interview

A discussion on genome-wide associations in pharmacogenomics

Alison Motsinger-Reif speaks to Sarah Jones, Commissioning Editor

Alison Motsinger-Reif began her research career in physiology and pharmacology at Wake Forest University (NC, USA) studying the turnover rates of dopamine, norepinephrine, serotonin, aspartate, glutamate and GABA in brain regions of rats self-administering cocaine. After matriculating to Vanderbilt University (TN, USA), she focused on classical immunology/virology in HIV/AIDS, and then joined the Center for Human Genetics Research at Vanderbilt University to study computational genetics. While there, she received a MS in Applied Statistics along with a PhD in Human Genetics. Since 2007, she has been at North Carolina State University (NC, USA) in the Department of Statistics, and an active Adjunct Assistant Professor in the Institute for Pharmacogenomics and Individualized Therapy at University of North Carolina at Chapel Hill (NC, USA). She is currently an Associate Professor and the Director of the Bioinformatics Consulting and Service Core of North Carolina State University. Her research is focused on development of computational methods to detect genetic variants that predict complex phenotypes, such as drug response. In particular, she is focused on methods to detect gene–gene and gene–environment interactions in large-scale genomic data.

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■ How did you first become interested in pharmacogenomics?

Well, I actually started my research career in physiology/pharmacology for and then moved into classical immunology/virology in HIV/AIDS. Initially, I had an interest in this area of biology and then in graduate school I became more of a quantitative scientist, trained in statistics and genetics, and so pharmacogenomics was a perfect blend of the biology I had been doing and the quantitative genetics that I always found a really exciting area of genetics and genomics to work in. It is a great subdiscipline of genetics in which to really see translation – very exciting.

■ How do you think that the area has changed since you first began your career?

One thing that I think has changed in genetics in general, and pharmacogenomics in particular, has been the advances in technology seen. When I began my career, it was possible to look at one SNP at a time, or even microsatellites. Now with the availability of the genome-wide association chip, and next-generation sequencing, and third-generation sequencing coming on the horizon, there has definitely been a change in scope in what you are able to do in pharmacogenomics.

■ So you can analyze much larger quantities of SNPs?

Absolutely. This has really changed our study design and all aspects of pharmacogenomics research.

■ I believe you also lecture at North Carolina State University, do you teach pharmacogenomics in your classes?

Yes, I teach a lot to graduate students in bioinformatics and statistical genetics, and I include a lot of pharmacogenomics, especially examples of successes in human genetics. I think they are some of the clearest examples of both discovery and effective translation. It is always great to give students success stories.

■ I imagine they like to hear examples of the techniques working.

Yes, it is one way to get them really interested. I also lecture to clinicians regularly at both the medical centre at the University of North Carolina at Chapel Hill (NC, USA), and to the clinicians in the vet school here at North Carolina State University (NC, USA). I lecture on how they can include pharmacogenomics in their clinical practice – genetics, genomics and association analysis.

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■ Do you find that they are quite receptive to the lectures on pharmacogenomics?

Yes absolutely, they are very excited.

■ As we are doing a special focus on genome-wide association studies, I wanted to ask how has the introduction of this technology has changed research in pharmacogenomics?

It allows you to move from candidate gene exploration to really try and interrogate the entire genome and find new signals. These technologies bring challenges in study design, particularly for pharmacogenomics. But, as we have done more gene-association studies in human genetics in general we have found that the effect sizes for the genetic markers that we were hoping to see were maybe a bit smaller than we had initially hypothesized. So there are some real challenges in pharmacogenomics, in particular in adapting sample sizes to fit study design.

For example, if you wind up doing a lot of pharmacogenomics nested within clinical trials, this can present a particular challenge because we have limited sample sizes and limited access to different study designs to be able to do the genome-wide association studies (GWAS). But it is a really exciting opportunity to probe new discoveries and not be looking at the same candidate genes again; to find new things.

■ What are the challenges that the research faces?

One of the biggest challenges for pharmacogenomics is that the effect sizes are smaller than we thought. Therefore the sample size you need to find the associations in GWAS are larger than initially when the technology entered the field, so that has become a real limitation in pharmacogenomics in terms of finding the sample sizes we need. It is also a challenge finding replication. In genetics, it is standard to do discovery then replication, so to produce independent data sets.

■ To clarify the results?

Yes, when you are trying to do pharmacogenetics with one clinical trial, how do you find a replication? Should it be across drugs of similar classes? Or across similar outcomes? Similar toxicities? That kind of

thing is a challenge. And some scientists are then trying to look at models systems trying to do GWAS. I work with a group at University of North Carolina at Chapel Hill led by Howard McLeod looking at *in vitro* models; chemotherapy drugs for example.

Therefore, some people are trying to find creative ways to do these GWAS where you can get enough samples to actually find these effect sizes in clinical trials. So it is an interesting time to see how these GWAS are being actually applied in a broader approach to pharmacogenomics than just genotyping trials.

■ Can you tell us about multivariate analysis of GWAS and how you think it will change GWAS research?

Part of what I do as a statistical geneticist is methods development, handling the statistical and computational aspects of high-throughput data sets. Multivariate analysis of GWAS was actually developed to look at multivariate responses in association studies as opposed to just binary traits such as toxicity, which is a simple univariate quantitative trait. So it is a statistical extension to these multivariate traits and was a focus of a dissertation of a former student of mine, Chad Brown. He developed the methodology as well the software and tried to make it user friendly, compatible with software packages like Plink, that are really becoming standards for data analysis.

■ Is it quite transferable so people can use it easily?

We hope to be able to analyze multivariate outcomes such as complex dose response. The technology means that you can examine the entirety of the multivariate information rather than just picking one summary statistic. We have found that if that is the case then it has much higher power. This is just one of the many attempts in the field to increase power from a statistical perspective.

■ Finally, where do you see pharmacogenomics going? How do you think the field will progress over the next 10 years or so?

We already have some great examples of translational successes, and I hope that over the next 10 years we will continue to have more examples. I think this will be really exciting. The term personalized medicine

gets thrown around a lot as a sort of buzzword, but I think we will start seeing more and more personalized approaches to drug choice, either at an individual level or, even if it is not individual, by applying medical strategies to specific populations. So I am very excited and hopeful that over the next 10 years we will see a lot more discovery with pharmacogenomics really leading the way in genetics and translating findings from GWAS or candidate gene studies into the clinic.

Financial & competing interests disclosure

A Motsinger-Reif has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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