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Use of Genetic Variation as Biomarkers for Alzheimer's Disease

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Abstract

Late-onset Alzheimer's disease (LOAD) is the most common cause of late-onset dementia in western societies. Despite remarkable achievements in human genetics throughout the years, in particular technological advances in gene mapping and in statistical methods that relate genetic variants to disease, to date only a small proportion of the genetic contribution to LOAD can be explained leaving several remaining genetic risk factors to be identified. A possible explanation for the difficulty in gene identification is that LOAD is a multifactorial complex disorder with both genetic and environmental components. Multiple genes with small effects each ("quantitative trait loci" [QTLs]) are likely to contribute to the quantitative traits associated with the disease, such as memory performance, amyloid/tau pathology, or hippocampal atrophy. The motivation for identifying the genetics of LOAD is clear. Not only could it shed light on disease pathogenesis, but it may also provide potential targets for effective treatment, screening, and prevention. Here, we review the usefulness of genetic variation as diagnostic tools and biomarkers in LOAD and discuss the potentials and difficulties researchers face in designing appropriate studies for gene discovery.

Keywords

Alzheimer's; biomarkers; genetics

Introduction

Late-onset Alzheimer's disease (LOAD) is among the most frequently encountered diseases in aging societies. It is estimated that approximately 5 million people in the United States and 17 million people worldwide suffer from the disease. By age 85 years and older 15–30% are affected, and the incidence rate increases from approximately 1% among people aged 65–70

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Conflicts of Interest

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years to approximately 68% for people aged 85 years and older.^{1,2} It is expected that these numbers will quadruple by the year 2040, by which 1 out of 45 Americans will be affected, leading to a considerable public health burden.³

To date, there are no definitive diagnostic tests or biological markers of the disease. The diagnosis of LOAD during life is based on clinical examination using the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association Work Group.⁴ Although these criteria have good reliability^{5–7} and validity,^{8,9} any measure that would increase diagnostic sensitivity and specificity would be highly valuable for improving early detection and intervention. Genetic variation can be particularly useful as it is stable across the lifespan and the disease process and is not influenced by confounding factors.

Twin studies suggest that 37% to as much as 78% of the variance in the age at onset of LOAD can be attributed to additive genetic effects.¹⁰ As a consequence, genes involved in LOAD could theoretically be highly valuable diagnostic tools. Untangling the genetics of LOAD would in addition help elucidate the disease pathogenesis and would provide potential targets for effective treatment and prevention.

Despite available improved analytic techniques, the continued pursuit of genetic variants associated with LOAD has, however, been limited. To date, only two genes have been implicated in the cause: the Apolipoprotein (*APOE*)- $\epsilon 4$ allele and the Sortilin-related receptor (*SORL1*) gene. Several additional genetic loci have been reported but remain to be confirmed. Together, these reported genes explain only a small proportion of the genetic contribution to LOAD leaving several genetic risk factors to be identified.

In this article, we review the genetic risk factors that have been implicated in LOAD, and review their usefulness as diagnostic tools and biomarkers in AD. In addition, we discuss the potentials and difficulties researchers face when performing studies for gene discovery in common complex diseases, such as LOAD.

Genetics of LOAD and Its Endophenotypes

Most of the studies assessing the role of genetic variants in dementia have used the diagnostic criteria of LOAD as the phenotype. The most frequently used endophenotypes are age at onset of dementia and cognitive test performance. Plasma amyloid β ($A\beta$) levels, a putative risk factor, have been studied rarely^{11–13} but have in particular been mapped to loci on chromosome 10q21–25. The rationale for use of endophenotypes in LOAD research is that quantitative traits provide more informative phenotypes than simply considering affection status and thus provide more statistical power to detect small polygenic effects.

Apolipoprotein E

APOE, a lipid-binding protein, is expressed in humans as three common isoforms coded for by three alleles, *APOE* $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$. The first reports linking *APOE* genotype with LOAD found a significant increase in the *APOE* $\epsilon 4$ allele frequency in patients with the disease. The large body of epidemiological data that subsequently accumulated clarified this effect by demonstrating that *APOE* $\epsilon 4$ decreases the age at onset of LOAD in a gene dosage-dependent manner,^{14–23} and that *APOE* $\epsilon 4$ is associated with lower cognitive performance, in particular the memory domain. It is thought that *APOE* may account for as much as 20–50% of LOAD risk.^{24,25}

In vitro studies have indicated that the *APOE*- $\epsilon 4$ isoform binds $A\beta$ peptides with a higher avidity compared to *APOE*- $\epsilon 3$.²⁶ Furthermore, there is a strong correlation between the

presence of an APOE- $\epsilon 4$ allele and a higher A β burden in the brains of AD patients,^{27,28} suggesting that APOE interacts with A β in enhancing its deposition in plaques. This is supported by the observation that homozygous APOE knockout (APOE $-/-$) mice develop fewer and more diffuse, nonfibrillar A β deposits.^{29–31} Some, but not all, studies assessing the effect of different APOE isoforms on A β fibrillization, showed that the $\epsilon 4$ isoform leads to increased A β aggregation *in vitro*.^{32,33} Similarly, *in vivo* studies in APOE $-/-$ mice indicated that A β fibrillization and plaques formation was increased in mice expressing human APOE- $\epsilon 4$ (APPV717F+/-, apo E $-/-$) compared to mice not expressing human APOE.^{34,35} Still, it is possible that APOE exerts its effects through different mechanisms, e.g., APOE is a major cholesterol transporter, and high cholesterol levels have been associated with an increased A β load in animal models^{36,37} and changes in amyloid precursor protein (APP) processing.^{38,39} Thus, APOE isoform-specific changes in cholesterol binding and transport in brain might also affect plaque formation in AD brains.

