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Use of Genetic Variation as Biomarkers for Mild Cognitive Impairment and Progression of Mild Cognitive Impairment to Dementia

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Abstract

Cognitive impairment is highly frequent in the elderly. The high estimates of conversion to dementia have spurred the interest in identification of genetic risk factors associated with development of cognitive impairment and or its progression. However, despite notable achievements in human genetics over 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 late-life cognitive impairment can be explained. A likely explanation for the difficulty in gene identification is that it is a multifactorial disorder with both genetic and environmental components, in which several genes with small effects each are likely to contribute to the quantitative traits associated with the disease.

The motivation for identifying the underlying genetic risk factors elderly is clear. Not only could it shed light on disease pathogenesis, but it may also provide potential targets for effective treatment, screening, and prevention. In this article we review the current knowledge on underlying genetic variants and the usefulness of genetic variation as diagnostic tools and biomarkers. In addition, we discuss the potentials and difficulties researchers face in designing appropriate studies for gene discovery.

INTRODUCTION

Late-onset Alzheimer's disease (LOAD) is among the most common diseases in aging societies. It is estimated that approximately five 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 about 1% among people aged 65–70 years to

approximately 6–8% 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 (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) Work Group.[4] Although these criteria have good reliability[5–7] and validity, [8,9] any measure that would allow detection at an early stage and would increase diagnostic sensitivity and specificity, would help improve early therapeutic intervention.

Mild cognitive impairment (MCI) is a clinical diagnostic entity that may represent this early stage. It refers to individuals who have cognitive deficits but who do not fulfill a diagnosis of dementia.[10–12] Studies using the criteria by Petersen et al. for diagnosing MCI in clinical and epidemiological settings, [11,13] report an incidence rate of 9.9/1,000 person-years for MCI among nondemented elderly, [14] and an annual conversion rate of 10% to 12% to AD in subjects with MCI, particularly amnesic MCI, in contrast to a conversion rate of 1% to 2% in the normal elderly population.[11] The high estimates of conversion rate of MCI to dementia has spurred the interest in establishing preclinical prognostic markers for MCI and the progression from MCI to dementia.[14,15]

Twin studies suggest that 37% to as much as 78% of the variance in the age-at-onset of cognitive impairment can be attributed to additive genetic effects.[16] As a consequence, genes involved in MCI or LOAD could be highly valuable diagnostic tools. The usefulness of genetic variation as biomarkers for cognitive impairment is further supported by the fact that genetic variation is stable across the life span and the disease process, and is not influenced by confounding factors. Despite available improved analytic techniques, the continued pursuit of genetic variants associated with cognitive impairment 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. Together these reported genes explain only a small proportion of the genetic contribution to cognitive impairment in late-life leaving several genetic risk factors to be identified.

In this article we review the genetic risk factors that have been implicated in MCI, LOAD and progression of MCI to dementia, and review their usefulness as diagnostic tools and biomarkers. In addition, we discuss the difficulties researchers face when performing studies for gene discovery in common complex diseases such as late-life cognitive impairment.

GENETICS OF LOAD AND MILD COGNITIVE IMPAIRMENT

Most of the studies assessing the role of genetic variation in cognitive impairment have used the diagnostic criteria of LOAD or endophenotypes of cognition such as age-at-onset of dementia or cognitive test performance. The motivation for use of endophenotypes is that quantitative traits provide more accurate phenotypes than simply considering affection status as a dichotomized variable, and thus provide more statistical power to detect small polygenic effects. Few studies have used MCI as the phenotype or have assessed the influence of genetic variation on progression of MCI to dementia.

1. Apolipoprotein E (APOE)

APOE, which maps to chromosome 19 in a cluster with Apolipoprotein C1 and Apolipoprotein C2, is a lipid-binding protein and is expressed in humans as three common isoforms coded for by three alleles, *APOE* $\epsilon 2$, $\epsilon 3$, and $\epsilon 4$. Early studies linked the *APOE*

genotype with LOAD and found a significant increase in the frequency of the APOE ϵ 4 allele in patients with the disease compared to healthy controls. The large body of epidemiologic data that subsequently accumulated clarified this effect by demonstrating that APOE ϵ 4 decreases the age-at-onset of LOAD in a gene dosage-dependent manner, [17–26] that APOE ϵ 4 is associated with lower cognitive performance, in particular the memory domain, that it is associated with MCI, the prodromal stage of LOAD, [27–30] and that it is associated with progression from MCI to dementia.[27–37] It is thought that APOE may account for as much as 20–50% of LOAD risk.[38,39]

In vitro studies have indicated that the APOE- ϵ 4 isoform binds A β peptides with a higher avidity compared to APOE- ϵ 3.[40] Furthermore, there is a strong correlation between the presence of an APOE- ϵ 4 allele and a higher A β burden in the brains of AD patients, [41,42] 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, non-fibrillar A β deposits.[43–45] Some but not all studies assessing the effect of different APOE isoforms on A β fibrillization showed that the ϵ 4 isoform leads to increased A β aggregation in vitro.[46,47] Similarly, in vivo studies in APOE $-/-$ mice indicated that A β fibrillization and plaques formation was increased in mice expressing human APOE- ϵ 4 (APPV717F+/-, apo E $-/-$) compared to mice not expressing human APOE.[48,49] 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[50,51] and changes in APP processing.[52,53] Thus, APOE isoform-specific changes in cholesterol binding and transport in brain might also affect plaque formation in AD brains.

