Editorial

Exome Sequencing and Molecular Diagnosis

Does It Help Patients and Their Families?

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Editorial to accompany the article:

“Exome sequencing in children—undiagnosed developmental delay and neurological illness” by Elisa A. Mahler et al.

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The integration of genomics into medical practice and the potential to provide molecular diagnostic information has transformed many medical specialties. This is the case in child neurology and developmental medicine, given that 84% of human genes are expressed in the process of building and maintaining a human brain and over half of all developmental disorders are genetically determined (1).

Distinct advantages

Clinical genomics is the sequencing and analysis of all human genes (genome sequencing, GS) or of gene coding regions (exome sequencing, ES). The clear advantages of ES compared to GS are the lower costs and more manageable data sets for analysis. The exome comprises only around 1% of the human genome, but pathogenic variants (previously referred to as “mutations”) of these coding regions cause about 85% of known Mendelian diseases.

Studies using ES in child neurology report a “diagnostic yield” in biologically-undiagnosed children of between 25 to 50%, and using the costlier and more extensive GS, a diagnostic yield up to 60% (2, 3). In the article on the following pages, Mahler et al. describe their experience with ES as a diagnostic tool in 50 children with undiagnosed developmental disorders (4). Not unexpectedly, these genome researchers from Hamburg-Eppendorf found a definite molecular diagnosis in 42 % of cases—at first glance, impressive results. In three of the 50 patients (6 %) they identified a medically treatable disorder. Two of these three patients had disorders that could have been diagnosed clinically, but ES may have brought about earlier diagnosis and treatment. In addition, the authors report that in 17 of the 50 study participants the identification of a pathogenic variant led to modification of the clinical management.

Considering the steadily falling cost of ES and GS, researchers and physicians hope that affordable sequencing will lead to more personalized medical care in ways that will benefit children, families, and society (5). But does clinical genomics actually help patients and their families? The answer could turn out to be yes, no, or uncertain. Primary ES results are generally reported in one of three basic categories:

- A positive genetic diagnosis, i.e., detection of a pathogenic variant that is associated with a known disease or disorder
- Negative, i.e., no clear molecular diagnosis
- Uncertain findings (variants of uncertain significance), i.e., results that may or may not turn out to have clinical implications.

ES may also generate unexpected secondary (incidental) findings, i.e., results unrelated to the primary medical reason for performing the procedure. Parents should be counseled before ES commences and it should be determined what they do or do not want to know about incidental findings (such as genetic risk for later-onset diseases) (7).

The value of ES seems to depend on multiple factors, including the actual test results, the interpretation of clinical utility, parental expectations and their appreciation of genetic uncertainty. The discovery of a molecular diagnosis and an effective medical therapy is obviously the most desired outcome following ES. Supportive therapies and services should, however, be based on need and not on the results of the gene test.

Benefits for affected families

Some of the clinical utility attributed to ES may relate to nonspecific changes in medical care, discontinuation of additional unnecessary testing, and effects on reproductive planning. Having a specific name for the disorder, knowing its cause and recurrence risk, and estimating its prognosis provides considerable value for families. Parents whose children receive a medically untreatable molecular diagnosis frequently find indirect benefit through internet-based resources and networking with rare disorder support groups.

Most families receiving molecular diagnostic ES results are informed about an ultra-rare disease or disorder, with limited available information about the disorder, its clinical course and possible interventions. Recent studies indicate that most parents of children with developmental disorders wish to receive all available diagnostic information, including variants of uncertain significance possibly linked to their child’s disorder, as well as information about secondary findings—even for incurable diseases (8).

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This quest for more diagnostic information by parents reflects their urgent need to understand all potential genetic risks, given the life-altering reality of the child's developmental disorder. The developmental disorder changes not only the life of the affected child, but also the lives of the parents and siblings. Even if it is not clear how to interpret the diagnostic data, parents need to know that all actionable medical options have been considered. Thereafter, most parental concerns remain primarily focused on practical uncertainties such as their child's likely maximal abilities, eventual disabilities, and the need of support services.

Both parents and physicians may have unrealistic expectations about the positive impact of ES. The overly simplistic "central dogma" (i.e., one gene, one protein, one phenotype) rarely applies to developmental neurobiology, where a more complex path from genotype to phenotype typically comprises "several genes, several proteins, one phenotype"—especially when the phenotype is as ambiguous as "global developmental delay" or "autism".

Cautious interpretation of sequencing data

Exome sequencing should not be pursued as a means to an end, as attempting to reduce diagnostic uncertainty often only reveals the reality of a greater "genomic uncertainty" (9, 10).

Instead, throughout the genomic sequencing process, emphasis should be placed on the expectations from genomic information and the recognition of its potential uncertainty. Even in the era of increasing democratization of information, genomic data needs careful interpretation.

The essential role of the physician will be to act as both translator and filter of genomic information for families looking for answers about biologically complex conditions.

Conflict of interest statement

The author declares that no conflict of interest exists.

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