LOAD as the Endophenotype—A large amount of studies assessed the relation between APOE genotypes and LOAD in population-based settings. In a meta analysis⁴⁰ that included data from 40 research teams on 5930 patients with LOAD and 8607 controls without dementia who were recruited from clinical, community, and brain bank sources, the risk of AD was significantly increased for Caucasians with genotypes $\epsilon 2/\epsilon 4$ (OR = 2.6, 95% CI = 1.6–4.0), $\epsilon 3/\epsilon 4$ (OR = 3.2, 95% CI = 2.8–3.8), and $\epsilon 4/\epsilon 4$ (OR = 14.9, 95% CI = 10.8–20.6), whereas the ORs were decreased for people with genotypes $\epsilon 2/\epsilon 2$ (OR = 0.6, 95% CI = 0.2–2.0) and $\epsilon 2/\epsilon 3$ (OR = 0.6, 95% CI = 0.5–0.8). The APOE- $\epsilon 4$ -AD association was weaker among African-Americans and Hispanics, but there was significant heterogeneity in ORs among studies of African-Americans ($P < 0.03$). The APOE- $\epsilon 4$ -AD association in Japanese subjects was stronger than in Caucasian subjects ($\epsilon 3/\epsilon 4$: OR = 5.6, 95% CI = 3.9–8.0; $\epsilon 4/\epsilon 4$: OR = 33.1, 95% CI = 13.6–80.5). The $\epsilon 2/\epsilon 3$ genotype appeared equally protective across ethnic groups. Figure 1 shows the pooled odds ratios (95% CI) of the 40 studies included in the paper. Taken together, it seems that one $\epsilon 4$ allele is associated with a two- to three-fold increased risk, while having two copies is associated with a five- to 10-fold increase.

Age at Onset as the Phenotype—In the vast majority of studies, both clinical and epidemiological, age at onset of LOAD was strongly related to the presence of the APOE- $\epsilon 4$ allele (Table 1).^{14–23} Taken together, these studies, which include both clinical and epidemiological studies, suggest that APOE $\epsilon 4$ may decrease the age at onset by as much as 7–9 years per allele. They further suggest that this effect is present across the lifespan including children and adolescents^{19,20,41–46} and across various ethnic groups, although it may be stronger in Caucasians and Hispanics than African-Americans.²³ Mak *et al.*⁴⁷ studied the APOE allele frequencies in Hong Kong elderly Chinese (65 LOAD patients and 82 age- and sex-matched controls). Both the mean and the median age at onset tended to be lower in subjects with one or two copies of $\epsilon 4$ compared to persons without $\epsilon 4$ allele (mean age of onset [SD] no $\epsilon 4$ versus one $\epsilon 4$, one $\epsilon 4$ versus 2 $\epsilon 4$ s: 73.3 [8.5] versus 72.0 [6.4] versus 71.2 [5.0]). There was in addition a tendency for the mean and median ages at onset to be higher in subjects with $\epsilon 2/\epsilon 2$ or $\epsilon 2/\epsilon 3$ than in subjects with $\epsilon 3/\epsilon 3$. Although these differences only approached statistical significance ($P = 0.078$, $Z = 1.419$), these findings suggest that APOE also exerts its effect in Chinese populations. This notion is supported by the fact that in the same study, the APOE- $\epsilon 4$ allele frequency was significantly higher in the AD group than in the control group (0.169 versus 0.067, $P < 0.01$), and the fact that in Chinese the $\epsilon 4$ frequency is low, which decreases the power to obtain statistical significant results.⁴⁸

In contrast to these studies, two studies found a higher age at onset for patients bearing the APOE $\epsilon 4$ allele. In a study by do Couto *et al.*,⁴⁹ among 68 patients with LOAD, the age at onset of disease was significantly higher in the patients with the $\epsilon 4$ allele (mean onset [SD] of $\epsilon 3/\epsilon 4$ and $\epsilon 4/\epsilon 4$, 65.7 [7.1], $n = 40$) compared with patients without the $\epsilon 4$ allele (mean onset [SD]

$\epsilon 3/\epsilon 3$, 61.6 [7.6], $n = 28$, $P < 0.05$, two-tailed Student's t -test). Among 101 LOAD patients, ⁵⁰ age at onset was highest for the $\epsilon 4$ -heterozygous subjects and lowest for the $\epsilon 4$ -negative subjects. The heterozygous subjects declined more rapidly on the Mini-Mental State Examination and the Category Fluency Test than the subjects without the $\epsilon 4$ allele or with $\epsilon 4$ homozygosity. The homozygous subjects declined only faster on the Physical Capacity subscale of the Psychogeriatric Dependency Rating Scale. It is important to note that these two studies included relatively younger patients. It remains possible that the presence of the $\epsilon 4$ allele represents a particularly high risk in the older patients. The bulk of data on age at onset is consistent with the large body of studies showing an association between the APOE $\epsilon 4$ allele and risk of LOAD and suggests that the $\epsilon 4$ allele decreases age at onset of LOAD in a dose-dependent manner.

Cognitive Performance as the Phenotype—Few studies, including the Cache County Study of Memory in Aging (CCMS),⁵¹ a study among 46 nondemented persons aged 85 years or above from a randomly selected group of 128 subjects in Vantaa, Finland,⁵² and the study by Murphy *et al.*,⁵³ observed no effect of the APOE locus on the rate of cognitive decline. It is important to note that these studies either had unspecific assessment of memory,⁵³ small sample sizes,^{52,53} or consisted of samples prone to survival bias,⁵¹ which may limit their ability to detect harmful associations. However, most studies exploring the association of APOE with cognitive performance were consistent with the studies reporting an association of the APOE genotype with LOAD or age at onset of LOAD and showed a harmful effect of the APOE $\epsilon 4$ variant with a dose–response relationship of the effect (Table 1). In general, these studies can be divided into studies including and excluding subjects with cognitive impairment or dementia. Studies that explore the effect of APOE on cognitive performance in nondemented subjects provide the ability to draw conclusions about the effect of genetic risk factors on cognition in cognitively normal persons or the preclinical stage of the disease.

