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Genomic Variants, Genes, and Pathways of Alzheimer's Disease: An Overview

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Abstract

Alzheimer's disease (AD) (MIM: 104300) is a highly heritable disease with great complexity in its genetic contributors, and represents the most common form of dementia. With the gradual aging of the world's population, leading to increased prevalence of AD, and the substantial cost of care for those afflicted, identifying the genetic causes of disease represents a critical effort in identifying therapeutic targets. Here we provide a comprehensive review of genomic studies of AD, from the earliest linkage studies identifying monogenic contributors to early-onset forms of AD to the genome-wide and rare variant association studies of recent years that are being used to characterize the mosaic of genetic contributors to late-onset AD (LOAD), and which have identified approximately ~20 genes with common variants contributing to LOAD risk. In addition, we explore studies employing alternative approaches to identify genetic contributors to AD, including studies of AD-related phenotypes and multi-variant association studies such as pathway analyses. Finally, we introduce studies of next-generation sequencing, which have recently helped identify multiple low-frequency and rare variant contributors to AD, and discuss on-going efforts with next-generation sequencing studies to develop statistically well-powered and comprehensive genomic studies of AD. Through this review, we help uncover the many insights the genetics of AD have provided into the pathways and pathophysiology of AD.

Keywords

Late-onset Alzheimer's Disease (LOAD); Alzheimer's Disease (AD); genome-wide association studies (GWAS); next-generation sequencing; pathway analysis

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Alzheimer's Disease: Characteristics, Epidemiology, and Genetic Contribution

Alzheimer's disease (AD) is characterized by an insidious onset and slowly progressing memory loss, and advancing to deficits in higher intellectual functions and cognitive abilities, typically across multiple domains (language, praxis, recognition, or executive functioning). In the 1900s, the disease was identified in a dementia patient by Alois Alzheimer, who described the characteristic histopathologic signs of the disease, senile (neuritic) plaques and neurofibrillary tangles (Alzheimer, 1907). At that time, AD was thought to be a rare cause of senility, a notion that was refuted in the 1960s with an autopsy series by Blessed, Tomlinson, and Roth performed on hundreds of brains affected with 'normal senility,' which revealed that the majority were affected by the plaque and tangle lesions characteristic of AD (1968). Subsequent work revealed that most dementias arose from specific pathological processes and were not normal features of aging, and efforts to characterize pathology and correlate clinical manifestations culminated in the development of common criteria for clinical diagnosis in 1984 (McKhann et al.). Clinical diagnosis of AD is accurate in 85-90% of cases (Dal Forno et al., 1996; Pericak-Vance et al., 1995; Welsh-Bohmer et al., 1997), but remains a diagnosis of exclusion, complicated by multiple factors: cognitive testing revealing considerable overlap in cognitive function between demented and non-demented elderly (Knopman, 2003); presence of multiple types of psychiatric co-morbidities including depression (25-75%) (Lee and Lyketsos, 2003; Olin et al., 2002), anxiety (20-70%) (Porter et al., 2003; Teri et al., 1999), and psychosis (41.1%) (Ropacki and Jeste, 2005); and co-morbid dementias including Vascular Dementia (VaD; 38-58%) (Fernando et al., 2004; Schneider et al., 2007). Definitive diagnosis still requires post-mortem neuropathologic examination of brain tissues.

AD is the leading cause of dementia in the elderly and sixth leading cause of death in the United States, affecting 5.3 million people in the United States including approximately 200,000 individuals under age 65 (Alzheimer's Association, 2015; Hebert et al., 2013). AD prevalence also increases with age, from 0.3-0.5% at age 60, to 11-15% at age 80 (Bachman et al., 1992; Prencipe et al., 1996; Rocca et al., 1991), although there is consider able variability in these rate estimates, with some reports finding prevalence as high as 47% after age 84 (Evans et al., 1989). Half of the beds in long-term care facilities are already devoted to patients with dementia, and a majority of those patients have AD (Katzman, 1986). As the population continues to age, the prevalence is expected to increase almost threefold by 2050 (Hebert et al., 2003), making AD not only a common, but also a growing health crisis.

Many lines of evidence point to a genetic basis for the development of AD. Familial aggregation studies demonstrated clustering of AD within families (Heyman et al., 1983; Nee et al., 1983; Sjogren et al., 1952), both among those with early-onset forms (St George-Hyslop et al., 1989) and the much more common late-onset form of AD (Pericak-Vance et al., 1988), where a more complex genetic etiology was suggested. Recurrence risk among siblings of those with AD (λ_S) have consistently ranged between four and five times higher than the risk to the general population (Hirst et al., 1994; Pericak-Vance et al., 1988; Sadovnick et al., 1989). Twin studies found higher concordance of AD among monozygotic

twins (22-83%) than dizygotic twins (0-50%) (Bergem, 1994; Bergem et al., 1997; Breitner et al., 1993; Breitner et al., 1995), lending further support to genetic contributions to AD over only shared environmental contributors. Among early-onset families, patterns of AD inheritance have been consistent with classical Mendelian autosomal dominant inheritance, while the late-onset families have tended to suggest a multifactorial inheritance involving both genetic and non-genetic factors (Farrer et al., 1991; Rao et al., 1994; van Duijn et al., 1993). These studies provided powerful evidence for a genetic contribution to AD risk, even before any specific genetic variants were described.

Genetics of Alzheimer Disease: Early-Onset AD

In the early to mid-1990s, genetic studies of AD focused on extended families with high burden of disease (two or more cases among first-degree relatives), and used linkage analysis of highly polymorphic genetic markers called short tandem repeats (STRs, or microsattelites) in order to identify genomic regions co-transmitting with disease in affected family members (Table 1). This strategy, followed by “fine mapping”- the positional cloning of candidate genes- was used to identify genes and genetic variants contributing to AD risk. The first three genes known to cause AD were identified among families with multiple early-onset cases (age-at-onset < 60 years): *APP*, encoding amyloid precursor protein (Goate et al., 1991), and *PS1* and *PS2*, encoding presenilins I and II respectively (Levy-Lahad et al., 1995; Rogaev et al., 1995; Sherrington et al., 1995), each transmitting disease-causing variants in the predicted autosomal-dominant fashion.

