

EDITORIAL

2012 highlights in translational 'omics

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This annual editorial from *Genome Medicine's* Section Editors highlights the most exciting research from the past year and the potential of these advances for medicine. Last year, we noted that medical 'omics continued its inexorable move towards the clinic; in 2012 it has truly arrived. DNA capture technologies and sequencing continue to lead the way, with implications for human genomics, personalized medicine, pharmacogenomics and drug labeling, public health screening, and public policy already apparent. There have also been technological advances in proteomics and other 'omic approaches, and in the integration of these approaches to provide more informative molecular signatures of health and susceptibility to disease.

De novo mutations: from complexity to the clinic

Genomic approaches to human disease have exploded during 2012, and the number of diseases for which the genes are being identified by exome sequencing are too numerous to list and too exciting to highlight any one study over another. Of particular interest is the ability of genomic analysis to reveal complex patterns of inheritance. The thrombocytopenia absent radius (TAR) syndrome was previously associated with either *de novo* or inherited deletion of 1q21.1; however, evidence suggested that variation at an additional locus was necessary for disease expression. Exome sequencing revealed that low-frequency regulatory single-nucleotide polymorphisms for *RBM8A* (which maps to the 1q21.1 region and encodes a component of the exon-junction complex), in combination with a 1q21.1 deletion, are necessary and sufficient to cause TAR syndrome [1]. Exome sequencing also revealed that a form of fascioscapulohumeral muscular dystrophy (FSHD2) results from digenic inheritance of an allele of the *D4Z4* microsatellite array on chromosome 4, which is permissive for the expression of the embedded *DUX4* gene, and single-nucleotide variation (SNV) at the *SMCHD1* locus (encoding structural maintenance of chromosomes flexible hinge domain

containing 1) [2]. Thus, an SNV or point mutation allele in *SMCHD1* on chromosome 18 acts as an epigenetic, epistatic modifier of the *D4Z4* allele and acts as a genetic determinant underlying the *FSHD2* disease trait [3].

2012 may perhaps be remembered as the year of *de novo* mutation (DNM). Three different approaches applied genomic sequencing to directly measure inter-generational DNM rates [4-6]. DNMs were experimentally measured to occur at about half the previously estimated rate of about 2.5×10^{-8} . Furthermore, these studies confirm and quantify a long-held observation of a paternal effect on DNM rates [7]. The DNM rate for SNV in the paternal germline is about four times greater than that in the maternal germline; it increases linearly by about two DNMs per year in line with spermatogonial stem cell turnover after puberty [7]. No such maternal age effect was observed. Thus, while maternal age has long been known to be associated with risk of aneuploidy and developmental disorders, DNM with paternal aging may have a similar impact on the risk of developmental disorders in progeny.

Genomics is rapidly being deployed in the clinic, as evidenced by two remarkable papers from Switzerland and the Netherlands [8,9] showing that a substantial percentage of sporadic intellectual disability of unknown etiology can be molecularly diagnosed using an exome sequencing 'trio-based' strategy, comparing the patient with their parents to identify DNMs. This has immediate clinical implications for counseling about the risk of recurrence and may eventually provide prognostic information and potentially genotype-directed therapeutic intervention. Genomic medicine is no longer the future - it has arrived!

James Lupski,
Section Editor,

Genomics and epigenomics of disease

Fifteen years of public health genomics

Public health genomics is a multidisciplinary field that deals with the effective and responsible translation of genome-based science to improve population health [10]. In 2012, the Centers for Disease Control and Prevention (CDC) [11] and the PHG Foundation [12] marked 15 years of public health genomics in the US and the UK, respectively. In addition, the European Public Health

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Genomics Network completed its second cycle with a scientific symposium in Rome, Italy [13].

What has the past 15 years produced, and where are we going next? A major achievement has been a better dialog between basic, clinical and population sciences. The principles of medicine and public health are increasingly converging on a foundation of evidence that can be applied to the translation of genome-based discoveries into population health benefits [10]. There is also increased emphasis on policy, training of the workforce, surveillance and epidemiology [10]. With rapid improvements in genomic and related technologies, we are seeing the leading edge of the applications of whole-genome sequencing (WGS) in practice in both pathogen [14] and human genomics [15]. However, much of the field will be work in progress for quite some time.

In 2012, the CDC Office of Public Health Genomics developed and implemented an evidence-based classification schema for human genomic applications, taking a population perspective so that public health programs can start to supplement clinical practice [16]. For hereditary breast and ovarian cancer (BRCA), Lynch syndrome and familial hypercholesterolemia (FH), public health programs can use counseling and testing to identify people at increased genetic risk for cancer and heart disease [17]. There are more than 2 million people affected with one of these three conditions in the USA, who are at increased risk for early heart attacks and stroke (FH), breast and ovarian cancer (BRCA) or colorectal cancer (Lynch syndrome), but most affected individuals and their relatives do not know they are affected [8]. Therefore, a public health approach of cascade screening (an active process to find individuals with a certain disease in families, starting with an affected proband and cascading to relatives) may complement the clinical approach of promoting access to genetic evaluation and preventive interventions. These three conditions are only the tip of the iceberg. The facts that there are now more than 2,500 Mendelian diseases with an available genetic test and more than 100 available pharmacogenetic tests, and that personal genomic testing services are now available directly to consumers, means that there will be challenges and opportunities for genomic implementation for years to come [16].

