Ask the Expert

GENETICS AND GENOMICS

I have a patient with depression who has two parents with Alzheimer's disease (AD), and she wants to know about the value of getting commercial genome mapping for AD. What should I say to her?"

Reply from Robert M. Cohen, Ph.D., M.D.

The patient's question raises therapeutic, scientific, and ethical issues that dictate a response based on four different roles that a psychiatrist at times must assume: therapist, decider, information provider, and adviser.

Therapist. Without detailed information about the patient and the context in which the patient's question was posed, I am left to conjecture about the likely interpersonal and personal issues that underlie the patient's question. For example, there may be issues related to how the patient interacted and possibly cared for or did not care for her parents with dementia and whether the patient might become a burden on her own children as she ages or how she is currently a burden on her own family. Feelings of guilt, punishment, abandonment, and lack of self-worth are among the usual emotions that are associated with these types of interactions and thoughts, particularly in depressed patients, and are worthy of close examination.

Decider. As psychiatrists, it is sometimes necessary for us to make decisions for our patients, e.g., with respect to institutionalization. In this particular instance, should responsibility fall to the psychiatrist or to the patient to decide whether to get commercial genome mapping for AD? Currently there is considerable debate about the right of individuals to know as much information about their genes and their bodies as they choose. Although, giving individuals this prerogative is consistent with the transformation of medical care away from a paternalistic model, a prescription model is consistent with the vast majority of diagnostic tests that are likely to be used to make medical decisions that are ordered and interpreted by physicians.

Information provider. Currently, the only Clinical Laboratories Improvement Amendments-approved laboratory in the United States that provides specific genetic testing for both early- and late-onset Alzheimer's disease is Athena Diagnostics, use of which requires a physician order. Athena Diagnostics tests include polymerase chain reaction-based sequencing for mutations in three different genes (APP, the amyloid precursor protein, PSEN1, presenilin 1; and PSEN2, presenilin 2), and genotyping for the different genes that encode the three different forms of the apolipoprotein E protein (APOE2, APOE3, and APOE4). Although mutations in APP, PSEN1, and PSEN2 are responsible for the autosomal-dominant early-onset forms of AD, they account for less than 1% of all AD. Therefore, their relevance to this particular patient depends on the age of onset of the disease in the patient's parents, usually in the fifth or sixth decade of life, and whether there are aunts and uncles who also had early-onset dementia. Because late-onset AD (after 65 years of age and often referred to as sporadic) is by far the much more common form, APOE genotyping is likely to be of greater relevance with respect to this patient's risk assessment. Individuals who inherit an APOEε4 allele from one parent are approximately three times more likely to develop AD with an earlier age of onset and those who are unfortunate enough to inherit APOEε4 alleles from both parents have an approximately nine times greater risk for even earlier onset of AD. Still it is important to note that not all APOEε4 carriers develop AD, and many individuals who do not carry an APOEε4 allele develop AD with

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~50% of all patients with late-onset AD belonging to this latter category. Currently, APOE genotyping is not recommended for healthy individuals for AD risk assessment.

Although many other genes have been associated with either an increase or decrease in the risk for AD, none approach the impact of the APOE genotype on risk for late-onset AD. Although a variety of methods have been used to discover these weaker genetic risk factors, the most prominent method has been genome-wide association studies (GWASs). GWASs use common single nucleotide polymorphisms (SNPs) and form the basis for most personalized medicine services, which generally use these same SNPs to assess genetic risk for a variety of complex chronic disorders including AD. Unfortunately, the information obtained from these SNP maps of genetic risk have had limited success with respect to predicting an individual's risk beyond what can be obtained on the basis of family history, sex, and age. [See, for example, Paynter et al. (1).] In the instance of AD risk, the impact on prediction through assessment of common SNPs is further eroded by the increased risk attributed to other diseases, such as diabetes and cardiovascular disease, as well as environmental factors, such as head injury.