APP, identified in 1987 (Goldgaber et al., 1987; Tanzi et al., 1987), was initially cloned and localized to chromosome 21. Down Syndrome (Trisomy-21; OMIM: 190685), which involves whole or partial duplication of chromosome 21, is the most common cause of mental retardation, and persons with Trisomy-21 often develop the neuritic plaques and neurofibrillary tangles characteristic of AD at an early age (Lemere et al., 1996). Further confirmation of the role of *APP* was revealed through mutational analysis of an individual with Down Syndrome who was free of Alzheimer’s type dementia and whose autopsy showed no neuritic plaque or neurofibrillary tangle development in the brain; the individual carried only a partial duplication of chromosome 21 which excluded duplication of *APP* (Prasher et al., 1998). Functional studies demonstrated the role of mutations in this gene appear to cause shifts in the proteolytic cleavage of APP toward amyloidogenic pathways, leading to accumulation of an isoform of beta-amyloid $A\beta_{42}$, which is less soluble than the common isoform $A\beta_{40}$ (Suzuki et al., 1994), and is neurotoxic (Hilbich et al., 1991).

Not all families with early-onset AD showed linkage signals on chromosome 21 or were affected by these mutations (Pericak-Vance et al., 1988; Schellenberg et al., 1987), and subsequent studies identified linkage to chromosome 14 (Schellenberg et al., 1992; St George-Hyslop et al., 1992; Van Broeckhoven et al., 1994). In 1995, AD-causing mutations were identified in *PSEN1* (Sherrington et al., 1995), which contributed to an aggressive form of AD (Selkoe, 2001) with relative abundance of $A\beta_{42}$ accumulation (Lemere et al., 1996; Mann et al., 1996). Even after *PSEN1* had been identified, there remained families with heavy burden early-onset AD who demonstrated linkage to neither chromosomes 21 nor 14. Many of these families shared common ancestral origins in the Volga river basin of Russia

(Bird et al., 1988), and showed linkage to chromosome 1 (Levy-Lahad et al., 1995). A large 7.5 kb alternative polyadenylation message was identified when cloning one gene in the linkage region, and the gene identified demonstrated a high degree of homology to *PSEN1*, and was thus identified as *PSEN2*. Mutations in *PSEN2* are rare, but have been described in the Volga German families and in one Italian pedigree (Levy-Lahad et al., 1995; Rogaev et al., 1995). Individuals affected by *PSEN2* mutations have highly variable ages of disease onset, as early as their 40s and as late as their 80s. A surfeit of evidence suggest that presenilins contribute to a partial loss of function in the γ-secretase complex, which affects several downstream signalling pathways, and increase the vulnerability of the brain to Aβ toxicity(De Strooper, 2007), however the precise roles of presenilin mutations continue to be investigated.

Genetics of Alzheimer Disease: Late-Onset Alzheimer Disease (LOAD)

LOAD cases comprise the majority (90-95% or more) of individuals affected with AD, and as noted earlier, there is considerable evidence to support a strong genetic component in the etiology of LOAD, including a greater lifetime risk for dementia among offspring in late-onset families compared to offspring in early-onset families (Farrer et al., 1990). Identifying genetic contributors to LOAD has posed great challenges, as while EOAD is characterized by highly penetrant mutations in a few known risk genes, LOAD is likely caused by multiple low penetrance genetic variants.

The first susceptibility locus for LOAD: APOE

The first confirmed susceptibility gene for LOAD, the Apolipoprotein E (*APOE*) gene, was initially discovered using linkage analysis (Pericak-Vance et al., 1991) in a subset of AD affected individuals with an age-at-onset (AAO) greater than or equal to 60 years of age, followed by association analysis (Strittmatter et al., 1993). Located on chromosome 19 (19q13.2) (Das et al., 1985; Olaisen et al., 1982), *APOE* encodes apolipoprotein E (ApoE), a serum protein synthesized by astrocytes (Mahley, 1988) involved in the transport, storage, and metabolism of lipid. The three known isoforms of the ApoE protein (ApoE2, ApoE3, and ApoE4) result from single amino acid substitutions at residues 112 and 158 (Rall et al., 1982; Weisgraber et al., 1982), and the corresponding encoding, ε2, ε3, and ε4, are estimated to be 8%, 78%, and 14%, respectively, in most Caucasian populations (Martins et al., 1995), while other ApoE isoforms (such as those encoded by ε1, ε5, and ε7) are extremely rare. Compared to the common ε3 allele, the ε4 allele has consistently been found to be positively associated with risk for sporadic and familial AD, whereas the ε2 allele appears to be a protective factor for risk of LOAD (Martins et al., 1995). The ε4 allele also has a dose-dependent relationship with LOAD susceptibility (Corder et al., 1994; Frisoni et al., 1995) with the relative risks of LOAD for ε4 homozygotes and for ε3/ε4 heterozygotes are approximately 15 and 3, respectively, compared to ε3 homozygotes (Farrer et al., 1997). The *APOE* ε2/ε3/ε4 polymorphisms also appear to have a dosage effect on AAO: the estimated mean AAO for subsets consisting of individuals carrying no ε4 allele, one ε4 allele, and two ε4 alleles, are 84.3, 75.5, and 68.8 years, respectively (Corder et al., 1993). In addition, the effect of ε4 allele on risk for LOAD is also age-dependent. The ε4 allele has a greatest impact on risk for LOAD among individuals that are between 60 and 79 years of

age, while its effect is gradually attenuated as an individual reaches ages in access of 80 years (Farrer et al., 1997; Lautenschlager et al., 1999). While *APOE* ε4 appears to influence AD risk and AAO, it is unclear if it affects AD progression, with studies indicating it may accelerate (Craft et al., 1998; Deary et al., 2002; Dik et al., 2000; Lehtovirta et al., 1996), slow (Frisoni et al., 1995; Stern et al., 1997) or have no effect on disease progression in LOAD patients (Basun et al., 1995; Growdon et al., 1996). *APOE* effects have also been shown to vary widely across ethnicities (Farrer et al., 1997), and differ between males and females (Barrett, 1999; Farrer et al., 1997), even after accounting for differences in mortality between groups. *APOE* has also been correlated with neuropathological features of the disease: several studies report that individuals carrying two *APOE* ε4 alleles have higher amyloid plaque density than individuals carrying one or no *APOE* ε4 alleles (Hyman et al., 1996; Nagy et al., 1995; Oyama et al., 1995; Rebeck et al., 1993; Schmechel et al., 1993; Zubenko et al., 1994).

