How to Use an Article About Genetic Association

C: What Are the Results and Will They Help Me in Caring for My Patients?

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In the first 2 articles of this series, we reviewed the basic genetics concepts necessary to understand genetic association studies, and we enumerated the major issues in judging the validity of these studies. In this third article, we review the issues relating to the applicability of the results in the clinical situation. How large and precise are the associations? Many genetic effects are expected to be smaller in magnitude than traditional risk factors. Does the genetic association improve predictive power beyond easily measured clinical variables? In some cases, the additional genetic information adds only a small increment in the predictive ability of a diagnostic or prognostic test. What are the absolute vs relative effects? Even if the genetic risk is high in relative terms, the baseline risk may be very low in absolute terms. Is the risk-associated allele likely to be present in my patient? A risk allele may have a strong effect but be rare in a particular ethnic group. Is the patient likely better off knowing the genetic information? Given that genes cannot be modified, one must weigh whether the genetic information is likely to be helpful in planning other health interventions or initiating behavior change.

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CLINICAL SCENARIO

In the first 2 articles in this series,[1,2] we introduced a clinical scenario dealing with the association of *APOE4* and the risk of dementia and focused on a relevant article.[3] We reviewed background concepts and terminology in genetics, presented criteria for judging validity (BOX), and concluded that the study met validity criteria sufficiently well to justify examining the results more carefully. This article discusses issues in understanding the results of genetic studies and applying them to clinical practice.

WHAT ARE THE RESULTS OF THE STUDY?

How Large and Precise Are the Associations?

Sometimes, investigators will tell you only whether an association is "statistically significant," which will be of little use to you. Application depends on knowing the magnitude of the association; it makes a difference whether the increase in risk is 1.4- or 8-fold.

Fortunately, investigators usually report the magnitude of a genetic association by using traditional measures of association: relative risks (RRs) in cohort studies, odds ratios (ORs) in case-control studies, and hazard ratios (HRs) in survival analyses that consider the timing of events.[4] If the variant allele is dominant, that is, it produces a protein isoform that dominates function, its presence in even 1 copy will result in maximal increase in risk. If the variant allele is recessive, that is, if present in only 1 gene, it produces a protein isoform that will fail to exert its biological effect; both variant alleles must be present to result in an increase in risk. In both cases, a single RR, OR, or HR describes the magnitude of the association.

If the effect of a variant allele is additive, its presence in one gene will lead to an increase in risk; its presence in both genes will lead to a further increase. Investigators may present the RR, OR, or HR associated with heterozygous (variant allele present in only 1 gene) and homozygous (variant allele present in both genes) individu-

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als. Alternatively, they may present the RR, OR, or HR associated with the presence of only a single variant allele, in which case you must calculate what the expected risk is for the homozygous individual. There are 2 ways to do this: one is to take the square of the risk (called log-additive or per-allele or multiplicative risk model), and the other is to take 2 times the risk (called the linear additive model). The choice of which calculation to use should be guided by the relevant biology, although this is often unknown.

Even for true genetic associations, initial positive results sometimes tend to overestimate the magnitude of the genetic effect. The phenomenon, sometimes referred to as the winner's curse, arises because overestimates are more likely to cross threshold *P* values for declaring an association. Thus, the population of studies with "positive" results will yield an upwardly biased estimate of treatment effects, and we should be conservative in interpreting genetic associations for newly discovered variants.[5]

Our confidence in estimates is also influenced by precision, reflected in the confidence interval (CI). Small genetic association studies have a lack of power and thus may fail to detect an association that is actually present.[6] If a CI around the RR has a lower boundary less than 1.0 and a higher boundary greater than 1.0, then the results are consistent with chance but do not exclude the possibility that the gene may have a protective effect or increase risk, ie, the possibilities of no association or an important association remain.

Slooter et al[3] showed that *APOE* e2 (*e* indicates epsilon) may decrease the risk of dementia, with an RR of 0.5 (95% CI, 0.3-0.9) for *e2/e3* heterozygous individuals compared with *e3/e3*; the *e2* allele is sufficiently rare that the *e2/e2* group is small. *e4* Increases the risk of dementia (OR for the *e3/e4* heterozygous individual, 2.1 [95% CI, 1.7-2.7]) and the presence of 2 *e4* genes increases the risk to 7.8 (95% CI, 5.1-11.9), even more than one would expect under either the log-additive model (2.1^2 or 4.4) or linear model (2.1×2 or 4.2). Given that this is a late-stage replication with many thousands of participants, the winner's curse is probably not an issue here.

