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***APOE* ϵ 4 and Depression: Following a Winding Road**

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Is there an association between having one or two copies of the *APOE* ϵ 4 allele and depression? If yes, what are the explanations for this association, and what clues does it provide about the mechanisms, prevention, or treatment of depression? Two notable features of the literature in this area are the variation in published reports concerning whether or not there is an association and the complexity of interpretation presented by these reports.

Variation is an almost universal characteristic of reports of associations between genomic features and risk of common diseases. Two broad approaches to identifying such associations, genome-wide association studies (GWAS) and studies of candidate loci, have been widely used to identify loci potentially associated with depression. The GWAS of depression have not replicated associations with most loci previously identified in studies of individual candidates including *APOE* (1). This situation may reflect the higher standard for statistical significance appropriately used in GWAS. The extent to which it also reflects study design issues, such as the age group investigated and differing definitions of depression, and the extent to which it is cause for concern about the solidity of the findings from candidate gene approaches in depression are unclear. Thus, the literature considering the *APOE* ϵ 4 allele and depression consists solely of studies of this locus as a candidate.

As pointed out by Skoog *et al.* (2) and others, approximately as many studies of *APOE* ϵ 4 and depression report positive results as null results. Small sample size may be an important contributor: many studies have not been large; larger ones have several hundred subjects, and most have many fewer subjects. Other features of study design and procedures have also varied widely. In this context, the article by Skoog *et al.* (2) in this issue is a valuable contribution. It does not definitively settle whether the association is real, but it provides some solid evidence that it is. The article has many more strengths than weaknesses. The sample size is larger than sample sizes for many previous efforts. The study is population-based, is longitudinal, and achieved a strong response rate; these features substantially enhance the comparability of subjects having the *APOE* ϵ 4 allele with subjects not having it, increasing readers' confidence in the results.

Entangling issues make interpretation of studies reporting *APOE* ϵ 4 and depression findings challenging. Whether an association exists in general is typically not the issue central to the study, but rather if it exists in a set of restricted circumstances and to what degree it accounts for a different association. One or more features of Alzheimer's disease are often the study

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focus because the *APOEε4* allele is the genomic variant with the strongest known association with Alzheimer's disease and because the degree to which depression may function as either a predictor or a consequence of Alzheimer's disease is an intriguing issue. Practically, many studies of Alzheimer's disease include measurement of *APOEε4* and depression, facilitating study of their potential association in this context. The particular restricted circumstances in which a study is conducted vary, reflecting differences in interests of investigators. Because our interest is in the association of *APOEε4* and depression, it would perhaps be more convenient to seek a general answer first and then examine more restricted circumstances secondarily, but this solution ignores practical realities, such as funding, investigator interests, and availability of *APOEε4* data.

In many ways, the most relevant questions are whether evidence concerning an association of *APOEε4* and depression provides clues about the mechanisms, prevention, or treatment of depression. Empirical evidence directly pertaining to these questions is very limited, and we are quickly reduced to making what inferences we can, trying to keep our speculations as informed as possible, and identifying the areas in which our need for new data is especially acute. Concerning insight into mechanisms of an association, the notion of the *APOEε4* allele and depression among older people having a shared association with neurodegeneration claims our attention first. The association between *APOEε4* and Alzheimer's disease has been extensively replicated, although its mechanisms are not well understood. Clinically evident depression and depressive symptoms have been seen as predecessors and consequences of Alzheimer's disease. An assumption that there is a shared association of *APOEε4* and depression with neurodegeneration is implicit in some studies (e.g., studies asking to what degree this shared association accounts for an observed association of Alzheimer's disease and depression).

Skoog *et al.* (2) excluded subjects having clinically evident dementia as well as subjects developing clinically evident dementia within 4 years. This exclusion likely makes the results much less affected by a shared association between *APOEε4* and depression with neurodegeneration. Many recent findings strongly suggest that the pathophysiologic processes underlying Alzheimer's disease develop over an extended period, so the possibility of a shared association with neurodegeneration that is not yet clinically evident is much harder to eliminate. The available literature on *APOEε4* and depression is dominated by studies of older people, and clinical evidence of neurodegeneration is strongly related to age. Is it worthwhile to examine *APOEε4* as a candidate locus for depression in younger people? Observing an association in a younger age group would substantially lower the likelihood of a shared association with neurodegeneration, but GWAS results are not encouraging for a general association of *APOE* and depression in all age groups.

Where should we go from here? Are we considering the phenotype of depression in a fashion highly suited to identifying associations with *APOE* or other genomic loci? Depression is a complex phenotype; criteria for its existence can be met in many different ways, and this heterogeneity may account for some of the wide variation in study results. Using standardized questions about depressive symptoms instead of a dichotomous classification of whether depression is present or absent to define the phenotype (2) may be attractive for three reasons. 1) It improves the uniformity of phenotypic classification. 2) It

permits classification along a continuum instead of a dichotomy, which typically leads to higher statistical power. 3) Defining the phenotype in a continuum may correspond more closely to the way in which depression occurs, especially in the general population rather than among people hospitalized for depression or people seeking medical attention for the condition.

In epidemiologic studies, evidence of a dose-response relationship is a widely accepted criterion for evaluating how meaningful an observed association is. Greater knowledge of the dose-response relationship between the *APOE*ε4 allele and depression would be highly useful. For *APOE*ε4, evidence of a stronger association for individuals having two copies of the allele would achieve this goal. The greatest obstacle to achieving this goal is adequate sample size, especially as *APOE*ε4 homozygotes are less common than heterozygotes or individuals without this allele. For depression, regarding the condition as existing along a continuum as noted earlier and comparing the strength of association for different parts of the continuum would also help achieve the goal.

Our knowledge of genomic associations with depression among non-European ethnic/racial groups is limited. Published large GWAS of depression exclusively comprise people of European ancestry, and most, but not all, studies of *APOE* as a candidate locus for an association with depression comprise this same group. For *APOE*, the assumption that findings among people of European origin can be directly transferred to other racial/ethnic groups may not be a good one. Caution seems especially warranted because the magnitude of the association between the *APOE*ε4 allele and risk of Alzheimer's disease is substantially lower among African Americans than among European Americans (3,4). One potential way to overcome the small sample sizes of many studies would be to perform a meta-analysis of the results of as many studies of the association as possible even though interpretation of the results would require considerable caution.

In conclusion, identifying genomic loci associated with depression in general and clarifying the potential role of the *APOE*ε4 allele in particular are not simple and straightforward problems. However, the burden of depression for affected individuals and for society is enormous (5) and is sufficient reason to keep following the winding road to solutions.

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