Studies Including Subjects with Cognitive Impairment or Dementia—Cosentino *et al.*⁵⁴ examined the impact of the APOE $\epsilon 4$ variant on the rate of cognitive change in one incident ($n = 199$) and two prevalent samples ($n = 215$, $n = 156$) of LOAD patients 65 years and older. The presence of at least one $\epsilon 4$ allele was associated with faster cognitive decline in the incident LOAD group ($P = 0.01$). Similar results were observed for the two prevalent dementia samples when adjusting for disease severity or excluding the most impaired participants from the analyses, indicating that the APOE $\epsilon 4$ may influence the rate of cognitive decline in both the early and late stages of LOAD. In a study by Wehling *et al.*,⁴⁶ which comprised 70 consecutively referred patients aged 50–75 years, APOE $\epsilon 4$ carriers showed a slightly poorer performance than noncarriers on the MMSE (27.5 versus 28.4, $P = 0.03$) and learning trials of the California Verbal Learning Test (CVLT; $F(1,68) = 5.46$, $P = 0.022$). Hirono *et al.*,⁵⁵ who explored the effect of APOE on cognition in 64 LOAD patients using the Alzheimer Disease Assessment Scale–Cognitive subscale (ADAS–Cog), observed that the presence of the $\epsilon 4$ allele was in a dose–response fashion associated with accelerated memory decline (mean ADAS–Cog score $-/-$ versus $4/-$ versus $4/4$: -0.2 versus 0.4 versus 1.0 , $P = 0.008$).

Studies Excluding Subjects with Cognitive Impairment or Dementia—Most studies exploring these associations among nondemented subjects yielded consistent results, indicating that APOE also exerts its effect in cognitively normal subjects or preclinical stages of the disease. In a study by Mayeux *et al.*,⁵⁶ presence of an APOE $\epsilon 4$ allele was in 563 nondemented elderly associated with a more rapid decline in a composite score of memory performance over a 7-year follow-up period. Among 669 participants of the Religious Order Study,⁵⁷ possession of one or more $\epsilon 4$ alleles was over a 8-year follow-up associated with faster decline in episodic memory compared to the $\epsilon 3/3$ genotype, whereas possession of one or more

APOE ϵ 2 alleles was associated with reduced decline. The rates of change in episodic memory were an average annual increase of 0.016 units in the ϵ 2 subgroup and annual decreases of 0.022 units in those with ϵ 3/3 and of 0.073 units in the ϵ 4 subgroup. In 2181 elderly participants (aged 70–74 years) from the Hordaland Health Study, the APOE ϵ 4 allele was in a dose-dependent fashion also associated with lower episodic memory performance. The strongest effect was seen in homozygous men (OR 10.7; 95% CI 4.7–24.0).⁵⁸ In a Dutch sample of 2208 related individuals, the ϵ 4 variant was associated with reduced test scores for the Adult Verbal Learning Test and within this test was strongest for the memory and learning sub domains.⁴⁴ Bondi *et al.*⁵⁹ explored the effect of APOE on cognition in 52 nondemented elderly using the CVLT. Consistent with the studies described above, APOE ϵ 4 carriers demonstrated significantly poorer mean performances than non-carriers. Six of the 14 APOE ϵ 4 carriers who completed annual follow-up evaluations developed either LOAD or questionable LOAD, whereas none of the 26 noncarriers demonstrated any cognitive decline.

The longitudinal population-based Longitudinal Aging Study Amsterdam⁶⁰ explored to what extent subjective memory complaints and APOE ϵ 4 allele carriage interact in their prediction of future cognitive decline. In this study of 1168 elderly subjects, APOE ϵ 4 carriers had after a 6-year follow-up a greater rate of cognitive decline measured by MMSE scores and slower information processing speeds. This effect appeared to be additive with the effect of memory complaints: subjects with both factors showed a two times higher cognitive decline than did subjects without memory complaints and ϵ 4 allele.

In the Canadian Study of Health and Aging⁶¹ and a consecutive sample of 66 patients from the Mayo Clinic Alzheimer's Disease Center/Alzheimer's Disease Patient Registry who met criteria for a diagnosis of a mild cognitive impairment (MCI) and who had at least one clinical reevaluation,⁶² possession of an APOE ϵ 4 allele increased the risk of conversion from cognitive impairment no dementia (CIND) or MCI to LOAD. In the Canadian Study of Health and Aging the presence of the APOE ϵ 4 allele was also associated with a decrease in the age at onset of LOAD.⁶¹

In two cross-sectional studies in younger subjects (average ages 46 and 56),^{42,43} the APOE ϵ 4 allele was relative to the noncarrier group associated with significantly poorer performance on learning and memory tasks and immediate and delayed recall, suggesting that age-related memory decline occurs earlier in cognitively healthy APOE ϵ 4 carriers than in noncarriers, and precedes clinically detectable LOAD.

Finally, these findings could also be replicated by twin studies. In a longitudinal study over 13 years⁶³ among 478 twins from the Swedish Adoption/Twin Study of Aging (SATSA), the APOE ϵ 4 variant was in a dose-dependent fashion at all ages associated with worse working and recall memory and rate of change in working memory. In a second longitudinal twin study among 626 twins in their 50s,⁴⁵ ϵ 4-carriers showed significantly lower performance on immediate and delayed recall than noncarriers (mean (SD) comparing ϵ 4+ versus ϵ 4-: immediate recall 22.19 (5.37) versus 23.8 (6.2); delayed recall: 19.5 (5.9) versus 20.12 (6.6)), supporting the genetic contribution of APOE to LOAD.

Sensitivity and Specificity of APOE—Studies, assessing the usefulness of the APOE genotype in the diagnosis of AD among persons with dementia, reported specificities of the ϵ 4 allele between 81 and 100%^{64–67} when used in combination with clinical or autopsy criteria but lower specificities when used alone.⁶⁵ Sensitivity estimates were lower and ranged between 19–75%.^{64,65,67,68}

Sortilin-Related Receptor

Identification of *APP*, presenilin 1 (*PSEN1*), and presenilin 2 (*PSEN2*) as susceptibility genes for early-onset AD (EOAD) has led to the initiation of the “amyloid cascade,” the basic biochemical formula for production of A β , the putative culprit of AD. The amyloid pathway involves two enzymatic steps (Fig. 2): In the first β -cleavage step, BACE cleaves APP near the N terminus of the A β peptide; in the second γ -cleavage step, the membrane-bound C-terminal APP fragment is cleaved by γ -secretase, a complex composed of transmembrane proteins PSEN1 and PSEN2, nicastrin, APH1, TMP21, and PEN2.⁶⁹