The effect of any single gene is likely to be small; in fact, *APOE* is a major exception: most genetic effects in the recent literature have RRs in the range of 1.1 to 1.4. These small, seemingly unimportant RRs have generated interest in combining the effect of many genes in polygenic models or panels, ie, creating a genetic risk "profile" that assigns points for the presence of various risk alleles and calculates an overall risk of disease.[7] For example, in a study of 5 single-nucleotide polymorphisms (SNPs) associated with prostate cancer, the investigators expressed the risk of disease associated with the increasing presence of risk alleles.[8] They found an OR of 1.6 for individuals who were homozygous or heterozygous for the risk allele at 1 SNP and up to 4.5 for those who were homozygous or heterozygous for the risk allele at 4 SNPs. However, there are potential problems in creating these polygenic models; in particular, a fundamental assumption, the independence of each genetic effect, may not hold.

No such polygenic score has yet been generated for genetic variants of Alzheimer disease. The synopsis of the association studies in AlzGene,[9] however, suggests that more than 20 SNPs have nominal statistically significant associations and they could potentially be considered for generating a risk profile. All but *APOE* confer small risk increases, on average ORs of less than 1.3.

Box. Critical Appraisal Guide to Genetic Association Studies

A. Are the results of the study valid?
- Was the disease phenotype properly defined and accurately recorded by someone blinded to the genetic information?
- Have any potential differences between diseased and nondiseased groups, particularly ethnicity, been properly addressed?
- Was measurement of the genetic variants unbiased and accurate?
- Do the genotype proportions observe Hardy-Weinberg equilibrium?
- Have the investigators adjusted their inferences for multiple comparisons?
- Are the results consistent with those of other studies?

B. What are the results of the study?
- How large and precise are the associations?

C. How can I apply the results to patient care?
- Does the genetic association improve predictive power beyond easily measured clinical variables?
- What are the absolute vs relative effects?
- Is the risk-associated allele likely to be present in my patient?
- Is the patient likely better off knowing the genetic information?

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?

Does the Genetic Association Improve Predictive Power Beyond Easily Measured Clinical Variables?

The immediate clinical utility of a genetic association is to provide prognostic information to patients and clinicians. To do this, the genetic marker must provide independent predictive power above and beyond traditional clinical predictive variables (age, sex, family history, exposures to other causal agents such as cigarettes, simple laboratory tests such as serum lipid levels, and other risk factors such as hypertension). This may well not be the case, particularly if the genetic polymorphism exerts its effect through some of these variables (eg, a gene controlling lipids exerts its effect through increases in low-density lipoprotein).

Typically, then, a useful gene predictor will exert a biological influence that we cannot measure at some other level. The one exception is if the biological factor measurement has large

measurement error and day-to-day variability, whereas the gene is measured with high accuracy. In the previous example, if there is large lifetime variability and measurement error in lipid levels for a single individual, assessing the patient's gene variants that control lipid levels may provide more decisive information.[10]

To determine whether the genetic information adds substantial predictive power beyond easily measured clinical and laboratory variables, the clinician must look for the appropriate analysis. Does the association persist after consideration of—"adjusting for" in statistical parlance—other clinical variables?

For dichotomous outcomes, there are a number of statistical tools to decide how much, if any, additional predictive power the genetic information adds. One is to calculate the area under the receiver operating characteristic curve, an approach often used for diagnostic tests.[11] As shown in the FIGURE, a receiver operating characteristic curve plots the true-positive rate (y-axis) against the false-positive rate (x-axis). A receiver operating characteristic curve with no greater predictive ability than chance would approximate a straight diagonal line from the origin (0, 0) to the upper right-hand corner (1.0, 1.0) (Figure 1A). The area under the curve would be 0.5. The visual representation of a perfectly predictive test would be a line that goes straight up the y-axis to 1.0 and then straight across the x-axis to 1.0 and would have an area under the curve of 1 (Figure 1B).

The Prospective Cardiovascular Munster study, which developed a risk prediction score for cardiovascular disease, provides an example of the use of the receiver operating characteristic curve (Figure 1C).[13] Fitting this model to the Northwick Park Heart Study II by using normal clinical variables gave an area under the curve of 0.65. Adding genetic information to this model did not significantly increase this area, thus demonstrating that genotyping would not add important predictive information.[12]

