Apolipoprotein E and Alzheimer's Disease: The Implications of Progress in Molecular Medicine

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ABSTRACT

We review the current status as well as the risks and benefits of a recently developed DNA test of risk for Alzheimer's disease: the apolipoprotein E genotype. While apolipoprotein E genotypes may indicate a degree of susceptibility, the gene is neither necessary nor sufficient to cause the disease; thus, many questions remain. Because risk prediction is not straightforward, practical issues related to the testing of complex diseases like Alzheimer's and to the ethical, legal, and social implications of genetic tests require careful consideration and unambiguous answers.

The use of apolipoprotein E genotyping in patients with Alzheimer's disease should be limited to research centers, and additional studies are strongly recommended. Apolipoprotein E genotypes should not be available to third parties such as insurers or employers until genotypic risks are fully understood. National policies that encourage scientific investigation while maintaining individual privacy and limiting unnecessary access to genetic information should be immediately developed. (*Am J Public Health.* 1995;85:1280–1284)

Introduction

Molecular genetics promises a greater and more precise understanding of how genetic factors influence disease and may lead to effective treatments or preventive strategies. Current and future disease risk can be established by a simple blood test indicating the power of these molecular tools. The association between apolipoprotein E genotypes and Alzheimer's disease serves as an example of the scientific, social, legal, and ethical questions raised by progress in molecular medicine.[1–8]

The Public Health Burden of Alzheimer's Disease

By the turn of the century, an estimated 10 million Americans will have Alzheimer's disease.[9] The disease begins with an insidious loss of memory or other cognitive skills and culminates in a state of complete dependence requiring total assistance for personal hygiene and nutrition or supervision in a nursing facility. The costs of caring for patients with Alzheimer's disease are enormous because the illness can last as long as 10 to 15 years; these costs are predicted to increase during the next decade.[10]

Families with a rare autosomal dominant form of Alzheimer's disease beginning before the age of 50 years have been linked to either chromosome 14 or chromosome 21, but these individuals represent less than 1% of all patients with Alzheimer's disease.[11–20] In 1991, Pericak-Vance and associates[21] reported linkage to chromosome 19 among relatives of families with the more common form of Alzheimer's disease. Subsequently, an association between late-onset Alzheimer's disease and apolipoprotein E located on chromosome 19 was reported.[2] In numerous cross-sectional and case–control studies that followed, patients with Alzheimer's disease were found to be more likely than their peers to have one or more copies of the ε4-type allele of apolipoprotein E.[1–8]

Apolipoprotein E genotypes may also influence fasting cholesterol levels, and they have been associated with fatal myocardial infarction.[22,23] An association between the risk of ischemic heart disease and the risk of Alzheimer's disease has been suggested, but whether this connection is mediated through apolipoprotein E has not been investigated.[24] Because nearly everyone receives one of the three common apolipoprotein E alleles (ε2, ε3, and ε4) from each parent, six common genotypes result, representing different combinations of these alleles. These alleles occur with varying frequency; the ε3 allele is the most frequently encountered worldwide, while the ε2 allele is the least common.[25,26] Some have associated the presence of apolipoprotein E ε2 with a delay in disease onset or even protection from Alzheimer's disease,[27,28] while others have reported an increased risk.[29,30] African Americans and Finns represent ethnic groups with higher population frequencies of the apolipoprotein E ε4 allele,[25] but their frequency of Alzheimer's disease is similar to that of other populations. This phenomenon has been attributed to comorbidity from heart

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disease.[31] African Americans appear to be at increased risk for Alzheimer's disease with both the ε4 and ε2 alleles,[6,25,32] while the risk in Finns is similar to that of other Caucasian populations.[31]