Genetic loci that pass high statistical significance cutoffs for association with complex diseases in GWASs sometimes have limited impact on disease prediction because they account for only a small percentage of heritability because of low penetrance (i.e., inheritance of the common gene variant at the identified locus results in only a small percentage of patients actually developing the disease) and disease heterogeneity. Moreover, the usefulness of finding gene loci for common diseases using common SNPs, as are used in GWAS, for the assessment of risk is predicated on the common disease-common variant hypothesis, which assumes that complex diseases are caused by a limited number of common variants each with small predisposing effects, but together, based on additive or interactive effects, lead to disease. Unfortunately, rare variants including gene duplications are likely to go undetected by GWAS, no matter how much of an impact they may have on disease risk.

McClellan and King (2) quoted a passage from *Anna Karenina* "Every unhappy family is unhappy in its own way" as an introduction to their article in which they propose an apt description of the misfortune of human disease in which "complex human disease is in fact a large collection of individually rare, even private, conditions"; i.e., that human complex diseases are characterized by marked genetic heterogeneity with rare alleles making important contributions to common complex human diseases. If true, then the promise of personalized medicine to allow for targeted preventative steps to avoid disease or for targeted early treatment to influence reproductive decisions or to facilitate wiser life style decisions will depend on our ability to combine and integrate a wide range of differing technologies. These improved methods are necessary if we are to determine the biological meaning of the numerous, i.e., the hundreds of thousands, of mutations and variants that are observed in any individual's genome. The challenge for personalized medicine based on currently available genetic approaches becomes even greater when one considers the impact of epigenetics, the environment, and gene-environment interaction on disease risk.

Despite these challenges to understanding their significance, individuals can currently avail themselves of a number of personalized medicine services without a physician order. Moreover, there was no clear understanding of where the U.S. Food and Drug Administration (FDA) stood with respect to regulation of the personal genetics industry; e.g., should it be part of standard medical care? Traditionally tests developed and offered by a single laboratory in contrast to test kits that were widely sold to physicians, laboratories, and hospitals, did not require FDA approval. However, the FDA recently sent letters to five companies involved in personalized medicine (23andMe, Navigenics, deCODE Genetics, Illumina, and Knome (offers consumers a complete sequence of their DNA), suggesting the need for premarket review to establish the ability of these tests to generate reliable results in analogy to medical devices, i.e., to make sure that the information provided to people is correct, given the potential medical consequences of receiving disease risk information.

Adviser. Given the current state of the field, should the patient be advised to seek out genetic testing? In part, this depends both on what the patient plans to do with the information and what kind of genetic tests are being contemplated. Most important is a discussion with the patient about whether he or she contemplates making any life-altering decisions based on this information. Depending on the age of the patient, for example, this could involve educational and career choices, savings versus spending choices, and issues related to plans for marriage, travel, retirement including long-term insurance, and decisions about whether to have children or not. Unfortunately, current preventive approaches to delaying the onset of AD primarily consist of heart-healthy diets and lifestyles that would be of value to the patient regardless of his or her risk of AD and keeping the brain active. Moreover, none of the above have been

demonstrated to have a strong impact on AD onset independent of other disease risk factors. Without means to prevent disease onset, would knowledge of increased risk, as for example, knowledge that the individual carries an APOEε4 allele cause the patient undue psychological stress? The only prospective study (REVEAL) of APOEε4 genotype disclosure did not find any clinically significant affect on psychological well-being (3). However, patients with high levels of emotional distress before undergoing genetic testing were more likely to have high levels of distress after disclosure, subjects with high depression or anxiety scores were excluded from the study, and subjects were relatively well-educated, willing to be randomly assigned with respect to the possibility of not receiving the test results, received genetic counseling, and follow-up was for only 1 year, all of which could limit the applicability of these findings to the patient in question. It is also commonly observed that even healthy individuals experience significant stress in the period waiting for the actual acquisition of the biological sample and for the results with greater impact and possible consequences for an individual who is already depressed. Assuming late onset of AD in this patient's family, it is unlikely that the patient will gain additional insight into her own genetic risk from commercially available genetic testing at this time; however, should the patient choose to do so and regardless of whether you choose to order it, I would recommend that genetic counseling be arranged for the individual. As a rule, however, I suggest that depressed patients postpone making those decisions that can be delayed with minimal adverse consequences be put off until they are feeling better. In this particular instance, information will only get better with time.

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SUGGESTED READINGS

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See AlzGene (http://www.alzgene.org) for up-to-date information on genes that may relate to risk of developing AD:

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