Muin J Khoury,
Section editor,

Genomic epidemiology and public health genomics^a

The 'hype' of pharmacogenomics that might be justified

In recent years, the personalized approach of pharmacogenomics-guided treatment has been acclaimed as one of the most promising innovative concepts in medicine and one of the first broad clinical applications of genomic

medicine. In the mean time, however, concerns and reservations have arisen as to whether genomic medicine will indeed substantially improve patient care or change treatment decisions towards targeted, personalized therapeutic options in clinical practice. Francis Collins' vision in 1999 of a genetically based, individualized preventive medicine was exciting, suggesting that by 2010, genetic tests might provide risk information for several diseases for which preventive strategies are available [18]. The pharmacogenomics hype recently gained support from extraordinary research activities demonstrating that specific host genotypes are important in the treatment of chronic hepatitis C (CHC) and cystic fibrosis (CF). In 2011, the US Food and Drug Administration (FDA) included pharmacogenomic information to the label of peginterferon alfa-2b and the labels of the direct acting antivirals boceprevir and telaprevir for treatment of CHC [19], given that several studies provided evidence that consideration of polymorphisms in the interleukin -28B (*IL28B*) gene can significantly improve the efficacy of these drugs [20]. In 2012 the first targeted pharmacogenomic therapy for CF patients became reality following the approval of the new agent ivacaftor by the FDA and European Medicines Agency. In patients carrying the *CFTR G551D* variant, which results in normal production of the CF transmembrane conductance regulator CFTR but abnormal chloride channel transport, ivacaftor specifically increases the channel gating activity of CFTR at the cell surface, thereby enhancing chloride transport and subsequently improving lung function in CF patients [21].

Yet it is notable that the progress of personalized therapy in clinical practice using pharmacogenomic information is taking place in small steps. This cannot be explained solely by the challenges of translational research partnerships or by the lack of prospective data on the clinical utility of new pharmacogenomic biomarkers. Knowledge from this past year about the enormous potential of an integrative personal 'omics profile of the individual patient indicates that we are just beginning to understand complex phenotypes such as drug responses, which may also change over time [22]. More intensive research activities are warranted to establish pharmacogenomic signatures with high predictive value to identify patients at risk of drug failure and/or drug-related side effects. Only those signatures better than isolated genetic variants will obtain high acceptance rates in clinical practice [23], thereby promoting the progress of personalized medicine. This means that pharmacogenomic research should profit from more comprehensive information provided by clinical and 'omics resources.

Matthias Schwab,
Section Editor,

Pharmacogenomics and personalized medicine

Top-down proteomics arrives

Proteomics has been dominated by bottom-up approaches, in which proteins are digested into peptides before mass spectrometry (MS) identification. Although this strategy has been effective, it effectively 'scrambles' the proteome before MS analysis, adding uncertainty in how to put the pieces back together. There are advantages to measuring proteins intact, but such top-down approaches have languished behind bottom-up methods because of issues related to fractionation, MS instrumentation and software. To many scientists, top-down proteomics is effective at identifying isolated proteins or confirming the identity of a protein, but its application to global discovery has been limited. This past year, however, we have seen tremendous advances in the ability to characterize complex proteomes using top-down methods.

What may be unexpected is that the major advances were not centered on the mass spectrometer but involved the way in which the intact proteins were fractionated before MS analysis. Kelleher and colleagues used a tube-gel electrophoresis (TGE) device to separate intact proteins by molecular mass before top-down MS identification [24]. Proteins were extracted from *Saccharomyces cerevisiae* and those in the 0 to 50 kDa molecular weight range were separated into 12 fractions using TGE. Each of these fractions of intact proteins was analyzed in triplicate using nanocapillary liquid chromatography tandem MS. Within 72 hours, a time period comparable to that required using bottom-up approaches, 530 unique proteins and 1,103 distinct protein species (including isoforms) were identified. This report [24] built upon a previous study [25] in which this group identified over 3,000 proteins from human cells using top-down MS. In this earlier study [24], however, a four-dimensional separation strategy was required. These reports represent the largest yeast and human proteome coverages demonstrated so far, and the yeast study [24] specifically showed that top-down proteomics can be conducted with the throughput capabilities and timescale of bottom-up approaches. These studies signify important advances in bringing the characterization of intact proteins, and their isoforms, to proteomic laboratories worldwide.