LOAD as the phenotype—A large amount of studies assessed the relation between APOE genotypes and LOAD in population-based settings. In a meta analysis[54] 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 LOAD was significantly increased for Caucasians with genotypes ϵ 2/ ϵ 4 (OR=2.6, 95% CI=1.6–4.0), ϵ 3/ ϵ 4 (OR=3.2, 95% CI=2.8–3.8), and ϵ 4/ ϵ 4 (OR=14.9, 95% CI= 10.8–20.6), whereas the ORs were decreased for people with genotypes ϵ 2/ ϵ 2 (OR=0.6, 95% CI=0.2–2.0) and ϵ 2/ ϵ 3 (OR=0.6, 95% CI=0.5–0.8). The association between the APOE- ϵ 4 allele and LOAD was weaker among African Americans and Hispanics, but there was significant heterogeneity in ORs among studies of African Americans ($p<0.03$). In Japanese subjects, the association was stronger than in Caucasian subjects (ϵ 3/ ϵ 4: OR=5.6, 95% CI=3.9–8.0; ϵ 4/ ϵ 4: OR=33.1, 95% CI=13.6–80.5). The ϵ 2/ ϵ 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 ϵ 4 allele is associated with a 2-3-fold increased risk, while having two copies is associated with a 5-10-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- ϵ 4 allele (table 1).[17–26] Taken together, these studies which include both clinical and epidemiological studies, suggest that APOE ϵ 4 may decrease the age-at-onset by as much as 7 to 9 years per allele. They further suggest that this effect is present across the life span including children and adolescents[22,23,55–60] and across various ethnic groups although it may be stronger in Caucasians and Hispanics than African Americans.[26] Mak et al., [61] 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 ϵ 4 compared to persons without ϵ 4 allele (mean age-of-onset (SD) no ϵ 4 vs. one ϵ 4, one ϵ 4 vs. two ϵ 4s: 73.3 (8.5) vs. 72.0 (6.4) vs. 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.[62]

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.[63] 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[64] 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), [65] a study among 46 nondemented persons aged 85 years or over from a randomly selected group of 128 subjects in Vantaa, Finland, [66] and the study by Murphy et al., [67] 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, [67] small sample sizes[66,67] or consisted of samples prone to survival bias[65] 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 non-demented 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.[68] 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., [60] which comprised 70 consecutively referred patients aged 50–75 years, APOE $\epsilon 4$ carriers showed a slightly poorer performance than non-carriers on the MMSE (27.5 vs. 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., [69] 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 $-/-$ vs. $4/-$ vs $4/4$: -0.2 vs. 0.4 vs 1.0 , $p=0.008$).

Studies excluding subjects with cognitive impairment or dementia—Most studies exploring these associations among non-demented 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.[70] presence of an APOE ϵ 4 allele was in 563 non-demented 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, [71] possession of one or more ϵ 4 alleles was over a 8-year follow-up associated with faster decline in episodic memory compared to the ϵ 3/3 genotype, while possession of one or more APOE ϵ 2 alleles was associated with reduced decline. The rate 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 2,181 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).[72] In a Dutch sample of 2,208 related individuals, the ϵ 4 variant was associated with reduced test scores for the Adult Verbal Learning Test, and within this test strongest for the memory and learning sub domains.[58] Bondi et al.[73] explored the effect of APOE on cognition in 52 non-demented elderly using the California Verbal Learning Test (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 non-carriers demonstrated any cognitive decline.

The longitudinal population-based Longitudinal Aging Study Amsterdam[74] 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 1,168 elderly subjects, APOE ϵ 4 carriers had after a six 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 Aging[34] 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, [28] 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.[34]

In two cross-sectional studies in younger subjects (average ages 46 and 56)[56,57] 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 years[75] 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[59] ϵ 4-carriers showed significantly

lower performance on immediate and delayed recall than non-carriers (mean (SD) comparing $\epsilon 4+$ vs. $\epsilon 4-$: immediate recall 22.19 (5.37) vs. 23.8 (6.2); delayed recall: 19.5 (5.9) vs. 20.12 (6.6)), supporting the genetic contribution of *APOE* to LOAD.

MCI and progression of MCI to dementia as the phenotype—Fewer studies assessed the relation between *APOE* genotypes and MCI or progression of MCI to dementia in population-based settings. The vast majority of these studies observed an increase in MCI risk or progression from MCI to dementia in $\epsilon 4$ -carriers.[27–37] Two studies[27,30] observed increased risks of MCI in $\epsilon 4$ -carriers compared to non-carriers but no association between the *APOE* genotype and progression to dementia. Potential reasons for these negative findings are the limited number of patients included in the studies, the short time of follow-up, the insufficient control of potentially confounding factors and the lack of consensus criteria for MCI leading to considerable heterogeneity. It has been well established that dementia risk varies with the definition of MCI used.

Sensitivity and Specificity of *APOE*—Studies assessing the usefulness of the *APOE* genotype (ie. *APOE* genetic testing) in the diagnosis of Alzheimer’s disease among persons with dementia, reported specificities of the $\epsilon 4$ allele between 81 and 100%[76–79] when used in combination with clinical or autopsy criteria, but lower specificities when used alone.[77] Sensitivity estimates, were lower and ranged between 19–75%.[76,77,79,80] These estimates and the relatively low frequency of the $\epsilon 4$ -allele in persons with AD and the general population limit the utility of *APOE* genetic testing. As described above the $\epsilon 4$ -allele increases the risk of developing AD but is neither necessary nor sufficient, meaning that not all persons with *APOE*E4* alleles will develop Alzheimer’s disease. If considered, genetic testing should only be undertaken after carefully discussing the benefits, ethical issues and risks (ie. potential harm such as anxiety through revealing the test results) with a physician or genetic counselor.

2. Sortilin-related receptor (*SORL1*)

Identification of *APP*, presenilin 1 (*PSEN1*), 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 $A\beta$, the putative culprit of AD. The amyloid pathway involves two enzymatic steps: In the first β -cleavage step, BACE cleaves APP near the N terminus of the $A\beta$ 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 presenilin 1 and 2, nicastrin, APH1, TMP21, and PEN2.[81]

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 $A\beta$ involves a transmembrane secretase enzyme acting on a transmembrane APP CTF 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 $A\beta$ production. Over 30% of all proteins are transmembrane proteins, [82] and most are typically sorted via the secretory and endocytic pathways.[83,84] 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. Important coat complexes initiating the transport of APP and BACE through this sorting itinerary are the clathrin coat and the retromer.[85–87] 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.[88] 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 (Figure 2). *SORL1* belongs to the VPS10 vacuolar protein sorting receptor family, [87] which in turn belongs to a group of protein trafficking molecules that are in the endocytic and retromer pathways, and are highly expressed in the central nervous system.[87] It is clear that the subcellular domains of these trafficking molecules are important sites for the generation of the amyloid β -peptide ($A\beta$), the main putative culprit in the pathogenesis of AD. The sub-cellular domain of *SORL1* interacts with the amyloid precursor protein (APP) and directs its trafficking into recycling pathways. As a consequence, APP is sorted into $A\beta$ -generating compartments when *SORL1* is under-expressed, leading to an increased risk of AD[89–91] Accordingly, knockout of *SORL1* in mice is associated with increased brain $A\beta$ levels.[89] It is also possible that *SORL1* contributes to the risk of AD through the nerve growth factor (NGF)-neurotrophin system. NGF promotes cell survival via binding to the tyrosine kinase receptor A (TrkA). Sortilin receptors bind, as a trimolecular complex, with p75^{NTR} to its precursor (proNGF) initiating apoptosis.[92,93] Whether proNGF can also act neurotrophically following binding to TrkA is still unclear.