Other candidate susceptibility loci for LOAD

While *APOE* is a critical contributor to genetic risk, more than a third of AD cases do not carry any *APOE* ε4 alleles, and as AD heritability has been estimated at ~80% (Bergem, 1994), this suggests much of the heritability has not yet been characterized. At most, *APOE* may account for 50% of the total genetic effect in AD (Farrer et al., 1997; Roses et al., 1995; Saunders et al., 1993). To identify other genomic contributors to AD risk, a variety of approaches have been used: regional and genome-wide linkage studies (GWLS) in multiplex pedigrees, candidate gene association studies, meta-analyses of linkage and association studies, genome-wide association studies (GWAS), and most recently, whole genome sequencing (WGS) and whole exome sequencing (WES) studies.

Genome-wide linkage studies (GWLS) for LOAD have been published on multiple independent datasets since 1997 (Ashley-Koch et al., 2005; Blacker et al., 2003; Farrer et al., 2003; Hahs et al., 2006; Hiltunen et al., 2001; Kehoe et al., 1999; Mayeux, 2004; Mayeux et al., 2002; Myers et al., 2002; Pericak-Vance et al., 1997; Pericak-Vance et al., 2000). While many of these studies have focused on US and Northern European Caucasian families (Blacker et al., 2003; Hiltunen et al., 2001; Kehoe et al., 1999; Myers et al., 2002; Pericak-Vance et al., 1997; Pericak-Vance et al., 2000), other scans have looked at different ethnic groups such as Caribbean Hispanic families (Mayeux, 2004; Mayeux et al., 2002) or very large families from population isolates (Ashley-Koch et al., 2005; Farrer et al., 2003; Hahs et al., 2006), using STRs with an average spacing of 8 centiMorgans (cM). Some chromosomal regions have been studied extensively (most notably chromosomes 9, 10, and 12), although no consistently replicated AD gene have yet been identified within these regions, with the potential exception of *C9ORF72* (Majounie et al., 2012). While the majority of follow-up studies have focused on these three chromosomes, several linkage regions have been identified in multiple studies that remain unexplored (Table 1, adapted from (Butler et al., 2009)).

Most genes examined as potential LOAD candidate genes have been identified due to their known biological functions, and thus have been hypothesized to play roles in AD development. Hundreds of genes have been individually tested for association with LOAD,

and associations have been reported for nearly 150 genes, but few have replicated and none have gained wide acceptance (AlzGene database (http://www.alzgene.org/) accessed March 1, 2016; (Bertram et al., 2007)). Several potential causes of these inconclusive findings include small sample sizes in these studies, limited knowledge of the actual effects of genetic variation in living brains, and potential etiologic heterogeneity among the cases included in these studies.

One approach used to overcome sample size limitations is meta-analysis of independent genetic studies. A meta-analysis by Bertram and colleagues (2007) served to catalogue association results across many candidate gene association studies in the AlzGene database, as described before, but also to identify associations with AD of by systematically combining data on genetic variants that had been genotyped commonly across multiple studies. Performing meta-analyses systematically on variants genotyped in three or more samples, this study identified variants with small to modest effect sizes in twelve candidate genes for further investigation (including *ACE*, *CHRNB2*, *CST3*, *R1*, *GAPDHS*, *IDE*, *MTHFR*, *NCSTN*, *PRNP*, *PSEN1*, *TF*, *TFAM* and *TNF*). One of these candidates is already known to be involved in familial, early-onset forms of AD (*PSEN1*), suggesting that this approach may have identified valuable candidates for further examination.

Genome-wide association studies

The study by Bertram and colleagues (2007) noted a major limitation of this approach: that candidate gene studies tend to examine genes with hypothetical functional roles in disease or proximity to strong linkage signals, and this has the potential to introduce bias from several sources into meta-analytic examinations. This limitation is partially addressed by the introduction of genome-wide association studies, which deal with several potential biases by examining high-density genotyping of single nucleotide polymorphisms (SNPs) capturing most variation across the genome, reducing overrepresentation of variant data from particular genomic regions. The application of meta-analytic approaches to GWAS data represent an additional improvement upon meta-analysis in candidate genes by improving sample sizes and allowing for small to modest effects to be observed with fewer inherent potential biases, provided appropriate adjustment is made for differences between high-density genotyping platforms and for relevant issues of study design.

More than 13 studies have tested association with LOAD on high-density, genome-spanning panels of SNPs. Grupe and colleagues (2007) pooled samples and tested association with more than 17,000 gene-based putative functional SNPs across the genome, finding a signal at *APOE* that reached study-wide statistical significance, with multiple weaker associations observed elsewhere, many occurring in regions of known linkage. Coon and colleagues (2007) reported results of association with a half-million SNPs across the genome genotyped on over 1,000 histopathologically-verified AD cases and controls, identifying only *APOE* as a major susceptibility gene. A follow-up study stratifying cases by *APOE* genotype detected strong associations with *GAB2* (MIM:606203) SNPs, and in follow-up worked observed altered *GAB2* transcript levels in vulnerable neurons, and an effect of *GAB2* levels on tau phosphorylation; replication studies have observed mixed results (Reiman et al., 2007). Abraham and colleagues (2008) genotyped approximately 550,000 SNPs in more than 1,000

pooled cases and 1,200 pooled controls, and in testing genetic associations, observed genome-wide statistical significance only for SNPs in or near *APOE*. Following up on the strongest signals that did not attain statistical significance with more individual genotyping identified the gene *LRAT* (MIM:604863), which is involved in the vitamin A (retinoid) cascade, a system previously implicated in AD. Bertram and colleagues (2008) analyzed 500,000 SNPs in 410 families, reporting a SNP associated with AD age-at-onset on chromosome 14q31, and providing additional evidence of associations near *APOE* and near *GAB2*. Beecham and colleagues (2009) previously reported a GWAS on approximately 550,000 SNPs in nearly 500 AD cases and 500 cognitive controls. This study confirmed genome-wide significant associations at APOE and identified a SNP on chromosome 12q13 meeting $\alpha = 5\times10^{-5}$, corresponding to a false-discovery rate (FDR) < 0.20. The strongest signals with less than genome-wide statistical significance in this study were identified in regions with prior linkage evidence, suggesting that some of these are likely to underlie true associations (Avramopoulos, 2009). A GWAS of AD originating at the Mayo Clinic (Carrasquillo et al., 2009), genotyping 314,000 SNPs on 844 cases and 1,255 controls, once again verified *APOE* associations, and in second-stage replication analysis, identified a novel signal on the X chromosome (combined $P = 3.9\times10^{-12}$) in the gene *PCDH11X* (MIM: 300246), encoding a protocadherin, a cell-cell adhesion molecule expressed in the brain. A study (Naj et al., 2010) using the original set of cases and controls from Beecham and colleagues (2009) and additional newly-identified cases and controls with high-density genotyping examined associations in a genome-wide set of markers (483,399 SNPs) identified an association with LOAD of genome-wide significance ($P = 4.70\times10^{-8}$) at 151.2Mb of chromosome 6q25.1 in the gene *MTHFD1L*, which encodes the methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 1-like protein, a gene involved in the pathway synthesizing methionine from homocysteine and thus may influence homocysteine levels, known risk factors for AD. Finally, a study from the University of Pittsburgh (Kamboh et al., 2012b) with 1,291 cases and 938 controls examining ~2.5 million imputed SNPs observed its most significant novel association in the chromosome 15q21.3 gene *PPP1R3B* (rs3848140; $P = 3.05\times10^{-7}$), though this association did not attain genome-wide statistical significance. *PPP1R3B* is also known to be associated with high density lipoprotein and cholesterol levels.