*Timothy Veenstra,
Section Editor,
Proteomics and metabolomics*

The move from reactive to proactive medicine is under way

Integration of an ever-increasing variety and quantity of biological, clinical, epidemiological, environmental, functional, genetic, genomic, pathological and physiological data through systems approaches is the cornerstone for the personalized treatment of individuals, the ultimate

goal of doctors since the Greek founders of medicine. In its modern form, personalized medicine is empowered by technological advances in experimental and computational platforms, triggering the transition from the current reactive practice of medicine to a more proactive mode of 'P4' (predictive, preventive, personalized and participatory) systems medicine [26]. A fundamental limiting factor in this process is our ability to distinguish causative, explanatory and actionable relationships from the wide range of correlations revealed, for example, in genome-wide association studies or clinical trials that require assessment of hundreds to thousands of patients and control participants to extract meaningful information [27]. This explains why very few of the large number of promising biomarkers and drug targets make their way to effective clinical practice, and thus why costs in drug development and healthcare have escalated [28].

During the past year, great advances have been made in overcoming these hurdles, as witnessed by two reports on the longitudinal follow-up of individuals and integration of extensive datasets [29,30]. In the first case, an integrated, dynamic 'omics profile for one person was recorded regularly over more than a year, combining genomic, transcriptomic, metabolomic and immunological profiles. It revealed a risk for type 2 diabetes and pathways and molecular mechanisms distinctive to the healthy and disease states for that individual [29]. The second case is a report on a decade-long quantitative recording of blood and stool biomarkers, tracking of nutrition, exercise, sleep and stress, combined with personal genetics and microbiome assessment of one individual. It detected a persistent source of inflammation that turned out to be an early pre-symptomatic sign of the development of late-onset inflammatory bowel disease [30]. These are important steps for these individuals, who were alerted on their potential or actual health risks earlier than they would have been in a classical medical situation. Most importantly, the two studies indicate that collection of datasets in regular time series and their combination with background genetic or genomic data on single individuals is sufficiently powerful to overcome the hurdles discussed above. Such findings should, in turn, inform studies in pharmacogenomics so as to tailor personalized treatments for larger groups of patients [23]. They should also facilitate the development of panels of indicators for disease control as part of decision-support systems for the monitoring of prominent complex diseases, such as chronic obstructive pulmonary disease, by patients and their physicians [31]. The P4 medicine that seemed to be a long-term possibility is thus now becoming a reality [32].

*Charles Auffray,
Section Editor,
Systems medicine and informatics*

The policy challenges of inexpensive whole-genome sequencing

Although many of the most common ethical, legal and social issues continued to stir debate - including the issues associated with human gene patents, return of results and consent for participation in biobanks - the challenges associated with inexpensive and efficient WGS attracted a significant amount of policy attention in 2012.

Because of the rapid increase in the speed and efficiency of sequencing technologies, it has long been speculated that routine WGS was a near-future inevitability. Over the past year, a range of developments, including the use of whole-genome technology in the prenatal context [33], have pushed the issue beyond mere speculation and heightened policy debates on the social implications of the technology. For example, there are emerging questions about the actual health value of routine WGS [34] and its potential adverse impact - from, for example, a cost perspective - on the health care system [35]. There seems little doubt that the technology will, among other effects, advance genomic research and our understanding of a range of diseases and help in the diagnosis of rare diseases. However, the limited predictive value of most genomic information (particularly in the context of common chronic diseases) [34], coupled with the fact that most health care providers seem ill equipped to use the information, has resulted in a call for more research and health policy analysis on how WGS technology can be used in a clinically beneficial and cost effective manner [36]. The prospect of cheap WGS has also heightened, rightly or not, concerns about privacy [37,38]. This is due, in part, to the vast amount of personal information (albeit largely uninterpretable) generated, the enduring perception that genetic information is unique and the related idea that genomic data will have biological relevance. This latter issue has raised interesting questions about the possible need to obtain consent from relatives prior to the public release of genomic information. Although all of these issues are worthy of further analysis, it is the use of this technology in the context of non-invasive prenatal genetic tests that generated the most controversy [39]. Indeed, *Scientific American* selected genome sequencing of fetuses as one of the world-changing developments of 2012 [40]. These developments seem certain to generate both intense social debate and a range of regulatory responses [41].

Timothy Caulfield,
Section Editor, Ethical, legal and social issues

Abbreviations

CDC, Centers for Disease Control; CHC, chronic hepatitis C; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane receptor; DNM, *de novo* mutation; FDA, US Food and Drug Administration; P4, predictive, preventive, personalized and participatory; SNV, single nucleotide polymorphism; TAR, thrombocytopenia absent radius; TGE, tube-gel electrophoresis; WGS, whole-genome sequencing.

Competing interests

The authors declare that they have no competing interests.

Endnote

[†]The views expressed here are those of the authors and not necessarily those of the US Department of Health and Human Services.

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