EDITORIAL

Translating ideas into action: two new features initiated by *Translational Research*, as genomics enters the clinics

As of this year, there were nearly 3000 single gene disorders with a known molecular etiology. Their discovery has already had a striking impact on refining a variety of clinical diagnoses.[1] What they have not had a substantial impact on, however, is development of new therapeutics. According to a recent review by Dr David Ginsburg, less than 1% of such genomic mappings have translated into clinical treatments, with most of those restricted to enzyme deficiencies.[1] Given the fact that life-span–restricting and common chronic diseases of cardiovascular, endocrinologic, and neuropsychiatric origin are complex and multifactorial, with substantial environmental components, the number of known ''medically actionable alleles''—the ones of most interest to clinicians—are vanishingly small.[2] But new genetic approaches involving genome-wide association studies (GWAS) and correlations between disease states and single nucleotide polymorphisms (SNPs) have contributed to our understanding of the molecular and biochemical pathways subserving a variety of common medical disorders. And this may eventually lead to novel therapeutic and prevention interventions.

But the cost of such genomic-based studies—in their initial design, scope, and need to encompass large populations of diverse ethnic origins—presents a daunting obstacle. Each individual human genome contains an average of 3.5 million SNPs, with one occurring approximately every 1 kb.[2] In addition, there are rare or ''private'' SNPs, unanticipated by large screening databases such as the HapMap project, which tack on another half million or so SNPs to each personal sequence.[2] Locus-specific SNP mutation rates are approximately 2×10^{-8} and may differ in male versus female gametes,[2] not to mention the diversity generated by short insertions or deletions, the penetrance of individual alleles, interactions between genetic loci, and some 1000 copy number variants.[2] Highly accurate analyses of many thousands of samples are required to define the frequency and population distribution of a given genetic variant and its disease association. Consider, for example, a recent report from The International Consortium for Blood Pressure Genome-Wide Association Studies: the primary analysis evaluated associations between an astounding 2.5 million SNPs and systolic and diastolic blood pressure in 69,395 individuals of European ancestry.[3]

In conjunction with a validation experiment using available genotyping resources from 133,661 additional individuals of European descent, 29 independent SNPs at 28 loci could be associated with blood pressure variations at the $P < 5 \times 10^{-9}$ level. This probability value, although it seems huge in comparison with P values generated in most experimental or clinical studies, was still only an order of magnitude beyond the generally accepted genome-wide significance level for a single-stage experiment; such significance levels are needed to control for the large number of possible associations screened.[3] In terms of mechanism, 16 of the loci were not previously correlated with blood pressure physiology. Of these, 6 are associated with genes known to influence blood pressure, and the other 10 may yield clues to its regulation. Based on these 29 SNP variants, a genetic risk score was developed and found to correlate with left ventricular wall thickness, stroke, and coronary artery disease. In addition, the blood pressure variants analyzed in individuals of European ancestry were examined among another 73,471 people of East Asian, South Asian, and African ancestries, confirming the associations for 6 to 9 of the loci. Whether a truly different underlying genetic architecture accounts for these differences in SNP associations remains to be determined. And yet, despite all this work in several hundred thousand individuals, any one of the 6 or 9 or 29 loci could have affected the systolic or diastolic BP by only approximately 1 mm of Hg.

To add to the myriad of roadblocks in translating data derived from current methods of genome analysis to anything of clinical utility, more than 80% of the SNPs implicated in these screens are intronic or intergenic, with a concentration in enhancer elements. But our functional understanding of such noncoding elements is

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limited.[4] In addition, SNPs generally account for less than 20% of overall genetic risk for most common, complex diseases, begging the question as to what accounts for the remaining ''missing'' heritability.[1]

And yet the promise of low-cost whole genome sequencing for a large segment of populations in the resource-rich and resource-poor world—recall that information must be derived from genomes of diverse populations worldwide in order to define accurately the genetic basis of common and region-restricted disease and that Africa is the home of the highest levels of human genetic diversity on Earth[5]—promises a deluge of sequencing information. All of this is very exciting to an editor of a translational research journal.