While many of the aforementioned non-*APOE* associations attained genome-wide significance and were found to be association in replication datasets, associations of these variants have not been found to be statistically significant in other independent studies, and for this reason, it remains unclear whether these genetic variations are truly associated with risk. A notable limitation of these studies is the lack of statistical power to detect small or even modest associations (odds ratio (OR) < 1.5) with samples sizes of ~1,000 cases and ~1,000 controls, or less. A second-generation of GWASes with greatly increased sample sizes were able to detect the first set of associations of variants with small effects on LOAD and that replicated in multiple studies. The first of these by the European Alzheimer Disease Initiative (EADI) (Lambert et al., 2009) examined associations in a total of 6,010 LOAD cases and 8,625 controls, and observed highly significant associations in *CLU* (combined $P = 7.5\times10^{-9}$), a chromosome 8p21.1 gene which encodes clusterin or apolipoprotein J, and in *CR1* (combined $P = 3.7\times10^{-9}$), a chromosome 1q32.2 gene encoding the complement

component (3b/4b) receptor 1. Effect sizes for associations of these variants were either slightly deleterious (for *CR1*, OR = 1.21) or slightly protective (for *CLU*, OR = 0.86). A second study by the Genetic and Environmental Risk in Alzheimer Disease (GERAD) Consortium (Harold et al., 2009), released at the same time as the paper by Lambert and colleagues, also observed genome-wide statistical significance for associations of non-*APOE* genomic variants in their independent dataset including a total of 5,964 cases and 10,188 controls. These included strong associations in *CLU* ($P = 8.5\times10^{-10}$, OR = 0.86), one of the genes with significantly-associated variants in the study by Lambert and colleagues, and novel associations in the *PICALM* gene ($P = 1.3\times10^{-9}$, OR = 0.86). As with the previous study, the study by Harold and colleagues observed small effect sizes for variants with genome-wide significance in each of the genes (ORs ≈ 0.86), suggesting that some genetic variants contributing to LOAD other than *APOE* may have weak, but nevertheless real, effects on disease risk. A third study by the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium (Seshadri et al., 2010), which incorporated data from both the EADI and GERAD consortia to investigate an overall 9,511 cases and 28,174 controls, identified associations with genome-wide statistical significance adjacent to two sets of previously unreported loci, near *BIN1* on chromosome 2q14.3 ($P = 1.59\times10^{-11}$, OR = 1.13) and near *EXOC3L2*/*BLOC1S3*/*MARK4* on chromosome 19q13.3 ($P = 6.45\times10^{-9}$, OR = 1.18). *BIN1* encodes the Bridging Integrator 1 protein, which is a nucleocytoplasmic adaptor protein that is heavily expressed in brain and muscle. Of the three genes proximal to the significant associations on chromosome 19q13.3 (signals which are independent of and not in linkage disequilibrium with associations in the *APOE* region), only two are potential biological candidates involved in AD-related pathways: *BLOC1S3*, which encodes subunit 3 of the biogenesis of lysosomal organelles complex-1 protein, influences endosomal to lysosomal routing, and is expressed in the brain; and *MARK4*, which encodes the MAP(mitogen activated protein)/microtubule affinity-regulating kinase 4 protein, is expressed exclusively in the brain, and participates in neuronal differentiation.

Meta-analysis of genome-wide association studies

The next generation of genetic studies to follow GWAS was meta-analysis across GWAS studies. By combining and meta-analyze findings within and across GWAS in large analytical consortia, and with the increase in sizes of these datasets to many tens of thousands of LOAD cases and controls, much greater power became available to identify and replicate newfound genetic associations with LOAD, and to uncover the biological mechanisms underlying disease pathology.

In 2011, the Alzheimer's Disease Genetics Consortium (ADGC), which integrated data on 11,840 AD cases and 10,931 controls of European ancestry (Naj et al., 2011) over 15 separate genome-wide association studies of LOAD, including case-control, prospective cohort, and family-based studies, confirmed associations in *APOE*, *PICALM*, *CR1*, *CLU*, and *BIN1* with genome-wide statistical significance ($P<5\times10^{-8}$), and identified novel associations in five other genomic regions with genome-wide statistical significance (*MS4A* gene cluster) or near it ($P<10^{-6}$) (*EPHA1*, *CD2AP*, *CD33*, and *ABCA7*), which were validated and attained genome-wide significance with replication *in silico*. Similarly, in a companion paper, a collaborative GWAS effort between the three previously-mentioned

consortia, EADI, GERAD, and CHARGE (Hollingworth et al., 2011), observed genome-wide significant associations at the five genes they previously identified as well as genome-wide significant association at *ABCA7*, and nearly significant associations at the same loci identified by the ADGC (*EPHA1*, *CD2AP*, *CD33*, and the *MS4A* gene cluster). Both groups replicated associations in each other's consortium datasets, as well as through *de novo* genotyping in independent replication samples without GWAS. As both sets of analyses used genome-wide genotyping from multiple studies collected on a variety of genotyping platforms from both Illumina and Affymetrix, all GWAS datasets were imputed using haplotype reference data from the International HapMap Project (International HapMap et al., 2007) to examine a common set of approximately 2.5 million SNPs across the genome. A number of subsequent studies provided independent replications of these findings (Biffi et al., 2010; Carrasquillo et al., 2010; Carrasquillo et al., 2011a; Carrasquillo et al., 2011b; Corneveaux et al., 2010; Gu et al., 2011; Jun et al., 2010; Kamboh et al., 2012c; Lambert et al., 2011; Omoumi et al., 2014; Piaceri et al., 2011).

