Movement Disorders
CLINICAL PRACTICE
CONTROVERSY

Will New Genetic Techniques Like Exome Sequencing Obviate the Need for Clinical Expertise? No

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A 51-year-old previously healthy woman developed a subacute onset of retrocollis while living in Jamaica. There was no family history of neurological problems, and she denied taking illicit drugs or having been prescribed dopamine-blocking agents. Evaluation by a neurologist showed that, apart from cervical dystonia, neurological examination was normal. Extensive laboratory investigations and neuroimaging were normal. Clinical exome sequencing (CES) revealed a variant of unknown significance in the GNAL gene. The neurologist concluded that the variant was significant given the clinical picture and recent excitement about this newly discovered gene, and a diagnosis of cervical dystonia secondary to a GNAL mutation was made. A movement disorders clinician saw her, and a careful history revealed that, in Jamaica, when she was undergoing a rather messy divorce, she had taken a "calming drug" prescribed to one of her friends who had schizophrenia. This calming drug happened to be haloperidol. Obviously, without a thorough history, the diagnosis of tardive dystonia would have been missed with clear prognostic and therapeutic implications.

Movement disorders is the last remaining bastion of clinical neurology. We pride ourselves in practicing the bedside art of careful clinical history and astute observation. This leads to targeted laboratory investigations that help make the appropriate diagnosis and direct management strategy.

Next-generation sequencing (NGS) utilizes a massively parallel approach which can effectively and efficiently sequence the entire genome within weeks. NGS includes CES, whole-exome sequencing, whole-genome sequencing, and targeted gene sequencing. For clinical purposes, CES is often used.[1] CES sequences 1% to 2% of the protein coding part of the genome called the exome. This only constitutes 1% to 2% of the whole genome, but is estimated to carry 85% of the known mutations. It is important to realize that CES does not detect triplicate repeat disorders, copy number variations (large deletions or duplications), and does not sequence the noncoding part of the genome.

Whereas NGS holds great promise in advancing and expanding our ability to diagnose genetic contributions to the etiology of our movement disorders patients, in our opinion the role of the clinical expert is now more crucial than ever.

The ability to sequence tens or hundreds of millions of short DNA fragments in a single run is enabling increasingly large experiments, and the technologies are improving exponentially. However, the interpretation of the results and understanding their clinical significance is lagging behind. Even as the cost of NGS is diminishing, a movement disorders neurologist consultation remains the most cost-effective assessment of any patient. In the absence of the clinical skills that should be the trademark of the movement disorders expert, physicians will be overwhelmed by the complexity of unexpected genetic findings, and this may lead to unnecessary tests and cause additional psychological and physical morbidity and expense. Widespread use of these tests in a vacuum created by a lack of movement disorders clinical skills will simply drive the total cost of genomic medicine upward with little benefit to patients or physicians (but with great financial benefits to the genomic testing industry), thus placing the overall societal benefit of genomic medicine into question.

On the other hand, NGS has the potential to save money by obviating the need for further costly, and sometimes invasive, testing. The key is to obtain a balance by using clinical judgment and assuring the validity of NGS results. Current ethical and legal norms require that doctors give priority to the interests of their patients, so that patients are not turned into research subjects without their informed consent. The physician-patient interaction is of paramount importance not only in selecting what question to ask, but also explaining the results to the patient and then making decisions regarding further testing

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and intervention. NGS takes time and is entirely inappropriate in acute situations where immediate intervention is needed. Purely environmental factors that lead to dysfunction of the nervous system, such as trauma, toxins, and drugs, with resultant movement disorders are not evaluable by NGS and could lead to misdiagnoses, as demonstrated by the patient example above. Admittedly, genetic predisposition to environmental factors does exist, and future advances in this field will be made possible through modern genetic techniques. Theoretically, a GNAL mutation could have predisposed to tardive dystonia in the patient example above. However, this possible relationship will require large population studies, will not influence individual patient care for some time to come, and does not diminish the importance of recognizing the role of the neuroleptic treatment in causing the patient's movement disorder.

Given that genomic sequencing is a phenotype-agnostic test, it is not surprising that the elephant in the room is the detection of incidental findings, also called secondary findings[2] (e.g., mutations in the BRCA1 gene predisposing to breast cancer). The situation here has been called an "incidentalome" and is comparable to "incidentalomas" that are well known to radiologists.[3] This requires a decision of whether and how these results should be communicated to the individual (patient, asymptomatic family member of a patient, or healthy control).[4] However, it is reassuring that the incidentalome rate may be lower than feared.[5]

Another issue is the finding of variants of unknown significance (VUS), which can be potentially confusing to the clinician and the patient. Any genetic testing should be preceded by a thorough genetic counseling session, led by a clinical geneticist or the treating physician with the experience to explain the significance of the test, its implications, and potential outcomes for the patient and family. If an NGS-based test is offered to the patient, the possibility of incidental findings should also be fully discussed in this session, and a written informed consent should be obtained. Similarly, the test results should be carefully explained to the patient, including any VUS. Without these fundamental steps, genetic testing is only likely to create further confusion and fear in patients.

