Commentary

Translating genomics into the clinic: moving to the post-Mendelian world

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Abstract

The challenge of genome medicine is *not* to make a significant move into the clinic over the next five years. The floodgates of genomic research have been opened, and the hopes are that the rising tide will spill over into medical practice in the form of diagnostic tests, risk assessment tools and therapeutics. The ability to perform genome-wide analyses using several different approaches has already provided tantalizing new clues to disease causation and therapeutic targets. Companies have sprung up to use these new technologies to provide information to individuals about predicted health and disease, and about behavioral traits. As exciting as these prospects are, it is far too soon to promise clinically useful information from genomic analyses. We have far to go to assure basic levels of analytical validity or clinical validity of the diagnostic or predictive tools on offer, and to determine their clinical utility in the medical context.

The main issue currently facing the translation of genomics research into clinical practice is that it will require researchers, clinicians and patients to make a significant conceptual shift from Mendelian ways of thinking to a post-Mendelian world. Ironically, in this new world, genes have a lesser role as we study ever more complex diseases and traits and begin to understand the interplay of gene-gene and gene-environment interactions and epigenetics. It is nearly 100 years since Wilhelm Johanssen first coined the word 'gene' and posited a relationship between genotype and phenotype. Since then, we have learned that there is a lot more to this relationship than we initially envisaged.

Currently, genome-wide association studies increasingly identify the contribution of multiple genetic loci to phenotypes by providing clues as to the biological pathways and interactions involved. However, we are far from knowing how the results of these studies are clinically relevant. As a result, we also do not yet know how to explain these results in a meaningful way to patients.

The shift to post-Mendelian genomics will require different ways of thinking about the validation, interpretation and explanation of genomic studies, especially with respect to their application to clinical practice. Recent comprehensive, large-scale studies such as that by the Wellcome Trust Case Control Consortium [1] have been very valuable at connecting biochemical pathways with diseases, such as age-related macular degeneration [2]. The challenge of establishing and replicating genotype-phenotype associations remains, however [3,4], leading to cautions about how to design and interpret genome-wide association studies [5-7].

Validation of genotype-phenotype associations is of course critical to the successful translation of genomic data to clinical practice. Basic issues of analytical validity must be addressed, especially as new analytical platforms are developed, such as array comparative genomic hybridization to determine copy-number variation. The biases and reliability of these relatively new methods is still in flux [8-10] and minimum standards of analytical validity must be established in order to use these platforms for clinical application [11,12].

The potential for rigorous statistical analysis to minimize false positive results has been widely discussed [5-7], as well as the need for sound study design, including care in subject selection and controlling for population substructure. However, even after a genotype-phenotype association has been identified and replicated, establishing clinical validity and developing a useful clinical diagnostic test requires much more work. The fact that the demonstration of an association is not the same as finding a causal variant, much less the majority of causal variants, is probably not well understood by clinicians and the general public. Personal

genomics companies imply that a scan of one's whole genome 'covers' health conditions of interest, such as Alzheimer's disease or breast cancer, but this idea is misleading. For example, the Navigenics Health Compass scans an individual's genome at 1.8 million loci for variants that are associated with 18 relatively common conditions and for which the association has been published in a peer-reviewed journal and the finding replicated at least once [13]. However, although the Health Compass claims to cover breast cancer, the test does not examine the *BRCA1* and *BRCA2* genes at the sequence level, which is something a patient with hereditary breast and ovarian cancer in their family would require and expect of a truly personalized genetic risk assessment.

The 23andme website [14] claims that "23andMe can help you discover how your genes may affect your chances of developing various diseases and conditions, as well as traits such as athletic ability". However, this statement is in contrast to those of genome researchers [2,15], who have stressed that the contribution of single genes is often small, commonly with odds ratios of less than 1.5, and thus perhaps clinically insignificant [16]. How to interpret the clinical significance of genetic contributions when some loci associated with traits and diseases contain no known genes is even more unclear.

How to interpret the effects of multiple genes associated with a particular condition poses a major challenge to clinical practitioners and patients. For example, analyses of Craig Venter's *DRD4* and *DRD3* genes (associated with 'novelty seeking') indicated that at one locus his genotype indicated that he had a variant not associated with higher novelty-seeking scores but at other loci his alleles were associated with higher novelty-seeking scores [17]. Given the multi-factorial nature of most traits, it still needs to be worked out how the growing amount of genomic information should be interpreted and explained when aggregated.

Fundamentally, the idea that genomic analysis provides only part of a very complex picture must be conveyed. In the Mendelian era, almost by definition, diseases were more obviously delineated because they were clearly inherited and the role of epigenetic and environmental factors did not need to be addressed. In the post-Mendelian world, the complexity of, and need for, defining and measuring phenotypes and environmental factors is only now beginning to be appreciated by the research community, but is not well understood by prospective patients and their health care providers.

Over the next five years, the challenge for genome medicine is thus *not* to make a significant move into the clinic. Although this is a desirable goal, it would be premature. Scientists, clinicians and the general public first need to change their way of thinking about the role of genes and genomes in everyday health.

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