To maximize sample size and thereby power to detect LOAD susceptibility loci with even more modest effects, the four consortia, ADGC, EADI, GERAD, and CHARGE, combined data and analytical resources to form a mega-consortium, the International Genomics of Alzheimer's Project (IGAP), to conduct a new GWAS. This GWAS was performed on 17,008 AD cases and 37,154 controls of European ancestry, with de novo genotyping of variants with genome-wide significant and suggestive associations ($P<0.001$) in a large replication dataset of 8,572 AD cases and 11,312 cognitive controls from multiple European datasets without available GWAS (Lambert et al., 2013b). Except for *CD33*, all previously-identified GWAS loci reached genome-wide significance in the discovery analysis, and an additional 11 loci (*HLA-DRB5/DRB1*, *PTK2B*, *SORL1*, *SLC24A4-RIN3*, *INPP5D*, *MEF2C*, *NME8*, *ZCWPW1*, *CELF1*, *FERMT2*, and *CASS4*) demonstrated genome-wide statistically significant associations with the inclusion of analysis of replication datasets. Among these, *SORL1* had been identified in a GWAS of Japanese, Korean, and Caucasian AD cases and controls (the lattermost taken from the ADGC), however, as a well-established functional candidate, it had not been observed in a GWAS of European ancestry until the IGAP analyses, likely due to its low minor allele frequency (MAF) of ~0.04. Subsequent replication efforts have provided confirmation of the signal in *ZCWPW1* (Ruiz et al., 2014) as well as evidence of association at *TRIP4*. Multiple validation studies (studies examining associations among different ethnicities) in Southeast Asian populations have demonstrated associations at many of these loci: *CLU* (Komatsu et al., 2011; Liu et al., 2014; Yu et al., 2013), *CR1* (Jin et al., 2012), *PICALM* (Chung et al., 2013; Liu et al., 2013; Miyashita et al., 2013), *BIN1* (Liu et al., 2013; Miyashita et al., 2013), and the *MS4A* gene cluster (Deng et al., 2012; Tan et al., 2013).

In addition to the Japanese/Korean/Caucasian meta-analysis previously described, multiple GWAS meta-analysis have been performed in non-Caucasian ethnicities, though sample sizes of these studies have been considerably smaller than those in the previously described studies. A GWAS of AD in 544 affected and 549 unaffected samples of Caribbean Hispanic ancestry (Tan et al., 2013) identified a number of strong but not genome-wide statistically significant novel associations ($P < 9\times10^{-6}$) and replicated associations at *CLU*, *PICALM*, and *BIN1*. A GWAS of AD in 5,896 African American subjects (including 1,968 cases and

3,928 controls) reported genome-wide significant associations in *ABCA7* (Reitz et al., 2013), with similarly strong signals in two adjacent loci, *HMHA1* and *GRIN3B* (likely part of the same signal), around 1-1.05Mb on chromosome 19p13.3. Gene-based analyses identified nominal associations of *CR1*, *BIN1*, *EPHA1*, and *CD33*.

Genome-wide association studies and meta-analyses of AD-related phenotypes

Genetic studies of phenotypes related to AD, including endophenotypes (phenotypes endogenous to the disease pathway (Flint and Munafo, 2007; Rice et al., 2001), are among alternative approaches to identifying genetic risk factors for AD. Alternative phenotypes for AD include characteristics of disease (e.g., age-at-onset), biomarkers capturing or correlating with disease pathology (e.g., cerebrospinal fluid (CSF) $A\beta_{42}$), and modified case definitions (e.g., cases with onset after 85 years of age). Since the advent of whole genome studies, a multitude of studies examining AD-related phenotypes have used genome-wide association in efforts to better characterize genomic contributors to AD.

Among the most thoroughly investigated endophenotypes are CSF $A\beta_{42}$ and CSF tau protein levels. An early CSF GWAS (Han et al., 2010) in the Alzheimer's Disease Neuroimaging Intitiative (ADNI) dataset did not find any genome-wide statistically significant associations with CSF biomarkers $A\beta_{1\text{-}42}$, T-tau, and P-tau_{181P} among AD cases, however two associations were observed to meet that threshold in cognitively normal individuals, one between a variant in *CYP19A1* (rs2899472, $P = 1.86\times10^{-9}$) and $A\beta_{1\text{-}42}$, and another between a chromosome 12 SNP upstream of *SRRM4* (rs1997111, $P = 1.10\times10^{-8}$) and T-tau. *CYP1A1* encodes aromatase, which is involved in estrogen regulation, while *SRRM4* regulates alternative splicing of microexons in the brain, and misregulation of which has been linked to autism spectrum disorders (Irimia et al., 2014). A subsequent reanalysis of these same data (Kim et al., 2011) identified genome-wide significant association with T-tau in the chromosome 2 gene *EPC2* (rs4499362, $P \approx 2.40\times10^{-8}$), which has been implicated in syndromes leading to mental retardation (van Bon et al., 2010). More recently, a GWAS of CSF biomarkers (Cruchaga et al., 2013) identified four genome-wide significant associations associated with CSF tau levels (including Tau and pTau): *APOE*; a chromosome 3q28 SNP rs9877502 ($P = 4.89\times10^{-9}$ for Tau; located between *GEMC1* and *OSTN*); a chromosome 9p24.2 SNP rs514716 located at 9p24.2 in the gene *GLIS3* ($P = 1.07\times10^{-8}$ for Tau and $P = 3.22\times10^{-9}$ for pTau); and a chromosome 6p21.1 SNP rs6922617 ($P = 3.58\times10^{-8}$ for CSF pTau) within the *TREM* gene cluster. Follow-up analyses on these SNPs showed rs9877502 to also be associated with AD ($P = 2.67\times10^{-4}$) and cognitive decline ($P = 4.86\times10^{-5}$), suggesting the identification of a novel, if weak, contributor to AD risk.