It is notable that APP and the secretases are all integral transmembrane proteins. Further, they are dynamically sorted through the plasma membrane and the membranes of intracellular organelles, and the liberation of A β involves a transmembrane secretase enzyme acting on a transmembrane APP C-terminal fragment substrate. Thus, from a cell biology perspective, sorting mechanisms that cause APP and the secretases to colocalize in the same membranous compartment are expected to play important roles in the regulation of A β production. Over 30% of all proteins are transmembrane proteins,⁷⁰ and most are typically sorted via the secretory and endocytic pathways.^{71,72} During the last two decades, the trans-Golgi network and the endosome were identified as the key organelles organizing the complex movement of the transmembrane proteins via secretory and endocytic pathways (Fig. 2B). Important coat complexes initiating the transport of APP and BACE through this sorting itinerary are the clathrin coat and the retromer.^{73–75} Clathrin coats are involved in the endocytic pathway connecting the cell surface to the endosome and the pathway connecting the trans-Golgi network to the endosome.⁷⁶ The retromer is involved in the trafficking from the endosome to the trans-Golgi network.

Recent studies showed that *SORL1* is involved in trafficking of APP from the cell surface to the golgi-endoplasmic reticulum complex (Fig. 3). Under-expression of *SORL1* leads to over-expression of A β and an increased risk of AD.⁷⁷ Most studies exploring the effect of *SORL1* on cognitive impairment or dementia used LOAD as a dichotomized trait in the analyses. Rogaeva and colleagues⁷⁷ first reported the allelic and haplotypic associations among LOAD and variants in *SORL1* (Table 2). Subsequently, several studies supported the initial finding by showing that genetic variants in *SORL1* contribute toward LOAD.^{78–83} The original study included four different ethnic groups, ranging from North American and European Caucasians, Caribbean Hispanics, African-Americans, and Israeli-Arabs. With this investigation on over 6000 subjects, two different sets of haplotypes were identified: (1) SNPs in the 5' end of the gene (SNP 8–10; 120873131 bp–120886175 bp) among Caribbean Hispanics (family study), Caucasians (case–control study), and Israeli-Arabs (case–control study); and (2) SNPs in the 3' end of the gene (SNP 22–25; 120962172 bp–120988611 bp) among multiple Caucasian samples (family and case–control studies) and African-Americans (family study). Haplotype analysis strengthened the statistical support further. However, as observed in many common diseases, these candidate SNPs confer a modestly elevated risk of LOAD, ranging from an odds ratio of 1.4 to 2.2, and the allelic association was not uniform across data sets or ethnic groups. The authors strengthened their allelic association findings by functional cell biology findings, which showed that suppression of *SORL1* led to elevation of A β levels.⁷⁷ Two subsequent studies by the same group broadly supported 1 or both haplotypes or some variations of the 2: Haplotype C–G–C at SNPs 8–10 or haplotype T–T–C at SNPs 23–25 or both. Lee and colleagues⁸⁰ showed that the same set of SNPs at SNPs 23–25 were associated with LOAD in Caucasians residing in northern Manhattan. They then confirmed the allelic and haplotypic associations in autopsy confirmed cases of Caucasian ethnicity for haplotype at SNPs 8–10 and haplotype at SNPs 23–25.⁷⁹

Seven other groups examined the relation between *SORL1* and LOAD or LOAD endophenotypes in different populations (Table 2).^{78,82–86} Three replication studies supported

the initial findings, while the remaining three showed either negative or weak results. Three clearly positive studies included one by Tan *et al.*⁸³ and the other by Seshadri *et al.*⁸² Bettens and colleagues⁷⁸ directly replicated SNPs 8–10 and showed support for SNPs 25–27 in 550 Belgians with LOAD and 637 unaffected individuals. Tan *et al.*⁸³ examined 223 cases and 263 controls from a Han Chinese population to show that haplotype G-C-A at SNP 19–22–23 were associated with LOAD (OR = 1.35; 1.04–1.74), but none of the haplotypes in SNP 8–10 were associated. Webster *et al.*⁸⁶ and Li *et al.*⁸⁵ reported weak associations.

Li *et al.*⁸⁴ and Shibata *et al.*⁸⁷ reported no associations between *SORL1* and LOAD. However, in the latter study the negative results were based on genotypic association analyses only. When Lee *et al.*⁸⁸ re-analyzed the data of this study using allelic association tests, SNPs 8 and 24 were significantly associated with LOAD, supporting the association in both the 3' and 5' regions of *SORL1*. Using the Framingham community-based family samples, Seshadri *et al.*⁸² extended the existing studies using cognitive performance as an endophenotype. The authors reported that *SORL1* was significantly associated with abstract reasoning ability as measured by the Similarity test ($P = 3.2 \times 10^{-6}$). However, they did not observe an association with memory. A possible explanation for this discrepancy may be that this sample consisted of 705 related persons, which can lead to limited power to uncover associations as compared to larger samples that include unrelated subjects.

Overall, these genetic and functional genomic studies provide compelling evidence for a role of *SORL1* in LOAD. Putative variants and their sensitivity and specificity for LOAD diagnosis, however, remain to be identified, as the reported variants do not affect coding sequence or splicing. In any case, the results of the above summarized studies imply that (a) there are several different LOAD-associated allelic variants in distinct regions of the *SORL1* gene in different populations; (b) these variants are likely to be in intronic regulatory sequences that might govern cell type-specific or tissue-specific expression of *SORL1*; and (c) these variants affect this risk by altering the physiological role of *SORL1* in the processing of APP holoprotein.