Most studies exploring the effect of *SORL1* on cognitive impairment or dementia used LOAD as a dichotomized trait in the analyses. Rogaeva and colleagues[89] first reported the allelic and haplotypic associations between LOAD and variants in *SORL1* (table 2). Subsequently several studies supported the initial finding by showing that genetic variants in *SORL1* contribute toward LOAD.[94–100] 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 6,000 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 datasets 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 amyloid β levels.[89] Two subsequent studies by the same group broadly supported one or both haplotypes or some variations of the two: Haplotype C-G-C at SNPs 8–10, or haplotype T-T-C at SNPs 23–25, or both. Lee and colleagues[96] 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.[95]

Subsequently various other groups examined the relation between *SORL1* and LOAD or LOAD endophenotypes in different populations (table 2).[94,98–105] Four replication studies supported the initial findings, while the remaining showed either negative or weak results. Three clearly positive studies included one by Bettens et al, [94] Tan et al, [99] Seshadri et al, [98] and Koelsch et al.[100] Bettens and colleagues[94] directly replicated SNPs 8 through 10 and showed support for SNPs 25–27 in 550 Belgians with LOAD and 637 unaffected individuals. Tan et al. 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 to SNP 10 were associated. In the study by Koelsch et al. which included 349 AD patients and 483 controls recruited from a multicenter study of the German Competence Network Dementias, [100] the SNP21G-allele and a *SORL1* haplotype consisting of the SNP19 T-allele, SNP21 G-

allele and SNP23 A-allele (T/G/A) were associated with an increased risk of LOAD and an earlier age at onset (SNP21: $p=0.002$; T/G/A haplotype: $p=0.007$). This effect was most pronounced in carriers of an additional APOE4 allele (SNP21: $p=0.003$; T/G/A haplotype: $p=0.005$). Webster et al.[103] and Li. et al.[102] reported weak associations.

Li et al, [101] Houlihan et al, [104] Minster et al, [105] and Shibata et al.[106] 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.[107] 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*.

Cognitive performance as the phenotype—Using the Framingham community based family samples, Seshadri et al.[98] 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.

MCI and progression of MCI to dementia as the phenotype—No study specifically explored the association between variation in *SORL1* and MCI, or *SORL1* and progression from MCI to dementia. However, in a study by Sager et al.[108] who explored the association between *SORL1* expression in brain tissue and MCI in participants from the Religious Order Study, *SORL1* expression was heterogeneous, forming low- and high-level *SORL1* subgroups. MCI subjects with low *SORL1* were significantly more cognitively impaired than the high *SORL1* subjects, suggesting that that reduced *SORL1* levels reflect disease severity and may predict progression to AD in a subgroup of individuals with MCI.

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 there are several different LOAD-associated allelic variants in distinct regions of the *SORL1* gene in different populations, that these variants are likely to be in intronic regulatory sequences that might govern cell type-specific or tissue-specific expression of *SORL1*, and that these variants affect this risk by altering the physiological role of *SORL1* in the processing of APP holoprotein.

3. Other genes

In addition to *APOE* and *SORL1*, several genes and putative loci have been reported, but independent replication remains inconsistent. There is little concordance between case-control and family-based studies[109–113] suggesting that both clinical and genetic heterogeneity influence the outcome of these analyses. The P86L polymorphism in the calcium homeostasis modulator 1 (*CALHM1*), which encodes an essential component of a previously uncharacterized cerebral Ca^{2+} channel that may control $A\beta$ levels, has been putatively associated with LOAD.[114] The GRB2-associated binding protein 2 (*GAB2*) may modify the risk of LOAD in APOE ϵ 4 carriers and has been associated with hyperphosphorylation of tau protein.[115] The butyrylcholinesterase K variant (*BCHE* K) allele has been shown to act in synergy with the APOE ϵ 4 allele to promote risk for AD. [116] *BCHE* blocks aggregation of $A\beta$ less aggressive long fibrils[117] and possession of the K variant allele is known to result in a 30% reduction in serum cholinesterase activity.

[117] The low density lipoprotein receptor-related protein 6 (*LRP6*), a coreceptor for Wnt signaling, has been associated with LOAD and confirmed in a case-control analysis.[118] Additional loci that have been reported but remain to be confirmed include the toll-like receptor 4 (*TLR4*), the cholinergic receptor (nicotinic beta 2, *CHRNA2*), alpha-2-macroglobulin (*A2M*), catenin (*CTNNA3*), glutathione S-transferase omega 1 and 2 (*GSTO1*, *GSTO2*) and the glyceraldehyde-3-phosphate dehydrogenase (*GAPD*)[119–122] and loci at 6p, 9q, 10q and 12p and 19q.[123–133]

Genes that have been reported to be associated with MCI or risk of progression from MCI to dementia include alpha1-antichymotripsin (*ACT*), [134] cholinergic receptor (nicotinic alpha 7, *CHRNA7*)[135], peptidylprolyl cis-trans isomerase (*PIN-1*)[27], transforming growth factor-beta 1 (*TGF-beta*), [136] vascular endothelial growth factor (*VEGF*), [137] a member of the cytochrome P450 superfamily (*Cyp46A1*)[138], and nitric oxide synthase 3 (*NOS3*) [139]. In particular genes mapping to chromosome 10q_{21–25}, have been reported to influence amyloid β levels in cognitive impairment. In a study by Ertekin-Taner et al., [140] amyloid β_{42} levels were related to a missense C/T polymorphism in exon 6 of the in the urokinas18 and 19 of the revised manuscript.e-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 amyloid β_{42} levels.[141] The latter finding is consistent with a study by Farris et al. [142] demonstrating that partial loss-of-function mutations in *IDE*, that induce diabetes, also impair degradation of amyloid β protein. *PLAU* [140] and *IDE*[141] were also associated with an increased risk of LOAD and cognitive impairment, supporting the usefulness of amyloid β levels as an endophenotype in cognitive impairment.

