

Rare *ABCA7* variants in Alzheimer disease

Guilt by association

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When evaluating patients with suspected or potential Alzheimer disease (AD), clinicians can consider screening 4 different genes. Three are deterministic genes (*APP*, *PS1*, and *PS2*) that typically cause early-onset, autosomal dominant AD. Mutation analysis of these genes rarely produces positive results. *APOE*, a risk gene whose status influences diagnostic confidence, is more diagnostically relevant to the vast majority but an *APOE* genotype does not definitively confirm or refute a clinical diagnosis. Genome-wide association studies (GWAS) have associated approximately 20 additional genes with AD,¹ but clinical tests remain commercially unavailable for these genes because their GWAS-identified contribution appears limited.

GWAS, however, are best suited to identify associations between diseases and common gene variants. Rare variants (uncommon polymorphisms or frank mutations), which can elude GWAS, may contribute more robustly to disease risk, and genes identified through GWAS should be considered rare variant candidates.² In other words, a common variant or common variants related to a particular risk gene may have a small effect, while rare variants in that gene may confer more robust effects. Testing this hypothesis requires high-throughput DNA sequencing in large numbers of patients, a technical hurdle effectively resolved by the development of next-generation sequencing approaches.

The ATP binding cassette subfamily A member 7 (*ABCA7*) gene, located at chromosome 19p13.3, was identified by GWAS as an AD risk factor, although with a small overall effect size.³ An overrepresentation of rare *ABCA7* variants with AD was recently reported.^{4,5} In this issue of *Neurology*®, additional studies provide insight into the commonality of rare *ABCA7* variants in patients with AD. The study by Le Guennec et al.,⁶ performed in French participants with early-onset AD (EOAD) whose age at onset was younger than 65 years, found that 6.6% of persons in the AD group had an *ABCA7* rare variant vs just 2.0% of control participants, a highly significant difference. These patients with EOAD, it appears, did not show readily recognizable autosomal dominant

inheritance patterns. One implication of this study is that *ABCA7* gene analysis (for rare variants or mutations) in patients with sporadic EOAD might return positive results in a reasonable number of cases.

In another study, Van den Bossche et al.⁷ considered Belgian patients with AD who had *ABCA7* rare variants. This analysis was not limited to persons with EOAD, as only 201 of the 1,302 studied participants with AD met the EOAD cutoff and the mean age of onset was about 73. Twenty-two patients with AD had rare variants of potential functional importance. The frequency of participants with *ABCA7* mutations, therefore, was about 1.6%. By far, the most common of these was a transcription-terminating frameshift mutation (p.E709fs) found in 15 persons. As detailed in a separate report, these variants were not detected in Belgian individuals without AD,⁵ which led the authors to conclude these variants genuinely associate with AD.

Van den Bossche et al. sought to define features that could help identify potential *ABCA7* rare variant carriers. The most telling characteristic was a higher likelihood of having a positive AD family history (45.5% in carriers vs 15.6% in noncarriers). Otherwise, *ABCA7* variant carriers resembled the broader AD population. Carriers showed relatively typical CSF biomarker, imaging, and (when available) histopathology profiles. Some carriers showed prominent atypical clinical features (including parkinsonism and behavior changes), although most did not, and atypical features were not profound enough to ultimately preclude a final AD diagnosis. This finding does raise the possibility that some *ABCA7* mutation carriers may ultimately receive a non-AD diagnosis or even develop other neurologic disorders. It could also simply indicate that *ABCA7* mutation-related AD cases show the same phenotypic heterogeneity that non-*ABCA7* cases do.

Most AD-associated *ABCA7* rare variants identified to date would appear to cause loss of protein function.⁵ Perhaps because of the presence of a functional second allele, the pathogenicity of heterozygous *ABCA7* rare variants is low enough to not generate an obvious mendelian inheritance pattern (although one kindred with autosomal dominant inheritance was reported by the

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Belgian group). This helps emphasize the fact that with sporadic-appearing diseases, associated nuclear DNA variants need to walk a fine line—they cannot have an effect so profound it leads to autosomal dominance or so weak it precludes finding association.

These studies advance AD knowledge but interpretive limitations apply. While the overall finding that rare *ABCA7* variants contribute to AD risk appears reliable, because they are so uncommon some variants could ultimately turn out to be incidental findings. Some persons could have other genetic characteristics that affected their presentation to a greater extent than their *ABCA7* variant did. Also, in the Van den Bossche et al. study, the age at clinical onset ranged from 54 to 90 years. In those who develop AD at extremely advanced ages, can a particular rare variant truly constitute a relevant prodisease risk factor?

Guilt by association studies such as these also provide some mechanistic insight that may, however, be limited at this point. While the *ABCA7* protein has a role in lipid handling,⁸ and data increasingly implicate a role for lipid metabolism in AD,⁹ exactly how *ABCA7* loss of function contributes to AD risk remains unclear. This caveat applies despite the fact that a relationship between *ABCA7* function and β -amyloid dynamics is observed in genetically altered mice.¹⁰

At a research level, these studies justify screening genes previously found to contribute to AD risk for rare variants. At this point, these findings will not alter clinical practice, but this could change if *ABCA7* variant screening becomes commercially available. If it does, *ABCA7* genotyping could prove particularly informative for patients with dementia onset before age 65, a positive yet non-autosomal dominant family history, and perhaps the absence of a more common potential genetic risk factor (i.e., those who lack an *APOE4* allele).

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