Other Genes

Several genes, in particular genes mapping to chromosome 10q_{21–25} have been reported to influence A β levels in LOAD. In a study by Ertekin-Taner *et al.*,¹² A β ₄₂ levels were related to a missense C/T polymorphism in exon 6 in the urokinase-type plasminogen activator (*PLAU*) gene at chromosome 10q24. In a second study by the same group, genetic variants in a haplotype block spanning the insulin degrading enzyme (*IDE*) mapping to 10q_{23–25} were significantly associated with plasma A β ₄₂ levels.¹¹ The latter finding is consistent with a study by Farris *et al.*,¹³ demonstrating that partial loss-of-function mutations in *IDE*, which induce diabetes, also impair degradation of A β protein. *PLAU*¹² and *IDE*¹¹ were also associated with an increased risk of LOAD, supporting the usefulness of A β levels as a LOAD endophenotype. Additional genes and putative loci have been reported, but independent replication remains inconsistent. There is little concordance between case-control and family-based studies^{89–93} suggesting that both clinical and genetic heterogeneity influence the outcome of these analyses. *LRP6*, a coreceptor for Wnt signaling, has been associated with LOAD and confirmed in a case-control analysis.⁹⁴ *GAB2* may modify the risk of LOAD in APOE ϵ 4 carriers and has been associated with hyperphosphorylation of tau protein.⁹⁵ The P86L polymorphism in *CALHM1*, which encodes an essential component of a previously uncharacterized cerebral Ca²⁺ channel that may control A β levels, has been putatively associated with LOAD.⁹⁶ Additional genes that have been reported but remain to be confirmed include *CHRNA2*, *A2M*, *CTNNA3*, *GSTO1*, *GSTO2*, and *GAPD*.^{97–100} There also continues to be support for linkage to LOAD at 6p, 9q, 10q and 12p and 19q,^{101–111} but specific causative loci could not yet be identified. In contrast, mutations in *APP*, *PSEN1*, and *PSEN2* genes are associated with EOAD (onset $\leq$ 60 years) with an autosomal pattern of inheritance.

Discussion

Theoretically, genes involved in AD could be used as diagnostic tools or potential novel therapeutic targets for treatment. However, in contrast to EOAD, which is caused by mutations in *APP*, *PSEN1*, and *PSEN2* that have almost complete penetrance (>85%), and a clear-cut autosomal dominant pattern of inheritance, LOAD is a complex genetic disorder, in which multiple genes with small effects each are likely to contribute. Although segregation analyses conducted in families of patients with LOAD support the presence of at least four to six major genes,^{112,113} only two genes have been firmly implicated as genetic risk factors: *SORL1* and *APOE*. Additional genes and genetic loci that have been reported but remain to be confirmed include *CHRNA2*, *A2M*, *CTNNA3*, *GSTO1*, *GSTO2*, *GAPD*, and loci at 6p, 9q, 10q and 12p and 19q.

The difficulty in gene detection in LOAD may reflect the continued use of small cohorts of patients underpowered for genetic studies in this complex disease, in which multiple genes with small effects each quantitative trait loci (QTLs) are likely to contribute to the various quantitative traits associated with the disease, such as memory performance, amyloid/tau pathology, or hippocampal atrophy. Alternatively, it could reflect a failure to develop or make use of better quantitative endophenotypes. Endophenotypes are closer to the action of the gene than affection status, exhibit higher genetic signal-to-noise ratios,¹¹⁴ and thus provide greater power to localize and identify disease-related QTLs than does affection status alone.¹¹⁵ It is possible that the endophenotypes that are commonly used in dementia research are too heterogeneous to observe an effect. Finally, genetic research is often hampered by uncontrolled population stratification, pleiotropic effects (a single gene influences multiple phenotypic traits), or locus or allelic heterogeneity (a single disorder is caused by mutations in different genes or various mutations in a single gene, respectively), which frequently lead to null associations.

As described above, with a population attributable risk that is estimated at 20–50%,^{24,25} the $\epsilon 4$ allele increases LOAD risk in a dose-dependent fashion; one $\epsilon 4$ allele is associated with a two- to three-fold increased risk, having two copies is associated with a five- to 10-fold increase. Also affected in a dose-dependent fashion is age of onset of AD. The two haplotypes in the 3' and 5' regions of *SORL1* that repeatedly were found to be associated with LOAD among Caribbean Hispanic and Northern European families, in case-control studies of Europeans, Americans, African-Americans, and Israeli Arabs, had effect sizes ranging from odds ratios of 1.4 to 2.2. However, *APOE* has only moderate diagnostic sensitivity and specificity, and both *APOE* and *SORL1* increase LOAD risk in a non-Mendelian fashion, are not fully penetrant, and environmental factors either exacerbate or modify their effects. Moreover, they are neither necessary nor sufficient by themselves to cause LOAD. The same is likely to be true for the remaining yet-to-be-identified genetic factors associated with LOAD. These facts suggest that genetic variants associated with LOAD are better suited as risk biomarkers than diagnostic tools.

While probably not suitable as diagnostic markers, both *SORL1* and *APOE* may be targets for prevention and treatment. However, several issues must be resolved before development of a drug based on these genes can be considered. First, for both genes, it is necessary to clarify the exact mechanisms through which they increase LOAD risk. Second, it is necessary to further characterize the molecular pathways in which they are involved or with which they interact. Clarification of the biological functions, risk-factor activities and pathways of *SORL1* and *APOE* will help to understand their role in LOAD and can provide targets for effective intervention. Third, for *SORL1*, the precise putative genetic variants have to be identified. The reported variants are nonfunctional and do not affect coding sequence or splicing. Fourth, the additional risk factor genes involved in LOAD need to be known. The accurate risks associated

with each gene involved can only be estimated when all putative and protective genetic variants are known. Fifth, it has to be clarified whether the genes mediating each endophenotype involved in LOAD are distinct from each other. This is a key assumption of the endophenotype approach, yet empirical proof of this remains to be determined. A substantial degree of overlap appears likely for a number of the known genes associated with EOAD and LOAD, at least including the APP, PSEN1, PSEN2, APOE, and SORL1, given that these genes are involved in either the production or processing of the A β peptide. Nevertheless, each gene has a unique role in this cascade, and it thus seems likely these loci will differ in their magnitudes of influence across the brain systems affected in this disorder. Sixth, it has to be clarified how *SORL1* and *APOE* (along with others that remain to be identified) coalesce in influencing liability to overt expression of LOAD. It remains unclear whether their effects are independent or additive or interactive. Finally, it has to be determined whether these genes are unique to cognitive impairment in LOAD or are shared by other diseases, such as Dementia with Lewy Bodies, Parkinson's disease, or depression. Lewy body inclusions and Lewy neurites, the key pathological hallmarks of dementia with Lewy Bodies and Parkinson's disease, are a frequent coexistent pathological change observed in autopsy-confirmed LOAD.