DISCUSSION

One of the most important challenges in research on cognitive impairment in the elderly is to identify genes that predispose to MCI and could be used to predict which subjects will progress to dementia. Individuals genetically predisposed to evolve to dementia could benefit of therapeutic intervention in the early stages of the disease in which the neurodegeneration has not progressed. Early intervention could significantly prevent or delay the onset, which in turn would improve quality of life of the patient and their relatives and would significantly reduce the public health burden.

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, several issues in research on late-onset cognitive impairment lead to significant difficulties in gene identification. First, current knowledge suggests that a variety of mechanisms underlie the various pathological and clinical changes, and that these have different genetic and environmental components. Thus, it is likely that late-onset cognitive impairment is a complex genetic disorder characterized by an interaction of multiple genes and the environment leading to genotypes with incomplete penetrance and a low magnitude associated risk. Consistent with this notion is the fact that to date only two genes (*APOE* and *SORL1*)with modest effect sizes each have been firmly identified as genetic risk factors although segregation analyses conducted in families of patients with LOAD support the presence of at least 4 to 6 major genes.[143,144] With a population attributable risk that is estimated at 20–50%, [38,39] the *APOE* ϵ 4 allele increases risk of cognitive impairment, LOAD, and age-of onset of cognitive impairment in a dose-dependent fashion: one ϵ 4 allele is associated with a 2–3 fold increased risk, having two copies is associated with a 5–10 fold increase. Similar effect sizes have been observed for progression of cognitive impairment to dementia. The two haplotypes in the 3' and 5' regions of *SORL1* that repeatedly were found to be associated with LOAD have effect sizes ranging from odds ratios of 1.4 to 2.2; their

associations with MCI and progression to dementia remain yet to be determined. The facts that both *APOE* and *SORL1* have only moderate diagnostic sensitivity and specificity, increase risk of cognitive impairment in a non-Mendelian fashion, are not fully penetrant, and that they are neither necessary nor sufficient by themselves to cause impairment further support the notion of a complex genetic mechanism. The same is likely to be true for the remaining, yet to be identified, genetic factors associated with cognitive decline. Additional genes and genetic loci that have been reported but remain to be confirmed include *TLR4*, *CHRNA2*, *A2M*, *CTNNA3*, *GSTO1*, *GSTO2*, *GAPD*, *ACT*, [134] *CHRNA7*, *PIN-1*, *TGF-beta*, *VEGF*, *Cyp46A1*, and *NOS3*, *PLAU*, *IDE* and loci at 6p, 9q, 10q and 12p and 19q.

Additional factors hampering genetic research on late-life cognitive impairment are pleiotropic effects, locus or allelic heterogeneity, small sample sizes leading to insufficient power to detect the expected small-moderate effect sizes, uncontrolled population stratification, and the failure to develop better quantitative endophenotypes. Endophenotypes are closer to the action of the gene than affection status, exhibit higher genetic signal-to-noise ratios, [145] and thus provide greater power to localize and identify the various disease-related quantitative trait loci (QTLs) associated with the disease such as memory performance, amyloid/tau pathology or hippocampal atrophy than does affection status alone.[146] It is possible that the endophenotypes that are commonly used in research on late-life cognitive impairment are too heterogeneous to be informative.

Four additional phenomena particularly complicating genetic research on rate of progression are the beginning of the observations in the middle of a developing pathologic process, survival bias, uncertainty in the timing of disease diagnosis, and nonlinear disease progression trajectories. MCI presumably is diagnosed in the middle of an ongoing, accumulating, pathologic process, which introduces problems if unmeasured factors influence both MCI onset and rate of disease progression. For example, among newly diagnosed MCI cases, *APOE* ϵ 4 status may be associated with unmeasured causes of MCI, even though it is independent from these causes in the population. As a consequence, in a study in which the sample is selected conditional on MCI diagnosis, the unmeasured factors will confound analyses of the association of disease progression and *APOE* ϵ 4 status ("selection bias"). Survival bias is often induced by selecting primarily elderly participants, as persons who did not die but survived into the study are more likely to have a lower frequency of risk factors associated with cognitive decline. Uncertainty in the timing of disease diagnosis is caused by the fact that cognitive functioning in patients with incipient MCI frequently fluctuates, for example due to intermittent periods of depression or medication changes. Thus, the threshold for MCI diagnosis is not clearly demarcated, and as a result, individuals may be prematurely diagnosed with MCI during brief periods of impaired functioning that subsequently remit, or may remain undiagnosed because they were assessed on a particularly lucid day. The consequence of premature diagnosis in turn would be that the apparent decline trajectory post diagnosis appears flatter than the true decline trajectory and that the time to dementia appears longer. In contrast, the consequence of delayed diagnosis would be that the apparent decline trajectory post diagnosis appears steeper than the true decline trajectory and that the time to dementia appears shorter. Nonlinear progression of cognitive impairment can occur if compensatory or resilience processes buffer functional consequences of neurologic damage in early disease. Neurologic damage may accumulate until the brain loses resilience to further damage and decline. The decline trajectory will be relatively flat in early stages and then suddenly collapse. Alternatively, the trajectory may flatten at the end stages of disease, when there is little function remaining to lose. When the decline trajectory is nonlinear, variables associated with where in the trajectory an individual is first observed will tend to predict subsequent rate of change. Modeling transition to dementia as a function of prior cognition without attempting to measure rate of decline directly can help circumvent this problem.