The biological relationship between apolipoprotein E and the brain pathology in Alzheimer's disease, as well as the consistent and strong association between apolipoprotein E genotypes and the disease phenotype, substantiates the claim for a major role in the pathogenesis of this disease.[1] It is also clear that the presence of an apolipoprotein E ε4 allele is neither necessary nor sufficient to cause Alzheimer's disease. Many develop the disease in the absence of apolipoprotein E ε4, and many never develop the disease despite having an ε4 allele. In part, this may be because of the genotypic distributions of age at disease onset: any individual's risk may be in the early, middle, or late portion of the age at onset curve for his or her genotype, and he or she may either develop the disease earlier than would be predicted on the basis of aggregate data or die before reaching the age at onset associated with the genotype.[27] If apolipoprotein E polymorphisms act primarily to affect the age at which symptoms develop, then other genes or environmental factors may also be related to the cause of Alzheimer's disease. The alternative explanation would be that the apolipoprotein E association results from disequilibrium to a nearby, tightly linked but as yet unidentified susceptibility gene. There is little evidence to support that view at present.

Plomin and colleagues[33] consider late-onset Alzheimer's disease an example of a complex disorder that is related to multiple genes, only one of which may be apolipoprotein E. Because complex disorders such as Alzheimer's disease result from variable contributions of several genes and possibly environmental influences, the risk of disease depends on the number and impact of the contributing risk factors and genes rather than on the presence or absence of a single polymorphism, as is the case in single gene disorders. Thus, two individuals with different combinations of genetic factors or environmental exposures would have different risks of developing Alzheimer's disease, even if they both had the same apolipoprotein E genotype. Therefore, apolipoprotein E genotypes are best viewed as genetic "risk factors" for, rather than genetic markers of, Alzheimer's disease.

Implications of the Association between Apolipoprotein E and Alzheimer's Disease: Screening and Testing

Clearly screening a population for the presence of the apolipoprotein E ε4 allele in order to identify individuals susceptible to Alzheimer's disease not only would be impractical but would be of no direct benefit. At least half of patients with Alzheimer's disease have no apolipoprotein E ε4 allele; many with this allele never develop the disease. Moreover, there is no basis for primary or secondary prevention related to apolipoprotein E. Therapeutics that delay the onset of Alzheimer's disease by mimicking the effects of apolipoprotein E ε2 or ε3 have been proposed, but it is not clear that such an agent would be beneficial given the current status of the data regarding risk prediction.

Diagnostic or predictive testing might be a more pragmatic use for the apolipoprotein E genotype, but again several factors make this option less desirable. Because the majority (approximately 60%) of patients presenting to physicians with dementia have Alzheimer's disease, the additional information gained by the apolipoprotein E genotype would be of benefit if it reduced the cost of an evaluation or if it confirmed the diagnosis. In the absence of an apolipoprotein E ε4 allele, a patient with dementia would still require the usual diagnostic tests. With a single ε4 allele, the probability that the patient has Alzheimer's disease is increased, but not enough to eliminate the need for the usual diagnostic evaluation. Patients who are homozygous for apolipoprotein E ε4 have the highest probability of disease, but this is a rare condition occurring in only 2% to 3% of the population, and among patients with Alzheimer's disease, only 15% to 20% have this genotype. It is also possible, although less likely, that there are other reasons for these patients' dementia, forcing the physician to make a choice based on his or her judgment of the possible existence of a competing cause.

