Genomics Reaches the Clinic: From Basic Discoveries to Clinical Impact

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Today, more than ever, basic science research provides significant opportunities to advance our understanding about the genetic basis of human disease. Close interactions among laboratory, computational, and clinical research communities will be crucial to ensure that genomic discoveries advance medical science and, ultimately, improve human health.

The potential for the burgeoning knowledge of genome structure and function to improve medical care has long been anticipated (Collins, 1999), but until very recently, the actual clinical application of genomics has been limited (Green and Guyer, 2011). Despite concerns about the pace of medically relevant genomic discoveries and the implementation of genomic medicine (clinical care based on or influenced by knowledge of a patient's specific genomic variants) (Varmus, 2010), growing numbers of encouraging examples are now in hand. Early case reports of genomic-based diagnoses leading to altered treatment and an improved clinical course, facilitated by advancing genomic technologies such as whole-exome and -genome sequencing, illustrate the potential of genomically informed medicine for improving clinical care. Such reports also demonstrate the critical role that basic science approaches play in characterizing implicated variants and pointing toward more effective treatments. Here, we describe several recent successes in genomic medicine that illustrate the critical interplay between basic and translational researchers that will be required to make the routine use of genomic medicine a reality.

The potential of whole-exome sequencing for identifying the genetic cause of a mysterious and disabling disease and, in some cases, for illuminating a path toward effective treatment was vividly demonstrated by the desperate case of a young boy with severe, intractable, and atypical inflammatory bowel disease (Worthey et al., 2011). He failed to respond to conventional treatment and progressively worsened. The only treatment option remaining was hematopoietic stem cell transplantation. In the absence of a clear diagnosis, clinicians were concerned about subjecting the boy to an invasive procedure with unknown chances for survival. Whole-exome sequencing provided the key diagnostic clue: a nonsynonymous change in *XIAP*, a gene involved in apoptosis. Functional studies quickly confirmed that the mutation caused aberrant XIAP function. These findings, and the known morbidity risk of *XIAP* deficiency-related hemophagocytic lymphohistiocytosis, tipped the balance in favor of stem cell transplantation. The patient survived the procedure and is now well 1 year later (D. Dimmock, personal communication). There is little doubt among the clinical and laboratory teams that this course of treatment—a high-risk gamble justified only upon identification of the presumed causal mutation—saved the patient's life.

Genomic analysis is a cornerstone of the National Institutes of Health's Undiagnosed Diseases Program (http://rarediseases.info.nih.gov/Resources.aspx?PageID=31), and it recently proved invaluable for studying three families with severe, symptomatic arterial calcifications (St Hilaire et al., 2011). Several of the affected individuals had disabling intermittent claudication with extensive occlusion of the iliofemoral arterial system due to heavy calcification. One family was consanguineous (a third-cousin marriage), so genome-wide single-nucleotide polymorphism arrays were used to identify genomic regions that were homozygous in all affected siblings but heterozygous in the unaffected parents. The only such region included three genes implicated in cellular pathways potentially involved in calcification. One of these, *NT5E*, codes for the protein CD73, which is involved in the same pathway as a gene associated with generalized arterial calcification of infancy. Targeted sequencing of the affected siblings revealed a homozygous nonsense mutation in *NT5E*, and quantitative PCR analysis demonstrated decreased *NT5E* expression in cultured fibroblasts from two of the affected siblings. Studies of two other affected families detected missense and nonsense *NT5E* mutations in homozygous or compound heterozygous states. A series of elegant experiments revealed markedly reduced CD73 levels and absent CD73 enzymatic activity in fibroblasts from affected patients, with the latter rescued by transfection with a CD73-encoding lentiviral vector. Fibroblasts carrying the *NT5E* mutation also showed excessive staining for tissue-nonspecific alkaline phosphatase (TNAP), a key enzyme for calcification, as well as abundant calcium phosphate crystal formation. These phenotypes were ameliorated by CD73 transfection or treatment with either adenosine or an inhibitor of alkaline phosphatase. Elucidating the precise molecular defect in this condition enables consideration of treatments affecting other components of this calcification pathway and may shed light on potential treatments for ectopic tissue calcification in other disorders.

These two notable successes are encouraging, but it is sobering to recognize that whole-genome analysis has failed to reveal the cause of a rare genetic disease in the majority of cases studied to date. More robust approaches for genome analysis are being developed to study the thousands of genetic disorders for which the molecular basis remains unknown.