Although -due to the low specificity and sensitivity- *SORL1* and *APOE* are probably not suitable as diagnostic markers, they 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 risk of cognitive impairment. 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 cognitive impairment and dementia 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 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. Finally, it has to be determined whether *SORL1* and *APOE* 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 pathologic change observed in autopsy-confirmed LOAD.

The issues posed above raise considerable challenges for investigators aiming to clarify the genetic complexity of cognitive impairment. 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, the major advantage of genetic studies is the ability to overcome limitations of classic epidemiological techniques, in particular residual confounding and reverse causation. Among the various genetic epidemiologic approaches, candidate gene studies with subsequent confirmation in independent datasets and functional analyses, is probably the method with the highest statistical power. 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 cognitive impairment.

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SUMMARY Odds ratios (OR)

All Studies

All Excluding HWE Deviations

All Caucasian Studies

STUDY-SPECIFIC Odds ratios:

- Fallin (1997)
- ‡ Kukull (1996)
- Benjamin (1996)
- Benjamin (1996)
- Maestre-USA (1995)
- Maestre-USA (1995)
- Maestre-USA (1995)
- Hendrie (1995)
- Lehtimaki (1995)
- Lehtovirta (1995)
- Martins (1995)
- Gearing (1995)
- St. Clair (1995)
- Tsai (1994)
- Kuusisto (1994)
- † Okuizumi (1994)
- Chartier-Harlin France (1994)
- Chartier-Harlin England (1994)
- Nalbantoglu (1994)
- Harrington (1994)
- Kawamata (1994)
- Frisoni (1994)
- Yoshizawa (1994)
- Galasko (1994)
- Corder (1994)
- ‡ Smith (1994)
- Talbot (1994)
- Betard (1994)
- Sorbi (1994)
- Pickering-Brown (1994)
- ‡ Lucotte (1994)
- Zubenko (1994)
- Van Duijn (1994)
- Rebeck (1993)
- Ueki (1993)
- Noguchi (1993)
- Poirier (1993)

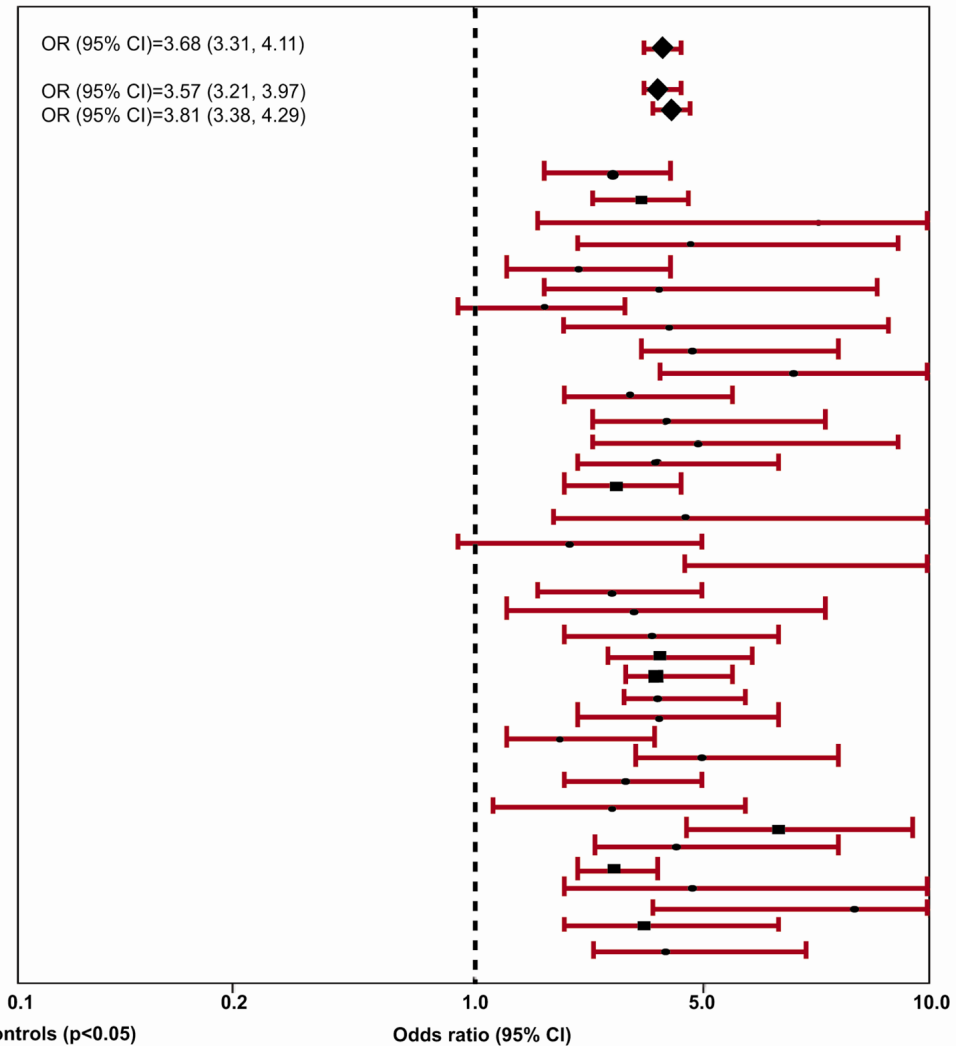


Figure 1. Pooled odds ratios (95% CI) of the 40 studies included in the meta-analysis by Farrer et al. [54] relating APOE genotype with LOAD ($\epsilon 4$ allele vs. $\epsilon 3$ allele). †No data provided; ‡HWE deviation in controls ($p \leq 0.05$)

