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Clinical Genomics Answers Questions Concerning the Etiology of Neurological and Developmental Disorders*

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Abstract

In the past decade, advances in the ability to detect both small sequence variants and larger copy number and structural alterations have augmented scientific and medical understanding of neurodegenerative and neurodevelopmental disorders. Technologies that have contributed to the advent of new knowledge include high-throughput deep sequencing techniques (next-generation sequencing or NGS) and artificial-intelligence based advanced bioinformatics that allows for careful examination of NGS results. In medical genetics clinics, the first round of testing may include a chromosomal microarray, biochemical analyses, or a single gene or panel sequencing test, yet a growing portion of the patients undergo whole exome or genome sequencing to uncover their genomic diagnosis. A review of patient histories and genomic results demonstrates the accuracy and efficacy of such testing to arrive at an answer to a long diagnostic odyssey for many patients. Knowledge of the cellular function of the genes associated with the underlying diagnosis has led to new therapies and changed the prognosis for some of these patients.

Keywords

Clinical genomics, neurological disorders, developmental disorders, neurodegeneration, molecular diagnostics, secondary findings.

Contents

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Introduction

Many patients with neurological and developmental disorders present as undiagnosed when first encountered by their clinicians. Work-up for these patients may be relatively simple. For example, consider an infant with a severe seizure disorder who undergoes single gene testing and is found to have a pathogenic variant in the first gene tested such as *SCN1A* [1]. In contrast, work-up may also be prolonged over time and may be very costly. For example, consider a patient whose molecular diagnosis is only clarified when detected by whole genome sequencing (WGS) after a series of other tests. Deep sequencing assays like whole exome sequencing (WES) or WGS provide an enormous amount of data, which may reveal a diagnosis more rapidly for many patients if performed early.

The introduction of artificial intelligence-driven bioinformatics platforms has provided methodology for the analysis of the sequencing data to rapidly sort through thousands of variants to arrive at alterations that may be diagnostic. These platforms use many of the same publicly available databases that look at evolutionary conservation across species, and in silico algorithms that estimate the effect of any alteration on the messenger RNA and protein product of a gene. Thus, the use of a robust bioinformatics platform remains essential for the analysis of WES and WGS data.

There are significant advantages to deep sequencing techniques for molecular diagnostics. With both WES and WGS, analysis of all of the approximately 20,000 genes can take place simultaneously. While coverage of some genes or regions of the genome is imperfect, pathogenic variants can be identified. Single nucleotide variants as well as small deletions, insertions, and more complex alterations can be accurately vetted for pathogenicity. While WGS is better at identifying larger deletions, duplications, and structural rearrangements, some may be detected by WES. WGS also allows for the identification of variants in the areas outside of the exome or in the introns. Published guidelines [2]–[5] help provide standards for the interpretation of both constitutional and somatic variants.

Large population databases that describe variations across all ethnicities have grown from those with approximately 1000 individuals (see the IGSR 1000 Genomes Project [6]) to those with tens of thousands of individuals (see the Broad Institute Genome Aggregation Database gnomAD [7]). By increasing the geoethnic diversity of the genomic data, analysts are better able to distinguish benign variants that are found in one or two specific ancestral groups from the more rare pathogenic variants that are associated with genetic disorders. The

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large number of previously published 'mutations' now known to be benign has influenced the development of open-access databases (see ClinVar [8] and ClinGen [9]) that rely on curation by expert panels with the data available online.

Another benefit of WES and WGS is the ability to identify secondary findings that are medically actionable. Subsequent clinical use of this knowledge is often lifesaving. The American College of Medical Genetics and Genomics (ACMG) has currently recommended the examination of 59 genes for known pathogenic and likely pathogenic variants [10]. These include alterations that have been shown to cause diseases such as colon cancer or cardiac arrhythmias.

However, there are limitations to this type of testing. It is difficult to detect repeat expansions. For example, consider the pathogenic variants that are associated with Huntington disease or fragile X syndrome. The mitochondrial genome is not always interrogated with this type of testing, although some WGS assays include the analysis of mitochondrial DNA. There are pseudogenes or inactive genes that can have sequence similarity to other genes and that can confound analysis. Not all nucleotides of all genes are covered well with this approach to diagnostic testing.

Clinical Examples

Case 1

A teenager with a life-long movement disorder including tremor, dystonia, and cogwheel rigidity as well as developmental delay had undergone extensive investigation including brain imaging, EEG, EMG and nerve conduction testing, karyotype analysis, array comparative genome hybridization, and other gene panel sequencing analysis without diagnosis. She underwent trio WES analysis with samples from her unaffected parents. (Trio analysis refers to WES analysis of each of the three individuals, *i.e.*, the patient and both parents.) Her family history included Parkinson disease in the maternal grandmother. Her parents denied that they were related to each other. However, both parents came from the same isolated village in Bolivia, suggesting the possibility of consanguinity.

WES analysis identified a homozygous pathogenic nonsense variant in the *DNAJC6* gene [11], associated with autosomal recessive juvenile Parkinson disease. In addition, the mother and the patient were both found to have a pathogenic missense variant in the *LRRK2* gene [12], which is associated with adult-onset Parkinson disease. The maternal grandmother was tested and the same *LRRK2* variant was identified in her sample.

Case 2

A young man with a three-year history of neurodegeneration underwent trio WES analysis (with samples from the patient and both parents). He had been an excellent student who wanted to attend medical school, when he found that he was having trouble with his memory. Within a year, he was unable to attend school and had to move back to his parents' home. He underwent brain imaging studies, karyotype analysis, array comparative genome analysis, and a series of molecular genetic tests all of which were normal. No family history was reported for similar presentations and the parents denied that they were related to each other. The family's geoethnic ancestry was mixed European.

WES analysis revealed a pathogenic missense variant in the *MAPT* gene [13] that was also found in his father. *MAPT* is associated with three disorders that include neurodegeneration, frontotemporal dementia, Pick disease, and progressive supranuclear palsy. The father underwent neurological examination, and was found to have signs of early dementia.

In addition to the MAPT variant, a pathogenic missense variant in the *BRCA1* gene [14] was found in both the patient and his mother. This gene is on the list of genes that ACMG recommends to be examined in order to identify secondary findings. The mother was examined and underwent mammography, which revealed a very small lesion that was biopsied, and found to be breast cancer. She then underwent bilateral mastectomy and salpingo-oophorectomy. Other members of her family were tested for this variant, and assessed for breast, ovarian, or other *BRCA1*-associated cancer.

Discussion

These two cases demonstrate the utility of WES or WGS in identifying the causal variants in neurological and developmental disorders. Both families benefitted from the identification of the alteration leading to the neurological disorder in the patients as well as the pathogenic variant found in the *BRCA1* gene in the second family. Both patients had undergone extensive, time-consuming, and expensive testing that did not lead to a diagnosis prior to WES.

With the advent of improved sequencers, methods, and bioinformatics, the turn-around time for routine deep sequencing assays has fallen to approximately two to three weeks in most labs. In addition, the cost of sequencing has fallen dramatically. Therefore, WES and WGS can be both time- and cost-efficient diagnostic tools.

Clinical genomics laboratories have the experience and expertise to use the patient's clinical details to guide the molecular diagnosis. The use of AI-driven bioinformatics platforms that incorporate the population data, in silico algorithms, evolutionary conservation, and prior sequencing data from assays run in the labs is crucial to the ability to handle the very large amount of sequencing data generated by WES and WGS analysis. These cases demonstrate the importance of arriving at a molecular diagnosis for patients with neurological or developmental disorders.

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