Predictive testing based on the apolipoprotein E genotype might also be conducted to detect presymptomatic susceptibility (e.g., as for phenylketonuria, Huntington's disease), for the purpose of establishing advanced directives or for the purpose of reproductive planning (e.g., as for Tay-Sachs). Predictive testing may be of use to persons with a family history of Alzheimer's disease. Indeed, a preliminary study indicates that cerebral metabolism of individuals at risk may differ depending on their apolipoprotein E genotype.[34] However, without a clear-cut therapeutic option, such early detection at this point does not seem beneficial. Not unexpectedly, family members of patients with Alzheimer's disease have been concerned about their status with regard to apolipoprotein E ε4, but it is difficult to present an unambiguous response to their questions about prognostic implications. Thus, while the apolipoprotein E genotype may be undeniable as a genetic risk factor for Alzheimer's disease, it does not provide sufficient information to be an adequate predictive genetic test. A good predictive genetic test requires a close correspondence between the presence of the susceptibility genotype and risk of disease, including the ability to predict age at onset and the clinical severity of the disease. Estimates of the risk of Alzheimer's disease associated with apolipoprotein E ε4 derived from aggregate data in case–control and family studies do not take into account the competing risks of morbidity and mortality associated with other health conditions related to advanced age or other effects of the apolipoprotein E system. Furthermore, if apolipoprotein E ε4 is only one of several genetic and environmental factors that influence the risk of Alzheimer's disease, its presence may or may not always predict disease, because other factors must also be present.[35,36] The sensitivity, specificity, and predictive value of a positive genetic test in a complex disorder such as Alzheimer's disease will ultimately depend on the proportion of the risk that is attributable to the allele being tested. For example, among those positive for mutations in BRCA1, the gene that predisposes women to early-onset familial breast and ovarian cancer, the risk of developing breast cancer is 80%; however, the gene accounts for only 5% of all cases of breast cancer.[37] Holtzman[36] has suggested that a high positive predictive value is critical in testing for complex disorders.

Consequences of Apolipoprotein E Testing

A commercial test for Alzheimer's disease risk based on the apolipoprotein E system is now available (Athena Diagnostics, Worcester, Mass). The availability of such a test before there is a consensus in the scientific community on the meaning of a "positive test" (the

presence of the apolipoprotein E ε4 allele) raises the potential for harm and conflict of interest. We believe that testing based on apolipoprotein E polymorphisms should not be conducted without a protocol for pretest and posttest counseling that permits an individual to fully explore the personal meaning that a positive or negative test result will have so that he or she can make informed decisions about the test.[38–40] The complexity of the counseling that will need to be provided with testing for complex disorders such as Alzheimer's disease has been outlined by the Committee on Assessing Genetic Risks.[41] The committee notes that the late onset of diseases such as Alzheimer's disease and the probabilistic nature of the diagnosis suggest that counseling may have to include a very large number of risk categories depending on particular constellations of genes at many loci.[41]

Experience with testing for Huntington's disease has shown the importance of understanding the different motivations that lead people to seek testing, the difficulty in describing the limitations of the test and of communicating risk estimates, the necessity of assessing individual costs and benefits of learning about risk status, and the often devastating psychological impact that such knowledge may have.[42–48] Experience with testing for Huntington's disease has also shown that the psychological consequences of testing negative have often been as devastating as those of testing positive.[44] People who have organized their lives around being "at risk" must reevaluate themselves and their relationships to friends and family members. Some people may experience "survivor guilt," especially those in families with affected members. Wexler[44] has cautioned that special training programs, detailed protocols for providing testing, and quality control in implementing protocols must be in place before presymptomatic genetic testing is offered. She suggests that many people can benefit from counseling that clarifies their knowledge of the disease and explores the impact of having disease risk information without actual testing. The opportunity to clarify knowledge about the disease and to explore one's personal motivation to take the test will be equally important in Alzheimer's disease. Because the quality of risk assessment and predictive value of a positive test are lower in this disease than in Huntington's disease, there is potential harm from false reassurance from a negative test and undue alarm from a positive test.

Knowledge that one might develop a chronic disease in late life would be advantageous if treatments or preventive measures were available; for Alzheimer's disease, however, investigators are only now actively exploring preventive strategies. Roses et al.[27] have suggested that apolipoprotein E genotypes might be useful in subdividing patients with Alzheimer's disease by biological risk to study the rate of disease occurrence or progression in evaluating new therapeutic agents. This application may be useful in the future once the biological effects of apolipoprotein E are better understood.

Privacy and Confidentiality

Serious ethical questions arise from the prospect that the genetic information contained in an individual's DNA may be entered into accessible computerized databases. Storage of DNA from clinical populations in a "DNA bank" for future analysis presents novel privacy issues that merit discussion and immediate action.[49] The association between Alzheimer's disease and apolipoprotein E is only one of several genetic associations that should provoke the establishment of policies to regulate access to genetic information.

