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Commentary

Welcome to the complex disease world Alpha2-macroglobulin and Alzheimer's disease

Aleister J. Saunders[a] and Rudolph E. Tanzi[b,*]

[a] *Department of Bioscience, Drexel University, Philadelphia, PA 19104, USA*
[b] *Genetics & Aging Research Unit, Center for Aging, Genetics, and Neurodegeneration, Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Charlestown, MA 02129, USA*

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The recent explosion in our understanding of Alzheimer's disease (AD) at both the molecular and biochemical levels is due, in large part, to the successful utilization of genetic and genomic analyses over the past two decades. Initial positional cloning efforts of the 80s and 90s led to the identification of three genes, amyloid precursor protein (*APP*) and presenilins 1 and 2 (*PSEN1* and *PSEN2*), that can harbor mutations leading to the rare, early-onset (<60 years) familial form of AD. Phenotypically, the majority of these early-onset mutations (>150 in total; a complete list of early-onset AD mutations can be found at the Alzheimer's disease mutation database (http://molgen-www.uia.ac.be/ADMutations) lead to increased generation of the highly amyloid plaque-prone Aβ42 peptide from APP (Haass and De Strooper, 1999; Hardy, 1997; Price et al., 1998; Tanzi, 1999; Tanzi and Bertram, 2001).

Similarly, genetic analysis of the more common, late-onset form of AD holds great promise for expanding our understanding of AD pathogenesis, accelerating means for early prediction of AD, and developing novel therapeutic modalities for the prevention and treatment of this devastating neurodegenerative disorder. Despite intensive efforts, only one gene to date, apolipoprotein E (*APOE*), has been universally established as a susceptibility gene for late-onset AD. In this case, the ε4 variant of *APOE* only increases age-related risk for AD, but does not guarantee onset (Blacker et al., 1997; Meyer et al., 1998; Saunders et al., 1993). Recent segregation analyses suggest that an additional four to seven AD susceptibility genes, of at least moderate effect, remain to be discovered (Daw et al., 2000). Intensive searches for the additional risk-conferring genes is under way in laboratories worldwide and has already resulted in reports of over 100 different genes tested for genetic association with AD. However, with the exception of *APOE*, none of these putative AD genetic risk factors have been universally replicated in independent samples. The reason for the dearth of confirmed susceptibility genes is the highly complex genetic nature of AD itself. Unlike Mendelian diseases, risk-conferring genes in complex diseases usually impart modestly increased risk with low penetrance and unknown inheritance patterns. These complexities make unequivocal identification of susceptibility genes extremely challenging. While these challenges are formidable, they are not prohibitive. In fact, the future for analyses of complex genetic disorders can be considered as quite bright due to the ongoing deciphering of the human genome, the accelerating discovery of DNA variants (primarily, single nucleotide polymorphisms; SNPs), and technological advances that continue to make high-throughput genotyping and sequencing increasingly fast and relatively inexpensive.

In the search for late-onset AD susceptibility genes, no gene besides *APOE* has been as widely investigated as that encoding α2-macroglobulin (protein: α2M; gene: *A2M*). *A2M* is an ideal positional candidate gene for late-onset AD. Biologically, α2M mediates Aβ toxicity, clearance, and degradation. α2M binds the Aβ peptide specifically and tightly (Du et al., 1998; Hughes et al., 1998) and consequently there are three biological manifestations of Aβ/α2M interactions that are directly relevant to the etiology and pathogenesis of AD. First, the interaction between α2M and Aβ prevents Aβ fibril formation and fibril-associated neurotoxicity (Du et al., 1998; Hughes et al., 1998). Second, α2M is a protease inhibitor; protease activation of α2M/Aβ complexes or protease activation of α2M followed by Aβ binding can promote the protease-mediated degradation of

* Corresponding author. Fax: +1-617-724-1949.
E-mail address: tanzi@helix.mgh.harvard.edu (R.E. Tanzi).

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α2M-bound Aβ (Lauer et al., 2001). Last, protease-activated α2M/Aβ complexes may undergo LRP-mediated endocytosis followed by trafficking of Aβ to the lysosome for degradation or translocation, e.g., out of the brain and into the plasma (Narita et al., 1997).

Genetic linkage analyses have previously suggested the presence of an AD locus on chromosome 12; three groups have reported linkage at the p-ter of chromosome 12 from ~6 to 30 cM, in the same vicinity (~20 cM) as the *A2M* gene (Mayeux et al., 2002; Myers et al., 2002; Rogaeva et al., 1998; Wu et al., 1998). A second, peri-centromeric linkage signal has also been detected on chromosome 12 from ~48 to 68 cM, in the same vicinity (~68 cM) as the *LRP* gene (Pericak-Vance et al., 1997; Rogaeva et al., 1998; Scott et al., 1999, 2000). However, genetic association analyses for AD and *A2M* have been controversial. Our group initially reported an association between AD and an intronic deletion polymorphism in the splice site of exon 18, *A2M*-18i [referred to as *A2M*-2 in our original report (Blacker et al., 1998)], in a sample of 104 discordant sibships ascertained through the NIMH Genetics Initiative. This initial finding was later confirmed in an enlarged 120-sibship subset from the NIMH sample (Blacker et al., 1999). While this association has been generally replicated in independent family-based AD samples (Rogaeva et al., 1999; Romas et al., 2000; Rudrasingham et al., 1999), case-control association studies of AD and the original *A2M*-18i deletion polymorphism have been largely negative (reviewed in Saunders et al., 2003) with five positive follow-up studies (Alvarez et al., 1999; Dodel et al., 2000; Jhoo et al., 2001; Nacmias et al., 2001; Zappia et al., 2002). A second polymorphism in *A2M*, a nonsynonymous SNP in exon 24 (*A2M*-24e) that results in Val to Ile substitution at amino acid position 1000, has also been widely investigated in association studies. However, two published family-based association studies did not find evidence for association of *A2M*-24e and AD (Romas et al., 2000; Wavrant-DeVrieze et al., 1999), while five of 16 case-control studies were able to (Liao et al., 1998; Myllykangas et al., 1999; Tang et al., 2002; Wang et al., 2001; Zappia et al., 2002).