Among the more widely collected and more frequently studied AD-related phenotypes is age-at-onset (AAO) of the disease, which is a marker for both risk and severity of AD. A GWAS of AAO by Kamboh and colleagues (2012a) of 2,222 AD cases identified no genome-wide significant associations outside of the *APOE* region, with the strongest non-A*POE* association being observed on chromosome 4q31.3 in the gene *DCHS2* (rs1466662; $P = 4.95\times10^{-7}$). A subsequent GWAS meta-analysis of 9,162 subjects (Naj et al., 2014), which included the Kamboh dataset, identified genome-wide significant associations only in and around the *APOE* locus, with the next most significant association in the chromosome

13q33.3 gene *MYO16* (rs9521011; $P = 7.62\times10^{-8}$). This study examined the overall contribution of the most significantly associated variants identified in the ADGC GWAS to variation in AAO, and determined that while *APOE* contributes to 3.9% of variation in AAO, the combined effect of all other risk loci contribute to 1.1% of AAO variation, suggesting that no AD risk loci modulate AAO as strongly as *APOE*.

Multiple GWAS of brain imaging datasets have been undertaken to characterize pathological progression in living subjects. An GWAS on hippocampal atrophy performed using ADNI data (Potkin et al., 2009) identified genome-wide significant associations only in the *APOE* region, with several candidate genes demonstrating associations in the range of $P < 10^{-6}$: *EFNA5*, *CAND1*, *MAGI2*, *ARSB*, and *PRUNE2*. A GWAS in the MIRAGE study (Melville et al., 2012) examined phenotypes related to hippocampal atrophy, in particular hippocampal volume (HV), total cerebral volume (TCV), and white matter hyperintensities (WMH), in 981 Caucasian and 419 African-American AD cases matched with cognitively normal siblings, with replication in the ADNI cohort. Novel genome-wide significant associations ($P < 5\times10^{-8}$) were attained for HV with SNPs in the *APOE*, *F5/SELP*, *LHFP* and *GCFC2* gene regions. Associations with different SNPs in the same gene ($P < 10^{-5}$ in Caucasians and $P < 2.2\times10^{-4}$ in African Americans) were also observed for *PICALM* (now a confirmed AD risk locus) with HV, *SYNPR* with TCV and *TTC27* with WMH. A 2010 GWAS (Shen et al., 2010) was performed on 142 measures of grey matter (GM) density, volume, and cortical thickness taken on 733 ADNI participants (175 AD cases, 354 individuals with amnestic mild cognitive impairment (MCI), and 204 congitively normal controls). Using hierarchical clustering and heat maps to analyze the results, investigators identified association in *APOE* with multiple brain regions, variants in *EPHA4* (rs10932886) showed nominal associations ($P < 10^{-6}$) with 27 voxel-based morphometry (VBM) phenotypes, while variants in *TP63* (rs7610017) and *NXPH1* (rs6463843) demonstrated associations with 19 and nine VBM phenotypes, respectively. *EPHA4* belongs to the same subfamily of ephrin receptors as the confirmed GWAS locus, *EPHA1*, whereas *NXPH1* encodes a protein which protein forms a very tight complex with alpha neurexins, a group of proteins that promote adhesion between dendrites and axons (Missler and Sudhof, 1998). A voxelwise genome-wide association study (vGWAS) (Stein et al., 2010) on the same data investigating morphometry differences in each of 31,622 voxels of the entire brain across 740 elderly subjects with AD, MCI, or normal cognition, did not identify any novel genome-wide associations in large part due to stringent multiple hypothesis testing correction. The investigators did find a common variant in the *GRIN2B* glutamate receptor gene to be over-represented in Alzheimer's disease and was associated with ~1.5% lower temporal lobe volume per risk allele in the elderly ($P < 5\times10^{-7}$). Most recently, a large GWAS of HVs on >20,000 cognitively-normal individuals (Bis et al., 2012) identified several possible AD candidate genes with effects on HV, which are involved in a number of processes: *HRK* (associated with apoptosis), *LEMD3* (transforming growth factor antagonism), *ASTN2* (neuronal migration), *MSRB3* (oxidative stress), *WIF1* (brain development), *FBXW8* (ubiquitin pathway), and *DPP4* (incretin pathway).

Haplotype, gene-based, and pathway analyses

Single variant analyses have been typically used to identify AD risk loci, but there may be limitations to examining only singe variants in each analysis. Among the strongest of these is the considerable correction for Type I error required (and thus larger sample size required) in order to account for multiple hypothesis testing. Other limitations include that if susceptibility is conferred by multiple different variants within a locus (Ioannidis, 2007; Neale and Sham, 2004), complex patterns of association might be observed where the same variants have different associations across different datasets despite similar expectations from power estimations (Moskvina and O'Donovan, 2007). Yet another limitation is that ungenotyped yet causal rare variants may not be captured adequately through 'tagging' approaches utilizing linkage disequilibrium. One way to address this last limitation is to phase alleles at multiple adjacent variants into haplotypes, especially if genotyping or sequencing rare variants is too costly for the study, or if there is evidence that co-transmission of alleles at different loci on the same chromosomal arm may uniquely elevate risk for disease. One such study to perform association analyses of haplotypes in AD utilized data from the GERAD and EADI consortia (Lambert et al., 2013a), with discovery analyses in EADI GWAS data (2,025 AD cases/5,328 controls), replication in GERAD GWAS data (2,820 AD cases/6,356 controls), and further replication by custom genotyping in five additional case-control datasets (including 5,093 AD cases/4,061 controls). This study reported genome-wide significant association at a haplotype in the chromosome 10p13 gene *FRMD4A* (OR (95% CI): 1.68 (1.43, 1.96); $P = 1.1\times10^{-10}$), for which secondary analyses demonstrated that *FRMD4A* polymorphisms were associated with plasma $A\beta_{42}/A\beta_{40}$ ratio (best signal, $P = 5.4\times10^{-7}$). Subsequent work found that the down-regulation of *FRMD4A* is associated with increased APP-β-secretase interaction, increased $A\beta_{40}$ secretion, and altered phosphorylation of tau (Martiskainen et al., 2015).

In situations where AD risk is driven by multiple different variants within a gene but there is inadequate power to detect individual effects in single variant analyses, an alternative approach for examining association is by performing gene-wide tests, or multilocus association tests that include all variants in the exonic and intronic regions of a genes, as well as potentially regulatory intergenic variants upstream or downstream of the gene in the immediate vicinity. Genome-wide gene-based analyses like those using imputed common variant data have also been performed in AD using the IGAP consortium data to identify genes with multiple strong variant associations that failed to meet genome-wide statistical significance when examined separately (Escott-Price et al., 2014). These analyses identified five genes where gene-wide association are $P < 2.56\times10^{-6}$ but where SNPs in single-variant analyses were not associated at $P < 5\times10^{-8}$, including *TP53INP1* (gene-wide $P = 1.4\times10^{-6}$) and *IGHV1-67* (gene-wide $P = 7.9\times10^{-8}$), and three genes near loci with genome-wide significant association signals in single variant analysis (*ZNF3*, gene-wide $P = 8.6\times10^{-7}$; *NDUFS3*, gene-wide $P = 4.8\times10^{-7}$; *MTCH2*, gene-wide $P = 2.5\times10^{-6}$). Evidence exists for a role in neurodegeneration for at least one of these genes, *NDUFS3*, for which a deficiency is known to cause Leigh syndrome (Benit et al., 2004), an early-onset, progressive neurodegenerative disorder with a neuropathology featuring focal lesions including areas of gliosis.