If the information contained in DNA were equivalent to clinical details from a direct personal interview or a medical record, current procedures to protect confidentiality and privacy could be applied. However, DNA tests are unlike medical records in that they provide information about future risks, or "genetic prophecy," and about risks among other family members,[50] all of whom may be currently unaffected; thus, the genetic code of an individual should be protected in either the absence or the presence of a medical condition.

Should Researchers Have Unlimited Access to Genetic Data That Might Be Related to Other Medical Problems?

There are benefits of access to stored DNA. For example, investigators have been able to study the relationship between apolipoprotein E and Alzheimer's disease because of stored samples. Others who might wish to study the genetic characteristics of a population would have an advantage if DNA were previously obtained and stored, because the cost and effort in identifying and obtaining blood would have been absorbed by the previous study. Tests of new gene–disease associations and risk modification by gene–environment interactions could be conducted in populations whose disease phenotypes, medical history, and history of exposure to environmental risk factors have already been well characterized. Presently, sharing of medical information in research is often stipulated with standard informed consent procedures. For individuals unable to make such decisions, as is often the case in patients with Alzheimer's disease, a surrogate consent has been obtained for previously acquired information. However, similar standards for the use of genetic data in clinical practice and research have only been described; they have not been implemented. It has been proposed that DNA samples from identifiable subjects be used only for the purposes for which they were initially collected, without waivers. This would probably preclude additional scientific investigation. An alternative suggestion has been to establish a policy for sharing of DNA-related data similar to the policy on public and private access to medical record information.[49] This policy would require public notice, a privacy impact statement, and a statement of the purpose for which the DNA will be used. It would further require prior written agreement for all current and future uses and for access to the DNA information by any third party. Exceptions would apply only to samples from anonymous subjects and to samples from previously identified individuals who would be anonymous when undergoing additional testing.

Discrimination and Stigmatization in Employment and Insurance

Employers benefit by identifying individuals who might develop medical problems that would affect their work performance, and, in turn, employees could potentially benefit by the recognition of risk for medical illnesses such as Alzheimer's disease. There is the possibility for discrimination by employers and insurance companies against individuals who work. As more and more individuals continue to work well into their 7th decade, employers will begin to worry about the risks and costs of their health coverage. Andrews and Jaeger[51] pointed out that certain diseases (Alzheimer's disease might represent such an example) are not transient conditions and could stigmatize an individual, leading to serious emotional injury and the potential for financial harm. As Murray[52] notes, preemployment genetic screening for common disabling diseases such as Alzheimer's

disease or cardiovascular disease is not designed to reduce the individual risk of disease associated with exposures in the workplace. Rather, such screening is intended to reduce health-related costs (e.g., health insurance, disability insurance, and lost productivity). Detection of susceptibility does not lower the burden of disease in the population but shifts its cost away from the employer. Once an individual has been denied insurance, it might be difficult for him or her to obtain insurance from other subsequent insurers. This becomes even more complex when one considers the possibility that employers and insurers could potentially make such decisions for an individual based on genetic information that could also affect future employment for the individual's offspring. Therefore, access by employers and insurers to genetic data would need to be limited, with requirements for permission from the individual and without personal identification until guidelines are developed. Protection for the individual worker would also require strict security and enforcement of penalties for unauthorized use of such data. Current legal guidelines do not as yet specify methods for disclosure of confidential genetic information to subsequent employers, spouses, and relatives who may themselves be at risk.[40]

Conclusions

There can be little doubt that investigators will want to incorporate molecular approaches into the study of other common public health problems. New scientific and technical capabilities create new ethical, legal, and social problems that affect both the medical community and the public health community. The case of Alzheimer's disease and apolipoprotein E illuminates only some of these problems. Agencies and public health groups are beginning to undertake a detailed review of these troubling questions, but time is not on their side. The rapid pace of scientific progress in molecular medicine suggests that all investigators concerned with public health questions should carefully consider the issues raised by this remarkable era of scientific progress. □

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