The issues posed above raise considerable challenges for investigators attempting to unravel the genetic complexity of LOAD. Only when these issues are better understood, development of preventive and treatment strategies based on genetic risk factors, including *SORL1* and *APOE*, can be considered. Nevertheless, we have entered a new era in which conjoint advances in functional genomics and genetic epidemiological techniques are enabling rapid progress with multiple gene discoveries. The major advantage of genetic studies is the ability to overcome limitations of classic epidemiological techniques through "Mendelian randomization."¹¹⁶ While in conventional observational studies establishing causal relationships between environmental exposures and common diseases is beset with unresolved confounding, reverse causation and selection bias that can result in spurious inferences, the laws of Mendelian genetics ensure that in a correctly designed genetic association study comparison of groups of individuals defined by genotype is equivalent to a randomized comparison. By definition, these groups will not differ systematically, except with respect to allelic associations (linkage disequilibrium) that extend through a short genomic region from the locus under study, as the inheritance of genetic variants is independent of the inheritance of other traits (i.e., "randomized").

If correctly conducted and carefully interpreted, the merge of modern functional genomics with large-scale studies of genetically at-risk samples and sophisticated statistical algorithms can be a powerful tool for identification of genes, and therefore biomarkers, associated with common complex diseases, such as LOAD.

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Figure 1. Pooled odds ratios (95% CI) of the 40 studies included in the meta-analysis by Farrer *et al.*⁴⁰ relating APOE genotype with LOAD ($\epsilon 4$ allele versus $\epsilon 3$ allele). †No data provided; ‡Hardy-Weinberg-Equilibrium (HWE) deviation in controls ($P \leq 0.05$). (In color in *Annals* online.)

Figure 2.

Protein sorting as a key mechanism in Alzheimer's cell biology. **(A)** A β (red bar) is liberated from its parent protein, APP (multicolor bar), in two enzymatic steps. In the first β -cleavage step, BACE (blue bar) splits full-length APP into an sAPP β fragment (brown bar) and a C-terminal fragment (CTF β , red/green bar). Then, in the γ -cleavage step, the γ -secretase (star) splits CTF β into A β (red bar) and amyloid intracellular domain (AICD, green bar). β -cleavage is the committed step in APP processing and may be upregulated in LOAD. **(B)** Both APP (red bar) and BACE (blue bar) are type-I transmembrane proteins that are sorted through multiple membranous compartments of the cell. The sorting triangle that interconnects the trans-Golgi network (TGN), cell surface, and the endosome is critically important for APP and BACE sorting. As indicated, clathrin is the coat complex that regulates transport from the cell surface and the TGN to the endosome, whereas the retromer is the coat complex that regulates transport from the endosome back to the TGN. APP and BACE interact within the membranes of the endosomal system, initiating the amyloidogenic pathway. (Illustration adapted from Small and Gandy.⁷⁵) (In color in *Annals* online.)

Figure 3.

Role of SORL1 in transmembrane sorting of APP. The green arrows track re-entry of APP from the cell surface when SORL1 is present. The red arrows show that, when SORL1 is absent, more APP moves into domains, such as the late endosome/lysosome, where the black arrows show how it is subsequently cut by beta-secretase (BACE1) and gamma-secretase (PS1 γ -sec), generating the neurotoxic amyloid beta-peptide (A β). (Illustration adapted from Rogaeva *et al.*⁷⁷) (In color in *Annals* online.)

TABLE 1

Summary of Studies Relating APOE Genotype with LOAD Endophenotypes

Author	Subjects	Age in years, mean (range)	Endophenotype	Finding
AGE AT ONSET				
Lehtovirta <i>et al.</i> , 117 1995	202 Finnish LOAD patients and 55 age- and sex-matched controls	Disease onset: $\epsilon 4$: $-/-$ 76 $\pm$ 10, $-/+$: 77 $\pm$ 8, $+/+$: 71 $\pm$ 7	Age at onset	Age at onset decreased from 76 to 69 as the number of $\epsilon 4$ alleles increased from 0 to 2
Gomez-Isla <i>et al.</i> , 16 1996	359 patients LOAD, age- and sex-matched 129 controls	LOAD group: mean age of 77.8 years; control group: mean age of 77.8 years	Age at onset	Age of onset declined significantly as number of $\epsilon 4$ alleles increased ($P < 0.0001$) for linear contrast $\epsilon 3/\epsilon 3$ to $\epsilon 3\epsilon 4$ to $\epsilon 4/\epsilon 4$
Holmes <i>et al.</i> , 17 1996	164 patients	60 years and older	Age at onset	Trend for decreasing age at onset of 3–4 years in carriers of the APOE $\epsilon 4$ –allele (mean age [SD]: no $\epsilon 4$ – versus $\epsilon 4$: 78.7 [7.9] versus 75.5 [5.9], $P = 0.004$)
Murman <i>et al.</i> , 20 1996	107 normal, elderly control subjects and 123 LOAD patients	45 years and older	Age at onset	Increased APOE $\epsilon 4$ frequencies associated with onset ages of 55 and 75 years, but not at the extremes of onset ages (i.e., onset between 45 and 54 years of age and after age 75)
Breitner <i>et al.</i> , 14 1999	5677 elderly residents of Cache County, Utah	65 years and older	Prevalence and Age at onset	Age-specific prevalence of LOAD reached in APOE $\epsilon 4$ heterozygotes the maximum at age 87, in homozygotes at age 73 and in noncarriers at age 95
Tang <i>et al.</i> , 23 1996	305 LOAD patients, 485 nondemented controls	LOAD cases: 76.4 $\pm$ 9.1 years, controls: 72.9 $\pm$ 6.7 years	Relative risk of LOAD, Age at onset	Relative risk (RR) for LOAD associated with APOE $\epsilon 4$ homozygosity increased in all ethnic groups (African-American RR = 3.0; 95% confidence interval [CI] = 1.5–5.9; Caucasian RR = 7.3, 95% CI = 2.5–21.6; and Hispanic RR = 2.5, 95% CI = 1.1–5.7), compared with those with APOE- $\epsilon 3/\epsilon 3$ genotypes. The risk was also increased for APOE- $\epsilon 4$ heterozygous Caucasians (RR = 2.9, 95% CI = 1.7–5.1) and Hispanics (RR = 1.6, 95% CI = 1.1–2.3), but not for African-Americans (RR = 0.6, 95% CI = 0.4–0.9). The age distribution of the proportion of Caucasians and Hispanics without LOAD was consistently lower for $\epsilon 4$ homozygous and heterozygous individuals than for those with other APOE genotypes
Kurz <i>et al.</i> , 19 1996	91 patients, 69 healthy age-matched controls	44–95 years	Age at onset	Inheritance of at least one $\epsilon 4$ allele associated with significant reduction of age at onset by 7.7 years among patients 83 years or older, and a weaker relationship among patients aged 44–63 years
Poirier <i>et al.</i> , 21 1993	91 patients with LOAD and 74 controls	Mean age (SD): 75.1 (10.3)	Prevalence of LOAD, Age at onset	Significant association between $\epsilon 4$ and sporadic LOAD ($\epsilon 4$ frequency 0.380 in LOAD and 0.122 in controls, $P < 0.01$). Age at onset in $\epsilon 4$ carriers earlier than in $\epsilon 2$ or $\epsilon 4$ carriers
Mak <i>et al.</i> , 47 1996	65 LOAD patients and 82 controls	Mean age of 76.5 years	Age at onset	Tendency toward lower age at onset in subjects with 1 or 2 copies of $\epsilon 4$ (mean age of onset [SD] $-/-$ versus $+/+$: 73.3 [8.5] versus 72.0 [6.4] versus 71.2 [5.0]), and higher in subjects with $\epsilon 2/\epsilon 2$ or $\epsilon 2/\epsilon 3$ than in subjects with $\epsilon 3/\epsilon 3$ but differences not statistically significant ($P = 0.078$, $Z = 1.419$)
do Couto <i>et al.</i> , 49 1998	68 patients with LOAD	Mean age (SD): 68.8 (7.9)	Age at onset	Age at onset significantly higher in patients bearing the APOE $\epsilon 4$ allele ($\epsilon 3/\epsilon 4$ and $\epsilon 4/\epsilon 4$, 65.7 [7.1], $n = 40$) compared with patients without $\epsilon 4$ allele ($\epsilon 3/\epsilon 3$, 61.6 [7.6], $n = 28$, $P < 0.05$)

