GSK gets its potpourri

By Lev Osherovich, Senior Writer

GlaxoSmithKline plc has rolled out a database of human genetic variation representing the most comprehensive geographical and ethnic sampling effort to date. The project, termed the Population Reference Sample, could help efforts to predict genetically influenced adverse drug reactions and is thus a step toward the development of personalized medicines. The database is accessible to outside researchers, and the pharma is already using it to optimize clinical trial designs.

The goal of POPRES is to establish a baseline for genetic variation among several major ethnic groups in industrialized countries. A study published in August in the *American Journal of Human Genetics* described the design and primary conclusions of the project.¹ The work was conducted by a consortium of academic and GSK researchers led by Matthew Nelson, manager of statistical genetics development at the pharma company.

"POPRES is first and foremost a collection of DNA samples," said Nelson. "We envisioned that it would be a large and diverse collection of subjects."

The study used DNA samples from 5,886 healthy subjects who had served as controls in 10 independent academic population studies. Among these samples were ones from ethnically homogeneous populations such as Japanese and Taiwanese, as well as from distinct ethnic groups in the U.S. such as African Americans and Caucasians.

Each subject's DNA was hybridized to a 500,000 SNP array from **Affymetrix Inc.** The resulting SNP data were analyzed by a statistical method called principal component analysis to identify groups of SNPs that distinguished each ethnicity from the population as a whole.

The resulting data showed that genetic variation among healthy subjects can be used to identify their geographic origin. Indeed, in a pair of accompanying studies, Nelson's team reported that European subjects from POPRES fall into clusters of genetic similarity that closely resemble the map of Europe.²

Thus, the POPRES database could be useful for identifying genes associated with drug sensitivities in certain populations and not others.

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"This is the first truly big, diverse population sample out there to be genotyped at high density and examined for both geographic correlations and practical utility in pharmacogenetics," said Andrew Kasarskis, scientific director of genetics at **Merck & Co. Inc.** "It therefore gives us a much better look at human genetic diversity than anything published to date."

Pardis Sabeti, assistant professor of systems biology at **Harvard University**, said that in the context of a growing body of genomic information for individual subjects, a central database of healthy control subjects is "a great resource."

She noted that although other public databases such as the **Wellcome Trust Case Control Consortium** (WTCCC) also offer SNP sets for healthy controls, POPRES is the first to stratify its data on ethnic and geographic lines.

"This lets us ask more intricate questions about population histories and demographics," said Sabeti.

Nelson and Cardon told *SciBX* that GSK is using POPRES to identify genes that influence adverse drug reactions. In principle, the data could also be used to find genes that improve drug response.

The database also has the potential to identify disease loci, although this isn't GSK's priority. As an example, Cardon cited Crohn's disease, an autoimmune disorder of the bowel that occurs primarily among Northern Europeans and is virtually absent among Japanese. The POPRES study identified a large group of SNPs that differ considerably between European and Japanese subjects.

"Characterizing this difference on a genome-wide level" could point to Crohn's disease susceptibility loci, he said.

Location, location, location

For GSK, the immediate value of POPRES is in selecting the right control subjects for clinical studies. Currently, it is difficult to predict whether a therapeutic that showed a favorable safety profile in clinical trials in one population will be safe in a different population.

"More people are trying to study genetic variation in the metabolism of drugs," said Sabeti. "So it's useful to investigate drugs in particular populations."

One company that has used SNP data to tackle the genetics of drug response is **deCode genetics Inc.**, which has a proprietary collection of Icelandic SNP data.³ However, because POPRES goes beyond Iceland's highly homogeneous population, it may potentially identify more drug-response loci than those found by deCode.

According to Nelson, comparing SNP data from patients who show an adverse drug reaction against ethnically matched controls drawn from POPRES will accelerate the discovery of drug susceptibility genes and help avoid adverse reactions in subsequent trials.

"We describe a resource for quick case-control study design," he said. "It might guide how we want to design future studies."

Indeed, the project has its roots in GSK's efforts to identify patients who are hypersensitive to Ziagen abacavir, the company's reverse transcriptase inhibitor marketed to treat HIV-1.⁴ Although a genetic locus called HLA-B* 5701 was suspected as risk factor for abacavir hypersensitivity, it took six years and several large-scale studies to prove the connection because of a scarcity of SNP data and differences in the prevalence of HLA-B* 5701 among ethnic groups.

With POPRES, the identification of HLA-B* 5701 as a risk factor for abacavir sensitivity could have gone considerably faster, according to another study by Nelson's team.⁵ Using the same Affymetrix chip and a genetically matched pool of controls drawn from POPRES, Nelson's team pinpointed HLA-B* 5701 as a likely culprit using only 10 cases and 200 controls.

However, Merck's Kasarskis suspects that the genetics of other adverse drug reactions may be more complicated. "It is unclear how many pharmacogenetic effects will have an abacavir-like profile where a single locus has a pretty strong effect," he said.

Kasarskis also noted the POPRES dataset is skewed toward Europeans and East Asians, whose genetic makeup is "generally quite similar" compared to more far-flung populations in South America and Africa. Hence, more SNP genotyping of other ethnicities will paint a truer picture of human diversity.

Nelson agreed that the next step is to collect more DNA samples to improve the ethnic and geographical resolution of POPRES, particularly for Asian populations. He told *SciBX* that future clinical trials will increasingly involve South and East Asian populations, which would

benefit from a precise genetic characterization of the ethnogeographic makeup of China and India.

GSK has made POPRES available through the Database of Genotype and Phenotype (dbGaP; <http://www.ncbi.nlm.nih.gov/sites/entrez?db=gap>), an open-access sequence bank managed by the National Center for Biotechnology Information at the NIH.

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