Recently, we extended these association studies in the complete NIMH AD genetics initiative sample of 437 families (Blacker et al., 1997) and found significant individual SNP as well as haplotypic association between several novel *A2M* polymorphisms and AD (Saunders et al., 2003). Specifically, the *A2M*-18i polymorphism was confirmed to be individually associated with AD. However, association with AD was also observed with a novel synonymous SNP in exon 12 (*A2M*-12e; Y432Y) and with a novel noncoding SNP residing in the intron close to the splice site for exon 21 (*A2M*-21i). Significant haplotype association was also observed in the 3′ end of the gene near a functionally important region of the protein that contains the bait region, the β-Cys-γ-Glu thiol ester bond between Cys-949 and Glu-952, as well as the Aβ- and LRP-binding domains (Du et al., 1997; Hughes et al., 1998). The strength and consistency of this most recent family-based association, as well as other family-based samples, suggest not only that the association of *A2M* with AD is genuine and readily detectable when using family-based samples.

The discrepancy between the generally positive association findings in family-based samples and the generally negative association findings in case-control samples further suggest that *A2M* may be a risk factor primarily in individuals with a family history of AD. While it remains unknown as to whether the novel AD-associated SNPs *A2M*-12e and 21i are pathogenic, it seems highly unlikely that the previously described AD-associated polymorphisms, *A2M*-18i or 24e, are pathogenic. Rogeava et al. (1999) first demonstrated that despite being located in the exon 18 splice site, the *A2M*-18i deletion polymorphism does not alter splicing of brain or liver *A2M* mRNA. Now, in this issue of *Experimental Neurology*, Birkenmeier et al. (2003) confirmed these negative findings in leukocytes while also testing for genotype-specific effects on α2m levels, conformation, stability, as well as ligand and receptor binding. Specifically, Birkenmeier et al. (2003) isolated α2m from single individuals harboring each of the three *A2M*-18i genotypes and, after performing a series of elegant biochemical analyses, observed no significant functional alterations in α2M that might be envisaged to lead to dysfunctional Aβ catabolism and onset of AD.

These new findings confirming and extending the nonpathogenicity of the *A2M*-18i polymorphism are not entirely unexpected given the previous functional studies of this variant. However, it should be noted that these findings still leave open the possibility that aberrations in α2m function could occur in a subset of *A2M*-18i deletion carriers owing to linkage disequilibrium of this variant with an as of yet unidentified pathogenic mutation/polymorphism elsewhere in *A2M* (or in a nearby gene). Consistent with this possibility is the fact the significant linkage disequilibrium continues to be detected among common polymorphisms throughout the *A2M* gene, and particularly in the 3′ end of the gene. Briefly, linkage disequilibrium requires only that alleles of two or more polymorphisms are inherited together more often than is predicted by their individual allele frequencies. However, their respective frequencies need not be similar. In other words, the frequency of an as of yet unidentified pathogenic mutation/polymorphism in *A2M* need not the same as that of *A2M*-18i, and need not be in 100% (complete) linkage disequilibrium with *A2M*-18i to explain association of the latter with AD. In fact, given the relatively modest linkage and association results for *A2M* and risk for AD, the prevalence of an actual pathogenic mutation/polymorphism in *A2M* (or a nearby gene) would almost certainly have to be considerably lower than that of the *A2M*-18i deletion allele (~30%). In view of these facts and considerations, one would then predict that the number of samples needed to reliably detect α2m dysfunction, resulting from linkage disequilibrium of *A2M*-18i with an as of yet unidentified pathological mutation/polymorphism in

or near *A2M*, would be much larger than the single homozygote and heterozygote *A2M*-18i deletion cases that were analyzed by Birkenmeier et al. (2003), and more along the order of ~100 cases. Similarly, sequencing efforts to find the actual underlying pathogenic mutation/polymorphism would require similar numbers of *A2M*-18i deletion carriers (preferably homozygotes).

Adding to these already complex issues is the possibility that the functional consequences of a pathologic polymorphism may only be realized in a tissue and/or developmentally dependent manner. Recently, it was shown that the mutation in the *IKBKAP* gene that causes familial dysautonomia, a splice site mutation, only causes splicing aberrations in a tissue-specific manner. RNA isolated from lymphoblasts of patients is unaffected, whereas in RNA isolated from patient brain reveals truncated forms (Slaugenhaupt et al., 2001). These issues make phenotypic characterization of diseased-associated genotypes all the more challenging. However, such complexities are now the norm in genetic and biochemical investigations of complex diseases. In this new era of complex disease gene analyses, genotypic association with disease does not ensure phenotypic association, as was common for most monogenic Mendelian diseases, e.g., Huntington's disease. As genetics and genomic approaches now traverse the foreign and often treacherous landscape of complex genetic disease, biochemical and proteomic approaches will need to comprehensively accommodate the many subtleties of these disorders in order to fully complement genetic investigations. Moreover, biochemical, molecular, and genetic approaches will need to continually inform each other (on the backdrop of very large sample sizes) if we are to ultimately unravel how genotypic changes relate to complex disease phenotypes.

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