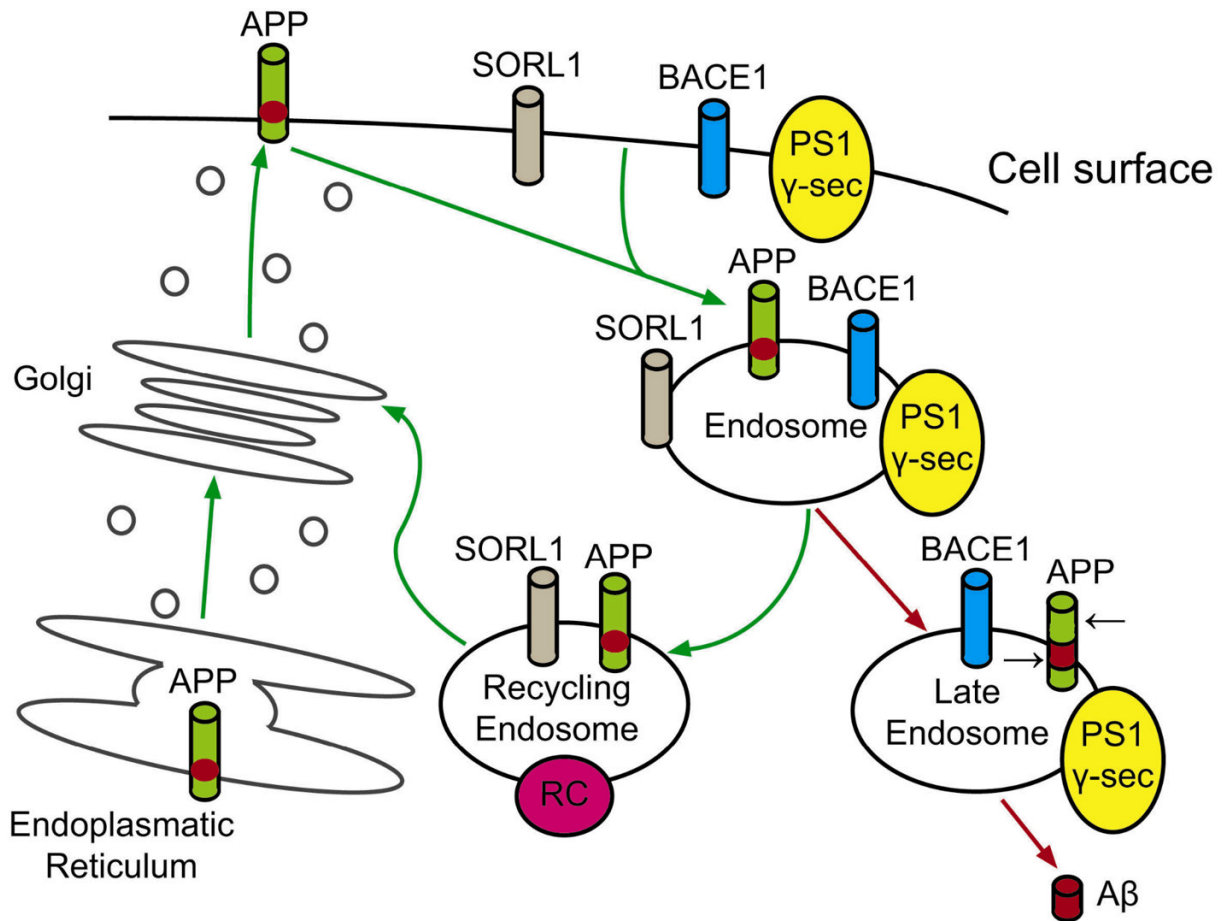


Figure 2.

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.[89]]

Table 1

Summary of studies relating APOE genotype with LOAD, LOAD endophenotypes, MCI and progression from MCI to Dementia

Author	Subjects	Age in years, mean (range)	Endophenotype	Finding
AGE-AT-ONSET				
Lehtovirta et al.[147],1995	202 Finnish LOAD patients and 55 age-and sex-matched controls	Disease onset: $\epsilon 4$: $- / - 76 \pm 10$, $- / +: 77 \pm 8$, $2, + / + 71 \pm 7$	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 et al., [148]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 et al., [20] 1996	164 patients	60 years and older	Age-at-onset	trend for decreasing age-at-onset of 3 to 4 years in carriers of the APOE $\epsilon 4$ allele (mean age (SD): no $\epsilon 4$ - vs $\epsilon 4$: 78.7 (7.9) vs. 75.5 (5.9), $p=0.004$)
Murman et al., [23] 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 et al., [17] 1999	5,677 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 non-carriers at age 95
Tang et al., [26] 1996	305 LOAD patients, 485 nondemented controls	LOAD cases: 76.4 ± 9.1 years, controls: 72.9 ± 6.7 years	Relative risk of LOAD, Age-at-onset	RR for LOAD associated with APOE $\epsilon 4$ homozygosity increased in all ethnic groups (African American relative risk [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

Author	Subjects	Age in years, mean (range)	Endophenotype	Finding
				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 et al., [22] 1996	91 patients, 69 healthy age-matched controls	44 to 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 year
Poirier et al., [24] 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 et al., [61] 1996	65 LOAD patients and 82 controls	mean age of 76.5 years	Age-at-onset	Tendency towards lower age-at-onset in subjects with one or two copies of epsilon 4 (mean age-of-onset (SD) -/- vs. 4/- vs. 4/4: 73.3 (8.5) vs. 72.0 (6.4) vs. 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 et al.[63], 1998	68 patients with LOAD	mean age (SD):68.8 (7.9)	Age-at-onset	Age-at-onset significantly higher in patients bearing

Author	Subjects	Age in years, mean (range)	Endophenotype	Finding
				the APOE ϵ 4 allele (ϵ 3/ ϵ 4 and ϵ 4/ ϵ 4, 65.7 (7.1), n=40) compared with patients without ϵ 4 allele (ϵ 3/ ϵ 3, 61.6 (7.6), n=28, p<0.05)
Dal Forno et al., [64]1996	101 LOAD subjects	mean age: 69.6 years	Age-at-onset	Age-at-onset highest for ϵ 4 heterozygous subjects and least for ϵ 4 negative subjects. Heterozygous subjects declined more rapidly on MMSE and the Category Fluency Test than subjects without ϵ 4 or ϵ 4 homozygosity
COGNITIVE PERFORMANCE				
Welsh-Bomer et l., [65] 2008	507 participants of the Cache County Study of Memory in Aging (CCMS)	70–110 years	Cognitive performance	No association
Salo et al., [66] 2001	46 nondemented persons	>85 years	Memory performance	No association
Murphy et al., [67] 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 et al., [68] 2008	one incident (n=199) and two prevalent samples (n=215, n=156) of LOAD patients	age 65 years and older	Memory performance	presence of an APOE ϵ 4 allele associated with a more rapid decline in memory performance over a 7-year follow-up period
Wehling et al., [60] 2007	70 LOAD patients	50–75 years	Cognitive performance	APOE ϵ 4 carriers had slightly poorer performance than non-carriers on the MMSE (27.5 vs. 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., [69] 2003	64 LOAD patients	60 years or older	Memory performance	presence of the APOE ϵ 4 allele in dose-response fashion associated with accelerated memory decline on Word Recall subtest of ADAS-Cog (mean score -/ - vs. 4/- vs 4/4: -0.2 vs. 0.4 vs 1.0, p=0.008)