To address the VUS issue, the American College of Medical Genetics and Genomics and the Association for Molecular Pathology recommended that variants be classified into five categories (pathogenic, likely pathogenic, uncertain significance, likely benign, and benign). Furthermore, it is recommended that VUS (as the GNAL reported in our patient) should not be used in clinical decision making.[6] In fact, some diagnostic labs only include those variants that are classified as pathogenic or likely pathogenic in their diagnostic reports. It is very important that clinicians understand that, at present, it is impossible to be sure whether VUS are benign or potentially damaging, and there is no ground to attribute any clinical relevance to VUS. The interpretation should improve with large databases and open sharing of data, but this will take quite some time.

Furthermore, it should be remembered that each individual could well develop two or more concomitant unrelated disorders, each with a distinct, and not necessarily genetic, etiopathogenesis. This is especially true of patients carrying a gene that is incompletely penetrant. For example, psychogenic/functional dystonia has been reported in a carrier of a GAG deletion in the torsin A gene.[7] Furthermore, we have observed overt evidence of functional movement disorders on videotapes presented at international conferences purporting to show patients with novel phenotypes attributed to genetic findings discovered on NGS.

In addition, carrying a pathogenic variant does not define an individual. The variant, in most cases, does not protect an individual from developing unrelated diseases. We have seen patients carrying one of the SCA gene pathogenic variants whose major neurological disability was attributed to coincidental multiple sclerosis (MS).[8] Similarly, 1 member of a sibship that we (A.E.L.) recently reported on[9] with peroxisomal D-bifunctional protein deficiency also had MS, and the clinical assessment finally trumped the geneticist's initial belief that demyelination was a novel manifestation of the genetic disorder (once again, we admit that genetic predisposition remains a possible factor).

Most genetic measurements only shift the probability of an outcome, which often depends on other environmental factors and chance. In many cases, a significant pathological disease burden never reaches clinical significance and is unrelated to the ultimate clinical outcome. To borrow examples from other branches of medicine, routine autopsies reveal a high number of incidental pituitary microadenomas,[10] and a large number of prostate carcinomas accurately diagnosed after the finding of an elevated prostate-specific antigen level in all likelihood will not contribute to an individual's death.[11]

And we have not even begun to discuss the inherent limitations of the technique. There are no universally accepted published standards to enable the consistent, widespread use of genomics in the practice of medicine. Lack of standardization and the variability from one laboratory to another is a major issue. There are multiple platforms, and without a gold standard, the concordance between different platforms is low. Unlike other data-intensive diagnostic modalities, such as MRI, there are no standards for use of computational tools to analyze the outputs of different NGS technologies for patient care. Genomic medicine will require such consensus and standardization to achieve widespread, routine, and reliable clinical use.

The "clarity challenge" critically highlighted this issue.[12] Here, 30 well-known NGS laboratories were given samples from 3 different individuals with known genetic disorders (centronuclear myopathy with bilateral sensorineural hearing loss, nemaline myopathy, and an individual with right-sided heart defects and conduction abnormalities). Despite the fact that all of the laboratories were experienced and received the same data, only 23 of them completed the task. Furthermore, remarkably, only two of the centers were able to make the exact genetic diagnoses in all three families. This exemplifies the complexities inherent in the current analyses and reporting of massive amounts of NGS data.

The fact that many teams did not appreciate the significance of GJB2 mutations in patients with centronuclear myopathy and

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sensorineural hearing loss suggests that additional detailed input from medical experts reviewing the clinical data would have been beneficial. This highlights the need to have a clinician with genetics expertise involved in preparing a carefully considered pretest differential diagnosis. This would include the consideration of the possibility of a large chromosomal deletion or a trinucleotide repeat disorder, which are not detected by NGS.

The detection of a genetic abnormality through NGS is just one step in studying the complexity of human disease. Defining mechanisms through a thorough understanding of cell biology is the next crucial step. However, without the careful interpretation of their clinical significance and proper explanation and compassionate care of patients by a clinical expert, all that are nothing more than interesting, and potentially very confusing, data.

The art of percussion may have been replaced by ultrasound, but it will be long before any laboratory technique, including NGS and neuroimaging, replaces a good movement disorders clinician.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

K.S.: 1B, 1C, 2A, 2B, 2C, 3A, 3B

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