Author	Subjects	Age in years, mean (range)	Endophenotype	Finding
Dal Forno <i>et al.</i> , ⁵⁰ 1996	101 LOAD subjects	Mean age: 69.6 years	Age at onset	Age at onset highest for $\epsilon 4$ heterozygous subjects and least for $\epsilon 4$ negative subjects. Heterozygous subjects declined more rapidly on MMSE and the Category Fluency Test than subjects without $\epsilon 4$ or $\epsilon 4$ homozygosity
COGNITIVE PERFORMANCE				
Welsh-Bohmer <i>et al.</i> , ⁵¹ 2008	507 participants of the Cache County Study of Memory in Aging (CCMS)	70–110 years	Cognitive performance	No association
Salo <i>et al.</i> , ⁵² 2001	46 nondemented persons	>85 years	Memory performance	No association
Murphy <i>et al.</i> , ⁵³ 1997	86 subjects with LOAD	Mean age of onset (SD): based on caregiver report: 65.3 (7.4); based on age when MMSE < 23: 68.8 (7.0)	Rate of decline on MMSE	No association
Cosentino <i>et al.</i> , ⁵⁴ 2008	One incident ($n = 199$) and 2 prevalent samples ($n = 215$, $n = 156$) of LOAD patients	Age 65 years and older	Memory performance	Presence of an APOE $\epsilon 4$ allele associated with a more rapid decline in memory performance over a 7-year follow-up period
Wehling <i>et al.</i> , ⁴⁶ 2007	70 LOAD patients	50–75 years	Cognitive performance	APOE $\epsilon 4$ carriers had slightly poorer performance than noncarriers on the MMSE (27.5 versus 28.4, $P = 0.03$) and learning trials of the California Verbal Learning Test (CVLT) ($F [1,68] = 5.46$, $P = 0.022$)
Hirono <i>et al.</i> , ⁵⁵ 2003	64 LOAD patients	60 years or older	Memory performance	Presence of the APOE $\epsilon 4$ allele in dose-response fashion associated with accelerated memory decline on Word Recall subtest of ADAS-Cog (mean score $-/-$ versus $4/-$ versus $4/4$: -0.2 versus 0.4 versus 1.0 , $P = 0.008$)
Mayeux <i>et al.</i> , ⁵⁶ 2001	563 healthy elderly without LOAD or questionable dementia	65 years and older	Memory performance over 7-year follow-up	APOE $\epsilon 4$ allele associated with a more rapid decline in memory performance
Wilson <i>et al.</i> , ⁵⁷ 2002	669 participants from the Religious Order Study	65 years and older	Summary measures of episodic memory, semantic memory, working memory, perceptual speed, and visuospatial ability	Average annual increase of 0.016 units in the $\epsilon 2$ subgroup and annual decreases of 0.022 units in those with $\epsilon 3/3$ and of 0.073 units in the $\epsilon 4$ subgroup
Lehmann <i>et al.</i> , ⁵⁸ 2006	2181 elderly of the Hordaland Health Study	70–74 years	Episodic memory	APOE $\epsilon 4$ effect on episodic memory: OR of cognitive impairment in women 1.8 (95% CI: 1.1–2.8) for heterozygotes and 1.1 (0.3–3.7) for homozygotes; OR in men 1.1 (95% CI 0.6–2.1) for heterozygotes and 10.7 (95% CI 4.7–24) for homozygotes
Liu <i>et al.</i> , ⁴⁴ 2008	2208 related individuals	50 years and older	Cognitive performance	APOE $\epsilon 4$ significantly associated with reduced test scores for Adult Verbal Learning Test, particularly on the memory and learning subdomains
Bondi <i>et al.</i> , ⁵⁹ 1995	52 elderly nondemented	59–83 years	Performance on California Verbal Learning Test (CVLT)	APOE $\epsilon 4$ associated with poorer performance on CVLT: Six of the 14 APOE $\epsilon 4$ subjects developed either LOAD or questionable LOAD, whereas none of the 26 non-APOE $\epsilon 4$ subjects demonstrated any cognitive decline