Author	Subjects	Age in years, mean (range)	Endophenotype	Finding
Mayeux et al., [70] 2001	563 healthy elderly without LOAD or questionable dementia	65 years and older	Memory performance over 7-year follow-up	APOE ϵ 4 allele associated with a more rapid decline in memory performance
Wilson et al., [71] 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 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
Lehman et al., [72] 2006	2181 elderly of the Hordaland Health Study	70–74 years	episodic memory	APOE ϵ 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 et al., [58] 2008	2208 related individuals	50 years and older	Cognitive performance	APOE ϵ 4 significantly associated with reduced test scores for Adult Verbal Learning Test, particularly on the memory and learning sub domains
Bondi et al., [73] 1995	52 elderly non-demented	59–83 years	Performance on California Verbal Learning Test (CVLT)	APOE ϵ 4 associated with poorer performance on CVLT. Six of the 14 APOE ϵ 4 subjects developed either LOAD or questionable LOAD, whereas none of the 26 non APOE ϵ 4 subjects demonstrated any cognitive decline
Dik et al., [149] 2000	1,243 subjects with a MMSE score between 21 and 30	62–85 years	Memory decline	APOE ϵ 4 allele associated with memory decline in cognitively impaired subjects (decline on immediate recall: OR:3.8 (1.,10.0); decline on delayed recall; OR:2.9 (1,2.7,0); decline on retention: OR 3.3 (1.1,10. 1), but not in cognitively normal subjects

Author	Subjects	Age in years, mean (range)	Endophenotype	Finding
				(MMSE score, 27 to 30)
Dik et al., [74] 2001	1,168 subjects from the population-based Longitudinal Aging Study Amsterdam	62 to 85 years	Performance on MMSE, immediate recall and delayed recall, and the Alphabet Coding Task-15	APOE ϵ 4 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 APOE ϵ 4 allele carriage were additive: subjects with both factors had a two times higher cognitive decline than did subjects without both factors
Caselli et al., [56] 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 APOE ϵ 4 homozygote group relative to the noncarrier group
Flory et al., [57] 2000	220 non-demented 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 APOE ϵ 4 allele, relative to adults with APOE ϵ 2 or APOE ϵ 3 genotypes ($p < .01$)
Reynolds et al., [75] 2006	478 non-demented twins from the Swedish Adoption/Twin Study of Aging (SATSA)	50 years and older	memory performance over 13 years	APOE ϵ 4 associated with working and recall memory ability levels and working memory rate of change, with ϵ 4 homozygotes exhibiting the worst performance at all ages over 13 year follow up
Schultz et al., [59] 2008	626 male twins randomly drawn from the Vietnam Era Twin (VET) Registry	In their 50s	memory performance	ϵ 4-carriers: lower performance on immediate and delayed recall than non-carriers (mean (SD) comparing ϵ 4+ vs. ϵ 4-: immediate recall 22.19 (5.37) vs. 23.8 (6.2); delayed recall: 19.5 (5.9) vs. 20.12 (6.6))
Small et al., [150] 2000	413 older adults from the Charlotte County Healthy Aging Study	mean age: 72.9	cognitive functioning, including episodic memory, implicit memory,	no association between APOE ϵ 4

Author	Subjects	Age in years, mean (range)	Endophenotype	Finding
			psychomotor speed, and attention	allele and cognitive functioning
Farlow et al., [151] 2004	494 MCI subjects	55–85 years, mean age: 70.8	cognitive functioning	APOE ϵ 4 carriers had lower MMSE ($p = 0.01$), higher ADAS-cog ($p < 0.0001$) scores, greater deficits on cued SRT and ADCS-ADL scale ($p < 0.001$), and smaller hippocampal volumes ($p = 0.002$) than non-carriers
Kleiman et al., [152] 2006	366 AD patients	ϵ 4 non-carriers: 73.4 \pm 9.6, ϵ 4-heterozygotes 74.4 \pm 7.3, ϵ 4 homozygotes: 71.6 \pm 7.0:	Progression of cognitive/functional decline in AD patients	No association between APOE ϵ 4 and cognitive or functional decline
Caselli et al., [153] 2007	43 ϵ 4 homozygotes, 59 ϵ 4 heterozygotes, and 112 noncarriers without cognitive impairment	50–69 years	Progression of cognitive/functional decline	Cognitive domain decline occurred in 4 of 10 APOE ϵ 4 homozygotes 60 years and older at entry (40.0%) compared with 5 of 66 APOE ϵ 4 heterozygotes and noncarriers (7.6%) ($P = .02$)
MCI/PROGRESSION FROM MCI TO DEMENTIA				
Petersen et al., [28] 1995	66 patients with MCI from Mayo Clinic	mean age: 79.8 years	Conversion from MCI to dementia	APOE ϵ 4 strong predictor for conversion to dementia
Tierney et al., 1996[37]	107 patients with memory impairment but no dementia	Patients developing AD:74.4 \pm 7.1, subjects developing MCI: 71.5 \pm 7.8	Conversion from memory impairment to dementia	APOE ϵ 4 allele predicts development of AD in memory-impaired individuals
Jack et al.[35], 1999	80 consecutive patients with MCI	Mean age: 77.7 \pm 6.8	Conversion from MCI to dementia	APOE genotype was reliable prognostic indicator of development of AD
Hsiung et al., [34] 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 VaD, age-at-onset of LOAD	possession of an APOE ϵ 4 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
Devanand et al., [32] 2005	136 patients with MCI and 57 age-and sex-matched healthy controls	mean age 66 years	Conversion from MCI to dementia	APOE ϵ 4 carrier status associated with conversion to AD in older patients after