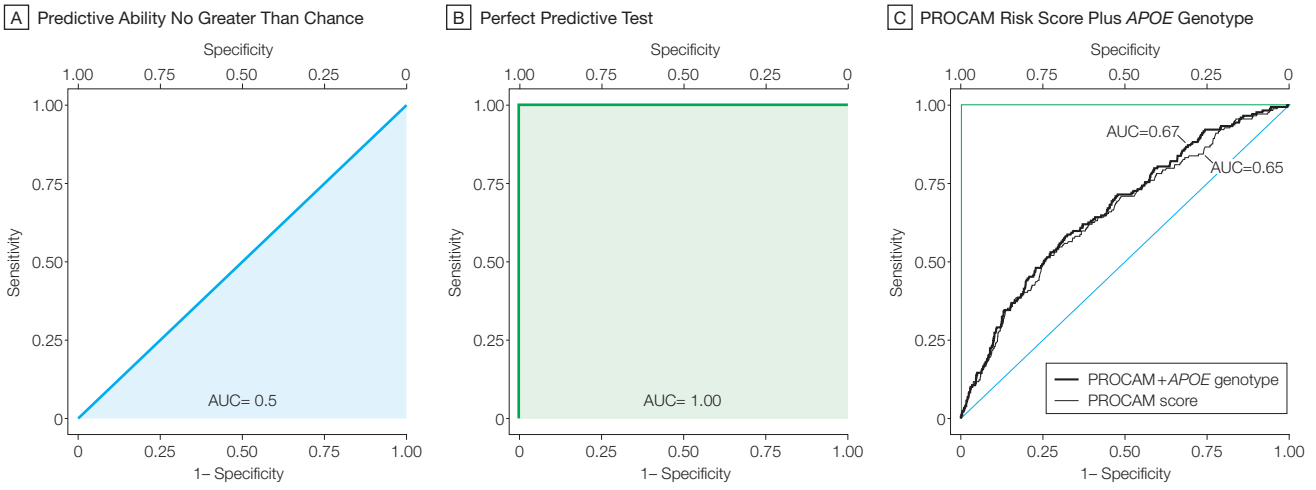
Slooter et al[3] added age, sex, and education to regression models that included the genetic information. The RRs they present have considered these clinical variables or adjusted for them. Their study would be stronger if they had considered other clinical variables that are also considered to affect Alzheimer risk, such as total cholesterol level and family history.

In general, it is important that investigators adjust for family history because this variable is potentially genetically linked. The failure of Slooter et al[3] to take family history into consideration, or indeed clinical criteria, results in some doubt about the utility of the genetic information and limits our use of the information in helping our patient. Other investigators have shown that *APOE* information provides additional predictive ability beyond family history[14] but not necessarily beyond expert clinical diagnosis with standardized criteria. Mayeux et al[15] found that adding *APOE* genotype to expert diagnosis by using standardized criteria increased the area under the curve from 0.84 to 0.87, an increment that was not statistically significant.

What Are the Absolute vs Relative Genetic Effects?

If the patient's risk of disease in the absence of a variant allele that increases risk is low, even a 5- or 10-fold in-

Figure. Example of a Receiver Operating Characteristic (ROC) Curve for Cardiovascular Risk Related to *APOE*



A, Example of an ROC curve for a test that performs no better than chance. B, Example of an ROC curve for a test with perfect predictive ability (sensitivity = 100%; specificity = 100%). C, ROC curves for cardiovascular disease calculated using PROCAM (Prospective Cardiovascular Munster study) risk score plus *APOE* genotype. Based on 2451 men (of 3012 eligible) who had complete data for PROCAM and *APOE* genotyping. *APOE* genotype was fitted as a class variable with 3 categories 33, 22/23, and 34/44. Factors included age, body mass index, total cholesterol, triglycerides, systolic blood pressure, and family history. Other factors in PROCAM were not measured in all men. For the PROCAM score, the ROC value (95% confidence interval) was 0.65 (0.61-0.70), with a detection rate of 11.7% for a false-positive rate of 5.0%. In univariate analysis, *APOE* genotype was significant at $P=.01$. In multivariate analysis, the area under the curve increased to 0.67 (0.63-0.71) (detection rate,14.0%), but this improvement was not significant ($P=.11$). Panel C data based on Humphries et al.[12]

crease in risk in the presence of the allele may represent a small absolute increase in risk. Conversely, if the baseline risk is high, even a modest increase in RR could affect clinical decision making. For example, factor V Leiden increases the risk of venous thrombosis by about 6-fold.[16] However, the baseline risk of thrombosis in the general population is sufficiently low, about 0.2%,[17] that one would not use genotyping as a screening test for the entire population. If, however, patients present with idiopathic deep venous thrombosis or pulmonary embolism, thus declaring themselves in a group with prevalence of factor V Leiden of 12% to 20%,[18,19] testing is worthwhile.

Slooter et al[3] estimated the RR of dementia in *APOE4* heterozygous individuals at 2.1 and the RR associated with *APOE4* homozygous individuals at 7.8. They took baseline risk into account to estimate an absolute risk of dementia by age 80 of approximately 15% to 20% for *APOE4* heterozygous individuals and 50% to 60% for *APOE4* homozygous individuals. Other studies confirm these high absolute risk estimates.[20]

Is the Risk-Associated Allele Likely to Be Present in My Patient?