Pharmacogenomics is another area where genomic discoveries can be leveraged to improve clinical care. Genotype-targeted treatment with clopidogrel represents a prototypic pharmacogenomic advance facilitated by basic science investigation of the effect of specific genetic variants. Clopidogrel is a widely prescribed antiplatelet drug that binds to the platelet P2Y12 receptor with wide interindividual variability in response (Roden and Shuldiner, 2010). Further study of clopidogrel's mechanism of action showed that it is a pro-drug highly dependent on cytochrome P450 2C19 for activation. Up to 30% of individuals carrying *CYP2C19* variants are unable to generate the active form, and inhibition of platelet aggregation was diminished in these individuals. Some, but not all, studies also point to an associated higher risk for thrombotic cardiovascular events among these *CYP2C19* variant carriers. An alternative but more costly anti-P2Y12 drug does not require bioactivation, raising the potential for genotype-targeted selection of individuals needing the higher-cost alternative. Another common 2C19 polymorphism can actually increase clopidogrel metabolism, whereas the effects of several rarer 2C19 variants remain to be studied. Several pilot studies are now underway examining the effectiveness of pre-emptive genotyping in patients. The effects of other 2C19 variants, the role of genotyping versus phenotypic platelet inhibition assays, and the therapeutic potential of other antiplatelet drugs provide fertile ground for basic science investigations that can generate more effective treatments to reduce the risk of thrombotic events. Clinical outcome improvements like these, in conjunction with appropriate changes in physician and patient behavior, will be essential for promoting adoption of such genomic approaches in routine clinical care. Findings from these and related studies will also inform policy development and regulatory oversight, as illustrated by the Food and Drug Administration's promotion of drug-labeling changes (www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm).

Other pharmacogenomic successes include the documented increased risk for life-threatening adverse reactions to carbamazepine in persons carrying the *HLA-B*1502* allele and the reduction of that risk following genotyping and drug avoidance by carriers of the risk allele (Wilke and Dolan, 2011). HLA-mediated risk for adverse drug reactions remains poorly understood but is suspected to involve HLA-allele-specific presentation of key drug moieties to immune-activating cells—an area ripe for basic investigation.

Another potent pharmacogenomic example is the BRAF kinase inhibitor vemurafenib. Patients with metastatic melanoma whose tumors carry the activating *BRAF* V600E somatic mutation respond dramatically, with improved rates of survival (Chapman et al., 2011). The potential for vemurafenib and other BRAF kinase inhibitors to improve health spans of other cancer patients carrying the *BRAF* V600E mutation is being investigated and may be an initial step in the long-anticipated classification of cancers based on molecular taxonomy rather than organ of origin and histopathology.

These examples demonstrate the enormous potential of basic research to contribute key insights about the phenotypic consequences of disease-associated variants that, in turn, lead to changes in patient care. Although genetic variants of large effect with clear functional impact may be more readily identified in familial or isolated cases of severe disease, such as those described above, recent studies have demonstrated the important new areas of research catalyzed by studying smaller-effect loci identified in genome-wide association studies (GWAS) (Ernst et al., 2011). For example, 80% or more of the genomic regions implicated in the GWAS conducted to date are intronic or intergenic (http://www.genome.gov/gwastudies), with disease-associated variants being significantly enriched in enhancer elements (Ernst et al., 2011). Together, these findings make detailed investigation of genetically associated noncoding genomic regions a high priority, yet our functional understanding of noncoding regions is in its relative infancy and will be complicated by their greater genomic variation compared to coding regions (1000 Genomes Project Consortium, 2010). Variants in gene regulatory regions will undoubtedly prove to be important in disease causation, but their role in pathogenesis will also be complex and difficult to define compared to the coding variants represented by the recent discoveries described above and the overwhelming majority of disease-causing mutations reported to date.

For genomic medicine to be successful, basic science advances are also needed to promote development of low-cost, rapid, and clinically available technologies for detecting genomic variants. Although the advent of genome-wide genotyping arrays revolutionized identification of disease-associated loci, this and other genomic technologies (such as genome sequencing) remain largely unavailable outside major research laboratories. The requisite data analysis and quality control will likely keep these technologies out of the typical clinical laboratory for some time. This is unfortunately also true for methods to detect variants in targeted genes recognized to have significant clinical implications. Although becoming increasingly available, whole-exome and -genome sequencing presents significant challenges with respect to data analysis, interpretation, and display. Robust yet easy-to-utilize bioinformatic tools are urgently needed for analyzing genome sequence data, providing to clinicians only the information about genomic variants that is relevant to a patient's care.

Our ability to define the role of genomic variation in human disease is growing at an ever-accelerating pace. As revealed in the above examples, using these advances to directly improve patient care will require close interactions between the basic and clinical research communities. The insights resulting from genomic knowledge moving freely between the laboratory and the clinic hold great promise for the implementation of genomic medicine.

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