Genomic medicine enters the neurology clinic

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Extraordinary advances in genetics and genomics are revolutionizing the practice of medicine. In this issue of *Neurology*®, 3 articles demonstrate the utility of exome sequencing for identifying the genetic cause of neurologic disorders. This issue represents a landmark in neurogenetics: the concurrent publication of 3 such examples highlights the rapidly changing landscape driven by exome and genome sequencing, and presages the widespread application of these methods for the diagnosis of neurologic disease. Landouré et al.[1] identify a novel mutation in *TRPV4* causing a Charcot-Marie-Tooth (CMT) 2C phenotype, missed by Sanger sequencing. They confirmed the pathogenicity of this dominant mutation using calcium imaging in vitro to show that a TRP antagonist reversed the pathogenic increase in calcium and cell death. Sailer et al.[2] used exome sequencing to identify the cause of spinocerebellar ataxia (SCA), another condition with marked locus heterogeneity. Here too, a conventional screen based on previously reported mutations failed to detect the novel mutation in *PRKCG* causing SCA14. Finally, Pierson et al.[3] identified 2 compound heterozygous mutations in *GLB1*, responsible for recessive juvenile-onset GM_1 in a family where initial β-galactosidase enzyme analysis was reported as normal.

In contrast to whole-genome sequencing, where all 3 billion bases of the human genome are sequenced, exome sequencing consists of the capture by hybridization and targeted sequencing of all the protein-coding regions of the genome. This corresponds to ~1%–3% of the human genome, for less than $1,000 in most centers. These advances are due to next-generation sequencing methods that reliably sequence billions of bases in a few days.[4] However, it is just a first step; whole-genome sequencing will likely become even faster and less expensive, and may replace exome sequencing.

We envision 4 mainstream applications of exome/genome sequencing in clinical and translational research:

1. *Discovery of novel causal genes in mendelian disorders.* Although it comprises a few percent of the human genome, the exome is estimated to include the majority of the large-effect size, disease-causing variants in humans. Indeed, causal mutations in a large number of mendelian conditions have already been found using this technique,[5] and the genetic etiology of the estimated ~7,000 mendelian diseases is expected to be solved within the next 5 years.
2. *Efficient screen of diseases with locus heterogeneity.* The utility of this approach is exemplified by the 3 articles published in this issue. For many diseases with marked locus heterogeneity, such as SCAs and CMT, multiple large genes are implicated, making conventional screening for each patient impractical. Exome sequencing provides a cost-efficient alternative to conventional Sanger-based methods. Since the first whole-genome sequencing in CMT,[6] examples of extensive targeted resequencing have been reported,[7] and we expect this application to soon enter patients' clinical charts.
3. *Identification of genetic modifiers within families with mendelian disorders.* Phenotypic studies in large families have shown that, despite the fact that all individuals in a single mendelian family share the same causal mutation, considerable phenotypic heterogeneity is present (e.g., Alzheimer disease due to *PSEN1* mutations). Identifying rare and common genetic modifiers of disease course in mendelian diseases is now a tractable problem, and provides a conceptual bridge between mendelian and complex diseases.
4. *Genetic characterization of complex heterogeneous disease categories.* The "missing heritability" is the single most important problem in complex disease genetics.[8] Signals identified in genome-wide association studies (GWAS) explain only a fraction of the estimated heritability, and many support the assumption that rare variants have

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larger effect sizes, or may underlie some of the GWAS association signals.[9] Such rare variants can only be detected by sequencing; examples include schizophrenia[10] and mental retardation.[11] Genome sequencing is revealing that we all carry many rare variants, including nonsense mutations, predicted to be benign.[12] Thus, the previous notion that most rare variation is pathogenic needs careful reappraisal. Complementary investigations, including gene expression and epigenetic profiling, will aid in interpreting large-scale sequencing data, by refining the search among massive numbers of variants and defining those most likely to be pathogenic. Paradoxically, after a decade of case-control association studies, we expect a reappearance of family-based studies for complex diseases, which permit analysis of segregation and de novo variant detection. This will be complemented by large-scale use of the electronic medical record (e.g., reference 13).

As for any other technology trying to enter the clinical arena, there are challenges and barriers to overcome. We will focus on 3 areas:

1. *Technical issues:* Current exome coverage is incomplete and researchers need to be aware of what they may miss (Sailer et al. show that exome sequencing did not provide sufficient coverage of 15 of their 36 target genes). Sequencing is handicapped in its ability to detect repeat expansions and certain structural rearrangements. The genetic bases of many major neurologic disorders (e.g., Huntington disease, CMT, Friedreich ataxia, most SCAs) would not have been found by current exome sequencing strategies. Certainly the existing, gold-standard methods used in clinical practice are not perfect either; the 3 articles discussed here demonstrate this clearly.
2. *Analytical challenges:* Each exome experiment identifies thousands of variants.[5] Catalogs of previously identified human variation (such as the Exome Variant Server, http://evs.gs.washington.edu/EVS, and the 1,000 Genomes Project, http://www.1000genomes.org) are key to identify benign rare variants. However, to obtain a clinical-grade sequencing assay, it is essential to standardize quality measures and analysis algorithms, and to agree on standards and guidelines for data quality and interpretation.
3. *Returning data to patients:* Regardless of the outcome of the primary analysis, such as the identification of a causal gene, genetic modifier, or risk factor, a large number of "unrelated" genetic findings (the "incidentalome"[14]) may be identified. For example, a sequencing study originally performed for dementia might determine that the patient is a carrier of a mutation for a recessive, potentially fatal disease, for which therapy is not available (a "nonactionable" finding). Are clinicians or genetic counselors expected to share this information with their patients? This is a much-debated but unresolved issue.[15] Although there are examples of sequencing that altered clinical management,[16] doctors and patients must accept that in most cases, even when genome sequencing points to causal or strong genetic risk factors, it may take years before they alter patient care.

Genome sequencing is expected to enter patients' charts in the near future. Once issues related to informed consent and data return to patients are addressed, we expect this to become a routine clinical test. We will increasingly be able to make sense of the large number of sequence variants identified in each patient, under the "sequence early, check often" model, leveraging the genetic knowledge derived from large-scale resequencing studies in patients, and periodically re-evaluating the contribution of genetic variants to disease.[13]

The last 20 years have been an exciting time in human genetics. The recent advances in sequencing will transform our knowledge of how genetic variation contributes to human disease. It will not be long before every patient will arrive to the clinic with a sequenced genome and expect us to incorporate it in our diagnosis and treatment plans.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. **Go to Neurology.org for full disclosures.**

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