Author	Subjects	Age in years, mean (range)	Endophenotype	Finding
Dik <i>et al.</i> , ⁶⁰ 2001	1168 subjects from the population-based Longitudinal Aging Study Amsterdam	62–85 years	Performance on MMSE, immediate recall and delayed recall, and the Alphabet Coding Task-15	APOEε4 carriers had a greater rate of cognitive decline shown by MMSE scores and slower information processing speeds after 6 years. The effects of both memory complaints and APOEε4 allele carriage were additive: subjects with both factors had a two times higher cognitive decline than did subjects without both factors
Hsiung <i>et al.</i> , ⁶¹ 2004	1469 cases with cognitive impairment, 582 controls	Control group: mean age 75.6, group with CIND: mean age 77.8, group with AD: mean age 82.7	Progression from normal cognition to CIND and from CIND to AD or vascular dementia, age at onset of LOAD	Possession of an APOEε4 allele associated with increased risk of LOAD developing from CIND (OR 2.6, 95% CI 1.48–4.92), and associated with decrease in the age at onset of LOAD
Petersen <i>et al.</i> , ⁶² 1995	66 patients with MCI from Mayo Clinic	Mean age: 79.8 years	Conversion from MCI to dementia	APOEε4 strong predictor for conversion to dementia
Caselli <i>et al.</i> , ⁴² 1999	100 nondemented individuals	Mean age 56 years	Immediate and delayed recall	Tests sensitive to immediate and delayed recall showed significant negative correlation with age in the APOEε4 homozygote group relative to the noncarrier group
Flory <i>et al.</i> , ⁴³ 2000	220 nondemented non-Hispanic Caucasian men and women	Aged 24–60 (average age = 46)	Verbal learning and memory (e.g., learning a list of words and recalling them 30 min later), visual memory (e.g., reproducing a previously copied figure from memory), and attention span memory	Performance on learning and memory tasks was significantly poorer in adults having any APOEε4 allele, relative to adults with APOEε2 or APOEε3 genotypes ($P < 0.01$)
Reynolds <i>et al.</i> , ⁶³ 2006	478 nondemented twins from the Swedish Adoption/Twin Study of Aging (SATSA)	50 years and older	Memory performance over 13 years	APOEε4 associated with working and recall memory ability levels and working memory rate of change, with ε4 homozygotes exhibiting the worst performance at all ages over 13-year follow-up
Schultz <i>et al.</i> , ⁴⁵ 2008	626 male twins randomly drawn from the Vietnam Era Twin (VET) Registry	In their 50s	Memory performance	ε4-carriers: lower performance on immediate and delayed recall than noncarriers (mean [SD] comparing ε4+ versus ε4−: immediate recall 22.19 [5.37] versus 23.8 [6.2]; delayed recall: 19.5 [5.9] versus 20.12 [6.6])

TABLE 2

Summary of Studies Relating SORL1 with LOAD

Author (Year)	Age	Haplotype 1				Haplotype 2			
		rs668387 SNP 8 / 2	rs689021 SNP 9	rs641120 SNP 10	rs3824968 SNP 23	rs2282649 SNP 24	rs1010159 SNP 25	Other Significant SNPs	
Significant Association									
Rogaeva <i>et al.</i> (2007)	Mean AAO: 70 ± 9 – 77 ± 8								
Caucasians (family data set)					T	T	C		
Caribbean Hispanics		C	G	C					
Caucasians (case-control data sets)		C	G	C	T	T	C		
Israeli Arabs		C	G	C					
African-Americans									
Lee <i>et al.</i> (2007) - Northern Manhattan	Mean AAO: 79.1 ± 5.1 – 84.4 ± 8.0								
Caucasians		C	A	T	T	T	C	rs3824966 (SNP 20)	
Hispanics								rs12285364 (SNP 12)	
African-Americans		C	G	T		C	C	rs12285364, rs1784933 (SNP 26)	
Meng <i>et al.</i> (2007) ²	Not released								
Caucasians					+	+	+		
Lee <i>et al.</i> (2007) - Autopsy	Mean AAO: cases: 80.5, controls: 79.9								
Caucasians		C	G	C	A	T	C		
Tan <i>et al.</i> (2007)	Mean AAO: 71.2 ± 8.9								
Han Chinese									
Seshadri <i>et al.</i> (2007) ³	Mean age: 62 +9				A	T			
Caucasians						+		rs1131497 (SNP29)	
Bettens <i>et al.</i> (2008)	Mean AAO: 79.0 ± 5.2								
Caucasians		C	G	C				rs560573 (SNP 6), rs1614735 (SNP 27)	

Author (Year)	Age	Haplotype 1				Haplotype 2			
		rs689021 SNP 9	rs641120 SNP 10	rs3824968 SNP 23	rs2282649 SNP 24	rs1010159 SNP 25	Other Significant SNPs		
rs668387									
SNP 8 ^{1,2}									
Lee <i>et al.</i> (2008), re-analyzing data by Shibata <i>et al.</i> (2008)									
Japanese									
C									
T									
Weak Association									
Webster <i>et al.</i> (2008) ²	Age ≥ 65 years								
Caucasians		+	+						
Grupe <i>et al.</i> (2007) ²	Mean age: 77.4 ± 7.5 (WU), 76.4 ± 6.1 (UK1), 76.5 ± 5.6 (UK2)								
Caucasians									rs2070045 (SNP 19)
No Association									
Li H (2008) ⁴	Mean AAO ≥60								
Caucasians									

¹ SNP numbers from Rogaeva *et al.* (2007) are presented. Alleles are presented only when significant alleles in bold were statistically significant in either allelic, genotypic, or haplotypic analysis.

² Used the nearest SNPs (indicated with a “+” sign) when different SNPs were used.

³ Endophenotype was studied.

⁴ No specific marker information for *SORL1* was available from the paper. AAO = age of onset.