SPECIAL COMMUNICATION

The "New Genetics" in Clinical Practice: A Brief Primer

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Major advances in human genetics have led to the identification of 4451 genes to date with disease-carrying mutations, thereby enabling precise diagnoses of all of these monogenic disorders. Limitations to the use of the "new genetics" do exist, however, including the recognition of genetic heterogeneity, many variants of unknown significance, and incidental diagnoses. This article reviews information to help use these advances to aid accurate diagnoses, identify carriers, and determine prenatal diagnoses, providing opportunities to avoid or prevent serious and fatal genetic disorders. (J Am Board Fam Med 2017;30:377–379.)

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Technological advances in human genetics have led to the identification of 4451 genes to date with phenotype-causing mutations.[1] Over 7000 rare genetic disorders are known, affecting about 1 in 12 individuals.[2] Prenatal or preimplantation genetic diagnosis is now available for virtually all monogenic diseases, providing opportunities to avoid or prevent serious to fatal genetic disorders.[3] A prerequisite is identification of the gene mutation in carriers and in affected family members.

A careful family history helps determine the mode of inheritance and variable manifestations of the disease in the family, which can aid in direct testing and the interpretation of test results. However, limitations exist. Commonly used family history checklists often address only a few genetic disorders. In light of advances in the "new genetics," such checklists are usually inadequate for deciding on specific genetic testing. Although difficult, it is best to encourage individuals and couples to be as specific as possible about the diseases that have affected family members over 3 generations. Ethnicity is important, as each person harbors 250–300 loss-of-function mutations,[4] and each ethnic group has a preponderance of certain genetic disorders for which carrier detection tests are available. Risks conferred by consanguinity are also especially critical. Extensive online resources about genetic disorders and genetic tests are available.[4] The vast majority of major medical centers employ either clinical geneticists and/or genetic counselors.

Single-Gene Sequencing

The occurrence of a serious autosomal-dominant genetic disorder with neither parent affected would point toward a de novo mutation (eg, about 66% of patients with tuberous sclerosis and 50% of patients with neurofibromatosis type 1 have a new mutation) or, rarely, a germline mutation. Single-gene sequencing is accomplished by analyzing DNA extracted from a small blood sample, cultured or noncultured amniotic fluid cells, or chorionic villi, or from any tissue. Cost varies according to the size of the gene (for sequencing), the use of a multigene panel, or more extensive whole-exome sequencing (WES). These and other genetic analyses have been invaluable in achieving precise diagnoses and obviating the need for unnecessary tests, such as magnetic resonance imaging (eg, Huntington disease and spinocerebellar ataxia), radiography (eg, bone dysplasias), muscle and skin

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biopsies (eg, many muscular dystrophies and neurofibromatosis), electroencephalography (eg, epileptic encephalopathies), and electromyography (eg, myotonic muscular dystrophy).

Variants of Unknown Significance

Mutations are now being reported as pathogenic, likely pathogenic, benign or likely benign, or a variant of unknown significance (VUS).[5] Unfortunately, the report of a VUS is common, leaving the clinician and the individual or couple uncertain. The possibility of a VUS should be brought up as part of informed consent, before any DNA test is done. It is also likely that with increasing knowledge of the genome and related phenotypes, some mutations that are now labeled as VUSs will be subsequently categorized as pathogenic or benign. Further, the interpretation of variants may differ significantly between laboratories.

Same Genes, Different Diseases

Predictive prenatal diagnosis for adult-onset genetic diseases is being used to determine whether a fetus has inherited a gene mutation that would result in a high risk of a serious or fatal disease in adulthood, including breast/ovarian cancer, colon cancer, and hypertrophic cardiomyopathy. Caution should attend analysis of a family history that reveals ≥2 members with different cancers, as certain genes and their mutations have the propensity to cause cancer in different organs in members of the same family. For example, a mutation in a breast cancer gene (*BRCA1* or *BRCA2*) may lead not only to breast and ovarian cancers but also to pancreatic, colon, or prostate cancer. Individuals with hereditary nonpolyposis colon cancer may have family members who share a mutation in 1 of the 5 genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*) that cause this syndrome but result in different cancers, including cancer of the colon, endometrium, stomach, biliary tract, prostate, small intestine, ovary, urinary tract, and brain.

Rare Diseases: Next-Generation Sequencing Gene Panels

Recognition of genetic heterogeneity has led to the development of targeted gene panels for many disorders using next-generation sequencing (NGS).[6] NGS enables simultaneous analysis of multiple genes and is available in some academic medical centers and major commercial laboratories. The cost varies by the size and number of genes. Most are covered by insurance, provided that the clinical and family criteria are met. Examples include long QT syndrome, cardiomyopathies, epilepsy, and connective tissue diseases. A similar approach has been pursued with expanded panels of 200 genes for autosomal-recessive (n = 277) and sex-linked (n = 37) disorders, for identification of carriers for up to 368 disorders.[7] Serious doubt exists regarding the wisdom of such extensive testing, especially given the rarity of the disorders. Expanded panels complicate the informed consent process, given the impracticality of discussing a large array of rare diseases. More often, however, the focus has been on common mutations of targeted genes. Patients need to understand that a report of no mutation found in an expanded gene panel only means that their risk of being a carrier is markedly reduced, and that some residual risk remains.[8] The American College of Medical Genetics and Genomics (ACMGG) issued guidelines for preconception and prenatal expanded carrier screening in 2013.[9] They recommend that disorders should be of a nature that most at-risk patients and their partners identified in the screening program would consider having a prenatal diagnosis to facilitate making decisions surrounding reproduction. Furthermore, that the inclusion of "disorders characterized by variable expressivity or incomplete penetrance, and those known to be associated with a mild phenotype, should be optional and made transparent."[9] The ACMGG also recommends that genetic counseling also be available and provided before genetic testing for those with a positive screening result.

Same Phenotypic Disease, Many Different Genes: WES

Conditions can arise as a consequence of abnormalities in very different genes. For example, to date, mutations in over 386 genes that result in intellectual disability have been identified.[10] WES enables analysis of about 180,000 exons, the coding regions of the genome. Precise diagnoses are achieved in 25% to 30% of these cases.[11] A noteworthy limitation of WES is that small deletions or insertions can easily be missed. In general, the sensitivity is approximately 90% to 95%.

Dual Diagnoses and Incidental Detection of Genetic Disorders

Given the large number of exons analyzed by WES, it is no surprise that dual diagnoses may be revealed; these are thought to occur in about 5% of cases.[12] Potentially more challenging, however, is the discovery of a secondary (incidental) finding of a genetic disorder not being sought. This very real possibility makes counseling an absolute requirement before WES. Patients (or parents on behalf of their minor children) should be offered several opportunities to opt in or opt out before proceeding. It is important to understand that ACMGG has mandated that incidental discovery of any 1 of at least 59 listed disorders must be communicated, given that this information provides actionable opportunities that include treatment, prevention, and surveillance.[13] However, neither WES nor NGS can be used to diagnose the trinucleotide expansion disorders, such as fragile X syndrome, myotonic muscular dystrophy, and spinocerebellar ataxias.

Conclusion

As valuable as WES has become and as whole-genome sequencing will become, an abundance of caution is necessary when using these technologies. A cogent need exists for physicians to be fully aware of the utility, value, and limitations of the "new genetics" and of opportunities to avoid and prevent serious and fatal genetic disorders.

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