In applying the results, clinicians must consider the likelihood that the culprit allele is present in a particular patient. For example, although factor V Leiden is relatively common in whites (about 1 in 20 individuals is heterozygous), it is virtually nonexistent in Chinese populations. Hence, in a Chinese individual presenting with idiopathic deep venous thrombosis, genotyping for factor V Leiden is potentially unnecessary and wasteful. Allele frequencies for various genes and populations of interest are available in the Allele Frequency Database[21] or at the HapMap Web site.[22]

Similarly, some gene-disease associations may be restricted to a select subgroup. For example, *BRCA1* was identified in patients with early onset breast cancer who had a strong family history.[23] This group of individuals, however, accounts for only approximately 5% of all breast cancers. Hence, although this genetic association is valid, individuals who present with late-onset breast cancer without a strong family history have no need to be tested for it. However, for certain ancestry groups such as Ashkenazi Jews who have a high prevalence of *BRCA1* mutations, testing may be appropriate in women with breast or ovarian cancer.[24]

In our clinical scenario, the Allele Frequency Database[21] shows that the *APOE4* allele frequencies are similar across a broad range of ancestries.

Is the Patient Likely Better Off Knowing the Genetic Information?

Knowing that one's genes increase the risk of serious health problem years in the future may have substantial adverse consequences, including worry, anxiety, and potentially increased payments for life or disability insurance. These adverse consequences become particularly compelling if there is no productive action that follows knowledge of increased risk.

On the other hand, genetic information may prompt specific beneficial action or avoidance of harmful actions. In particular, some associations pertain to outcomes that are also related to the likelihood of satisfactory and unsatisfactory responses to specific treatments. For example, a SNP in the *TPMT* gene identifies children with acute leukemia who are at increased risk of a life-threatening adverse event with the chemotherapeutic agent mercaptopurine.[25] Genotyping this SNP can avoid substantial morbidity and mortality by substitution of an alternative chemotherapeutic agent in individuals with the high-risk genotype.

When associations pertain to risk related not to treatment but to development of disease, genetic information may facilitate behavior change to reduce non–genetically mediated risk.[26] For example, early evidence suggests that providing information about glutathione-*S*-transferase genotypes (which affect nicotine metabolism) may influence smoking cessation rates.[27]

Understanding genetic risk may be problematic for lay people,[28] and there is still uncertainty about how to use and convey genetic information and how to optimize genetic services. A systematic review on the influence of genetic services[29] found that

- behavioral outcomes have shown mixed results and clinical outcomes were less well studied;
- genetics knowledge tends to be poor;
- the most consistently identified barrier has been the self-assessed inadequacy of the primary care workforce to deliver genetic services; and
- additional barriers have included lack of oversight of genetic testing and concerns about privacy and discrimination.

These deficiencies need to be addressed quickly, particularly given the "direct-to-consumer" availability of genetic testing.[30] Several companies are already marketing genetic tests for common variants, including intense direct-to-consumer advertisement campaigns, often for indications without proven validity or usefulness.[31]

RESOLUTION OF THE SCENARIO

Recapping our critical appraisal, Slooter et al[3] used an optimal study design for the question (a longitudinal cohort), characterized dementia well (separating Alzheimer from vascular dementia), ensured similar ethnicity in diseased and nondiseased populations, and demonstrated Hardy-Weinberg equilibrium in the genotype results. Their results are consistent with a large number of other studies addressing the association. The RRs associated with 1 or 2 copies of *APOE4*, 2.1 and 7.8, respectively, are substantial, the culprit allele is common (≈25% of the white population has at least 1 *APOE4* allele), and the absolute risks of 15% and 50% heterozygous and homozygous variant populations, respectively, are impressive. Perhaps the most important limitation is that the incremental increase in risk with *APOE4* beyond family history was not considered. Other studies suggest that *APOE4* geno-

type can provide additional information beyond family history[12] but not necessarily beyond expert clinical diagnosis.[15] Nevertheless, there may be a role for *APOE* genotyping in helping nonexperts arrive at a diagnosis.

You can therefore inform the patient that results of genetic testing may reveal an increased risk of Alzheimer dementia, though we cannot be certain of the exact magnitude of the increased risk beyond his already greater risk associated with family history. More extensive testing (eg, using a genome-wide platform, as offered by several companies) may reveal information for a number of other gene variants that have small contributions to Alzheimer risk, but the interpretation of this extra information is uncertain.

Discussion with the patient about why he is seeking the genetic information would be worthwhile. If knowledge of increased risk would increase his resolve to modify other factors that would affect his risk of dementia, eg, quitting smoking and ensuring adherence with antihypertensive medication, the genetic information may offer a useful stimulus. Such actions would not only decrease his risk of dementia but also his risk of stroke and other diseases. On the other hand, if a negative result would give him a false sense of security and even increase risky behaviors, the outcome of genetic testing may be less desirable. Ultimately, understanding the article and its implications will help you to work with the patient to arrive at the optimal course of action.

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