Beyond the identification of groups of variants or whole genes contributing to elevated AD susceptibility, the ultimate goal of these genomic studies are to identify the key biological pathways influencing development of AD as targets for the development of therapeutic interventions to treat and ideally cure the disease. Yet another study design attempts to ask this question directly: using existing knowledge about biological pathways and which genes are involved in these pathways, is it possible to identify the most important pathways to target for developing treatments? Pathway analyses attempt this by combining associations across multiple variants from GWAS data not at the gene-level, but at the pathway-level by examining variants in all genes clustered in defined biological pathways. Pathway gene-sets can be derived from a variety of sources, including using network analysis tools to identify gene-sets from pathologically-relevant data (e.g., co-expression networks in disease-specific tissues), or curated in publicly-available databases such as the KEGG (Kyoto Encyclopedia of Genes and Genomes) and GO (Gene Ontology) resources. Among the early pathway analyses performed, a 2010 study by Jones and colleagues (2010) utilized GERAD GWAS data (in which the first genome-wide associations of *CLU*, *CR1*, and *PICALM* were observed) and a gene-set enrichment analysis (GSEA) approach as implemented in the program ALLIGATOR (Wang et al., 2007) to identify gene-sets with stronger associations than expected by chance alone. This approach found a significant overrepresentation of association signals in pathways related to cholesterol metabolism (strongest pathway: cholesterol transport [GO:0030301], $P < 10^{-5}$) and immune response (strongest pathway: complement activation [GO:0006958], $P = 2\times10^{-5}$). An analysis in the ADNI GWAS dataset (Ramanan et al., 2012) used a pathway enrichment analysis based on a composite measure of memory generated applying modern psychometric theory to item-level data from the ADNI neuropsychological test battery, and identified 27 canonical pathways that were enriched (FDR-corrected $P < 0.05$) against this memory score, including cell adhesion, neuronal differentiation, and inflammation-related signaling pathways. More recently, a network analysis by Zhang and colleagues (2013) examined gene-regulatory networks in 1,647 postmortem brain tissues from LOAD cases and unaffected individuals, and demonstrated reconfiguration of the molecular interaction structure in specific ways in LOAD, which highlighted genes involved in pathogen phagocytosis regulated by TYROBP, which is upregulated in AD. Expression of TYROBP is restricted to cells involved in innate immunity, including microglia in the brain (Schleinitz et al., 2009).

Rare variant association studies and the future of AD genetic studies

Multilocus association studies like those described in the previous section have the potential to capture some of the contribution from low-frequency ($0.005 \leq MAF < 0.05$) and rare ($MAF < 0.005$) genomic variants, however capturing genotypes on rare variants in large datasets have until the last 5 years remained a prohibitive challenge, either due to technological limitations or cost. In addition to cost-lowering advances in WGS and WES, technologies such as the exome array have greatly improved the ability to capture genotypes on hundreds of thousands to millions of rare variants throughout the genome in large datasets. While these approaches have advanced the ability to characterize rare variation in study participants, there still remain substantial analytical limitations, most of these stemming from the lack of adequate sample sizes to detect associations of variants with $MAF < 0.01$ at genome-wide statistical significance levels.

Thus far, exome array studies of AD have lacked adequate sample sizes to detect novel low-frequency and rare variant associations (Chen et al., 2015; Chung et al., 2014), despite the relatively small number of coding region variants genotyped (~250,000) on these platforms. A large-scale exome array study in the IGAP consortium is nearing completion with discovery data on ~17,000 AD cases and cognitive controls and may identify novel rare variants using this approach.

Exome and genome sequencing approaches have recently yielded novel insights into the genetic contributors to AD. Rare loss-of-function mutations R47H and R62H in the chromosome 6p21.1 gene *TREM2* have recently been found to lead to an increase of as much as 400% in AD risk (Guerreiro et al., 2013b; Jonsson et al., 2013). *TREM2* implicates innate immunity pathways (Golde et al., 2013), is involved in the regulation of phagocytic pathways, and has been found to inhibit cytokine production and secretion in microglia, reducing inflammatory response (Jiang et al., 2013). Mutations in *TREM2* have been previously implicated in Nasu Hakola disease (Paloneva et al., 2002) and early-onset dementia without bone cysts (Chouery et al., 2008). The identification of this gene has reinforced the growing consensus that “neuroinflammation” as driven by microglia is a critical component of AD pathogenesis. A whole-genome sequencing study examining genotypes of 1,795 Icelanders found a coding mutation in the *APP* gene (A673T) that protects against Alzheimer’s disease and cognitive decline in the elderly without Alzheimer’s disease (Jonsson et al., 2012). *SORL1*, which was first an AD candidate gene (Rogaeva et al., 2007) and then observed in the IGAP GWAS of AD, was recently found through exome sequencing to carry mutations causing a form of early-onset AD with autosomal dominant inheritance (Pottier et al., 2012). Exome sequencing of a Turkish family with AD identified a mutation in *NOTCH3* (R1231C) (Guerreiro et al., 2012), which has previously been implicated in a subtype of vascular dementia, CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy). A 2014 study by Cruchaga and colleagues (2014) identified rare coding variants in the chromosome 19q13.2 gene *PLD3*, encoding an enzyme of the phospholipase D family, however this association not been observed consistently in follow-up studies (Cruchaga and Goate, 2015; Heilmann et al., 2015; Hooli et al., 2015; Lambert et al., 2015; van der Lee et al., 2015).