Author	Subjects	Age in years, mean (range)	Endophenotype	Finding
				controlling for confounders (RR: 2.77; 95% CI: 1.1–7.3; P = 0.03), but not by itself
Aggarwal et al., [154] 2005	181 patients with MCI from the Religious Order Study	mean age: 78.7 ± 6.9	Conversion from MCI to dementia	APOEε4 allele associated with a 93% increase in the risk of developing AD (95% CI: 1.02, 2.63)
Tschanz et al., [155] 2006	120 participants with cognitive impairment from the Cache County Study	≥65 years at baseline	Conversion from MCI to dementia	Among individuals with ≥1 APOEε4 allele, those with prodromal AD or other cognitive syndromes exhibited a 22- to 25-fold higher risk of dementia than cognitively unimpaired individuals (vs 5- to 10-fold higher risk in those without ε4)
Tyas et al., [30] 2007	470 nondemented participants from the Nun Study	>75 years	Risk of MCI and progression to dementia	APOEε4 allele significantly associated with MCI but not with progression to dementia.
Barabash et al., [27] 2007	89 patients with amnesic MCI	mean age: 75 ± 7.1	Risk of MCI and progression to dementia	APOEε4 allele associated with an increased risk of MCI (OR: 6.04, 95% CI: 2.76–3.23; p < 0.001) but not with progression to AD
Fleisher et al., [156] 2007	539 participants with amnesic MCI	Mean age: Progressors: 74.9 ± 6.6, non-progressors: 71.5 ± 7.4	Progression from amnesic MCI to AD	Progression from amnesic MCI to AD was best predicted by combining APOE status and the Symbol Digit Modalities Test, Delayed 10-Word List Recall, NYU Delayed Paragraph Recall Test, and the ADAS-cog total score (estimated predictive accuracy: 81% (95% CI: 0.79 to 0.83))
Ramakers et al., [36] 2008	180 subjects with MCI	Mean age: ε4 non-carriers: 55.2 ± 9.2, ε4-carriers: 58.9 ± 9.9	cognitive functioning	APOEε4 allele strongly related to subjective organization in middle-aged subjects (p = 0.011) and strongly related to delayed recall performance in

Author	Subjects	Age in years, mean (range)	Endophenotype	Finding
				elderly subjects (p = 0.02)
van der Flier et al., [157] 2008	749 memory clinic patients and 2,233 controls	mean age:66.0±11.0	subjective complaints, MCI, AD, other types of dementia	Compared with controls (15%) the prevalence of APOEε4 increased among patients with subjective complaints (22%), MCI (36%), AD (42%) and other types of dementia (25%)
Sasaki et al., [29] 2009	1433 Japanese subjects	≥65 years	MCI	frequency of APOEε4 allele higher in persons with amnesic MCI compared to persons with non-amnesic MCI or controls
Blom et al., [31] 2009	47 AD patients, 58 patients with MCI and 35 healthy control subjects	Mean age: controls: 57.0±8.1, MCI: 62.9±8.2, AD: 71.7±8.1	Conversion from MCI to dementia	MCI subjects with high CSF T-tau or P-tau and APOEε4 homozygosity progressed faster from MCI to AD

Table 2

Summary of studies relating *SORL1* with LOAD. No study specifically assessed the association between genetic variation in *SORL1* and MCI or Progression from MCI to Dementia.

Author (Year)	Age	Haplotype 1			Haplotype 2			Other Significant SNPs
		rs668387 SNP 8 (1,2)	rs689021 SNP 9	rs641120 SNP 10	rs3824968 SNP 23	rs2282649 SNP 24	rs1010159 SNP 25	
SIGNIFICANT ASSOCIATION								
Rogaeva et al. (2007)	Mean AAO: 70±9-77±8							
Caucasians (family dataset)					T	T	C	
Caribbean Hispanics		C	G	C				
Caucasians (case-control datasets)		C	G	C	T	T	C	
Israeli Arabs		C	G	C				
African-Americans								
Lee et al. (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 et al. (2007) (2)	Not released							
Caucasians					+	+	+	
Lee et al. (2007) - Autopsy	Mean AAO: cases: 80.5, controls: 79.9							
Caucasians		C	G	C	A	T	C	
Tan et al. (2007)	Mean AAO: 71.2 ± 8.9							
Han Chinese					A	T		
Seshadri et al. (2007) (3)	Mean age: 62 +9							
Caucasians						+		rs1131497 (SNP29)
Bettens et al. (2008)	Mean AAO: 79.0 ± 5.2							
Caucasians		C	G	C				rs560573 (SNP 6), rs1614735 (SNP 27)
Lee et al.(2008), reanalyzing data by Shibata et al. (2008)								
Japanese		C				T		
Koelsch et al. (2009)								

Author (Year)	Age	Haplotype 1			Haplotype 2			Other Significant SNPs
		rs668387 SNP 8 (<i>L</i> ²)	rs689021 SNP 9	rs641120 SNP 10	rs3824968 SNP 23	rs2282649 SNP 24	rs1010159 SNP 25	
Caucasians	Mean age: cases: 71.91 ± 8.2 years; controls: 71.56 years							SORL1-18ex26 (SNP21), haplotype: rs2070045 (SNP19)/ SORL1-18ex26 (SNP21)/ rs3824968 (SNP23):T/G/A
WEAK ASSOCIATION								
Webster et al. (2007) ⁽²⁾	Age ≥ 65 years							
Caucasians			+					
Li Y, Grupe, et al. (2008) ⁽²⁾	Mean age: 77.4 ± 7.5 (WU), 76.4 ± 6.1 (UK1), 76.5 ± 5.6 (UK2)							
Caucasians						T		rs2070045 (SNP 19)
NO ASSOCIATION								
Li H, Roses et al (2008) ⁽⁴⁾	Mean AAO ≥ 60							
Caucasians								
Houlihan et al.(2008)	Mean age: 70							
Caucasians								
Minster et al. (2008)	Mean AAO: cases: 72.8 ± 6.2 years; controls: 74.1 ± 6.2 years							
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