So, how can we at *Translational Research* be of help?

NEW SECTION: "GENETIC POLYMORPHISMS AND DISEASE ASSOCIATIONS"

There are many venues to publish manuscripts with the breadth and depth of the paper I summarized at the opening of this editorial. We have published such studies in the past, although with considerably fewer study participants, and have review articles addressing these associations in press (eg, SNPs in inflammatory bowel disease[6]). We have also weighed in on ethical issues surrounding ''genetic tests'' used clinically, which is a topic of growing concern to many.[7,8] But what about the vast majority of SNP-related manuscripts that we and other biomedical journals receive, review, and reject because of small sample size, limited ethnic/racial distribution of subjects tested, failure to consider adequately linkage disequilibrium and appropriate statistical analysis, and/or lack of primary supporting *in vitro* data related to mechanism?

Many of these submissions do have a plausible underlying hypothesis based on the experimental or clinical work of others. But they are still typically rejected by triage. We are now instituting a new section of one-leaf (2 printed pages) summaries as a forum for such preliminary SNP-based disease association observations. Citations are limited to 12; figures/tables will be counted in the 2-page limit, and direct links to supplemental data cannot be provided. There will be a generic notation indicating that these are preliminary communications meant to guide, stimulate, or redirect future studies of these polymorphisms. Authors may submit a manuscript directly for consideration for this section. Or, following the recommendations of reviewers of a submitted full manuscript that has been rejected, the editorial staff of *Translational Research* may suggest to the authors that they consider resubmitting their work, appropriately revised to fit this format. The first contribution to the new section appears in this issue of the journal.[9] This is an editorial experiment, and we are anxious to see whether it has value, even if archival, to our audience.

GENETIC POLYMORPHISMS AND DISEASE ASSOCIATIONS

We are pleased to introduce a new section of Translational Research where authors can publish letter-length reports of preliminary investigations into the associations between disease states and single nucleotide polymorphisms (SNP). These preliminary communications are meant to guide, stimulate, or redirect future SNP-based studies. We welcome feedback from our readers as to the utility of this section.

NEW AWARD: BEST FEATURED NEW INVESTIGATOR (FNI) MANUSCRIPT

The president of Cornell University, David Skorton, MD, is a cardiologist by training and a strong advocate for translational research. In a recent Medical Grand Rounds that he gave at Weill Cornell Medical College, he emphasized the motto of the Association of American Medical Colleges: ''Tomorrow's Doctors, Tomorrow's Cures.'' Dr Skorton then expanded on what he believed are the 4 basic attributes of the academic physician, qualities that must be fostered by these medical colleges. They are the following:

- Engagement in the total care for a patient, through diagnosis, treatment, and prevention
- Teaching throughout one's career, involving not only students but also fellow practitioners and faculty
- Engagement in public discourse and policy (Skorton noted that academic medicine is a ''soft target'' for funding cuts in Congress; we all need to inform Congress, presidential candidates, and our representatives of its great health and economic benefits.)
- Fundamental, applied, and translational research

The Central Society for Clinical Research (CSCR) has and continues to support all of these efforts. And, to be of further support, the CSCR council recently approved an award for the best FNI manuscript published in our journal in the preceding year. It carries a $1500 stipend plus domestic travel expenses to present the work on which the manuscript is based at the annual CSCR meeting, which is held each April in Chicago. Our first such award will be announced in April 2012. The FNI must be the first or senior author of the paper. Both MDs and PhDs within 7 years of completing their postdoctoral or fellowship training are eligible to complete. Applicants of foreign universities are eligible, although airfare will be provided only within the United States. I look forward to increased submissions from potential FNI candidates

and encourage divisional and departmental chairs to suggest to their residents, fellows, and young faculty that they submit their work for consideration.

Jeffrey Laurence
Editor-in-Chief

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