The next generation of rare variant studies in AD is currently in development and includes the integration of multiple analytic strategies for the identification of novel variants affecting Alzheimer’s disease risk, including linkage and association. The upcoming Alzheimer’s Disease Sequencing Project (ADSP; https://www.niagads.org/adsp/content/home) is a joint project by the National Institute on Aging and National Human Genome Research Institute to identify novel risk and protective variants for AD in nearly 600 whole genomes of from 110 multiplex pedigrees heavily burdened with AD and approximately 10,500 whole exomes on unrelated AD cases and non-demented controls. Preliminary work on the sample sets being incorporated into the ADSP includes whole genome linkage analyses using GWAS data on multiplex White and Caribbean Hispanic pedigrees to identify candidate genomic regions for particular focus in an upcoming genome scan of WGS data (Barral et al., 2015; Kunkle et al., 2016). These and other studies promise to do much to characterize

the yet-undetected heritable components in Alzheimer's susceptibility, the "dark matter" of the genomic risk of AD.

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Table 1

Genomic regions of linkage to Alzheimer's disease observed in two or more independent linkage datasets.

Chr	Region	# Studies	Studies	LOD Scores	Relevant Genes
1	1p13.3-q23.3	2	(Butler et al., 2009; Liu et al., 2007)	5.2	*GSTM4*; *GSTM1*; *GSTM3*; *CSF1*; *NGF*; *HMGCS2*; *PRKAB2*; *APH1A*; *CTSS*; *THEM5*; *FAM63A*; *CHRNB2*; *LMNA*; *PMVK*; *FDPS*; *APOA1BP*; *GBA*; *NTRK1*; *CRP*; *NCSTN*
	1q23.3-q32.3	4	(Blacker et al., 2003; Butler et al., 2009; Kunkle et al., 2016; Liu et al., 2007)	2.1–4.0	*F11R*; *USF1*; *FCER1G*; *RGS4*; *APOA2*; *RXRG*; *POU2F1*; *PRDX6*; *SOAT1*; *PTGS2*; ***CR1***
3	3q12.3-q27.3	4	(Barral et al., 2015; Butler et al., 2009; Cummings et al., 2012; Kunkle et al., 2016)	3.5–4.5	*DRD3*; *GSK3B*; *TF*; *MME*; *BCHE*; *SLC2A2*; *AHSG*; *SST*
5	5p13-p15	8	(Barral et al., 2015; Blacker et al., 2003; Curtis et al., 2001; Kunkle et al., 2016; Lee et al., 2006; Myers et al., 2002; Olson et al., 2002; Pericak-Vance et al., 2000)	1.4–2.8	*SLC6A3*; *PRKAA1*
8	8p22-p21.1	2	(Butler et al., 2009; Lee et al., 2008)	> 2.0	*NAT1*; *NAT2*; *LPL*; *ADRA1A*; *CHRNA2*; **CLU**
	8q22.3	2	(Cummings et al., 2012; Kunkle et al., 2016)	0.9-3.6	*DPYS*
9	9p21-9p22.1	6	(Curtis et al., 2001; Hamshere et al., 2007; Kunkle et al., 2016; Myers et al., 2002; Pericak-Vance et al., 2000; Scott et al., 2003)	> 1.0–4.6	*IFT74*
	9q22-q34	9	(Barral et al., 2015; Blacker et al., 2003; Curtis et al., 2001; Hamshere et al., 2007; Holmans et al., 2005; Lee et al., 2006; Myers et al., 2002; Olson et al., 2002; Pericak-Vance et al., 2000)	1.6–4.2	*FBP1*; *GOLM1*; *ABCA1*; *DFNB31*; *TLR4*; *NDUFA8*; *PSMB7*; *HSPA5*; *POMT1*; *DBH*; *RXRA*; *TRAF2*; *ABCA2*
10	10q21-q22	7	(Blacker et al., 2003; Curtis et al., 2001; Hamshere et al., 2007; Holmans et al., 2005; Liu et al., 2007; Myers et al., 2002; Olson et al., 2002)	1.8–4.2	*ZWINT*; *UBE2D1*; *TFAM*; *BICC1*; *ANK3*; *CDC2*; *EGR2*; *CTNNA3*; *LRRTM3*; *DNAJC12*; *SIRT1*; *SRGN*; *SUPV3L1*; *TSPAN15*; *VPS26A*; *HK1*; *TACR2*; *NEUROG3*; *SAR1A*; *SGPL1*; *PSAP*; *CHST3*; *PPP3CB*; *SEC24C*; *NDST2*; *CAMK2G*; *PLAU*; *VCL*; *AP3M1*; *MYST4*; *KCNMA1*
11	11q12.1-q14.1	2	(Barral et al., 2015; Kunkle et al., 2016)	1.0–4.7	*CNTF*; *CHRM1*; *RTN3*; *GSTP1*; *GAL*; *FADD*; *INPPL1*; *UCP2*; *GAB2*; **PICALM**
12	12p11-p13	4	(Curtis et al., 2001; Holmans et al., 2005; Myers et al., 2002; Pericak-Vance et al., 1997)	1.4–3.9	*TNFRSF1A*; *CNAP1*; *GAPDH*; *GNB3*; *C1R*; *APOBEC1*; *MMP3*; *A2M*; *PZP*; *A2MP*; *OLR1*; *LRP6*; *GRIN2B*; *GYS2*; *ABCC9*; *PKP2P1*
14	14q12-q13.3	2	(Barral et al., 2015; Kunkle et al., 2016)	2.1-3.9	*CTSG*; *NFKBIA*
19	19q12-q13.33	10	(Blacker et al., 2003; Butler et al., 2009; Curtis et al., 2001; Hamshere et al., 2007; Holmans et al., 2005; Kunkle et al., 2016; Li et al., 2002; Myers et al., 2002; Olson et al., 2002; Pericak-Vance et al., 2000; Sillen et al., 2008)	1.6–7.7	*LRP3*; *USF2*; *GAPDHS*; *PSENEN*; *AKT2*; *TGFB1*; *LIPE*; *XRCC1*; *BCL3*; **APOE**; *PVRL2*; *TOMM40*; *APOC1*; *APOC2*; *ERCC2*; *CARD8*; *GYS1*; *LHB*; *CD33*; *NR1H2*
21	21q21-q22	4	(Blacker et al., 2003; Holmans et al., 2005; Myers et al., 2002; Olson et al., 2002)	1.6–4.5	*PRSS7*; *NCAM2*; *APP*; *C21ORF63*; *C21ORF55*; *RUNX1*; *DYRK1A*; *KCNJ6*; *BACE2*

Notes: Chr = chromosome; Bolded gene names are known GWAS signals with genome-wide statistical significance

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Table 2

Genomic risk loci for sporadic/late-onset Alzheimer's disease observed in linkage and/or association studies (adapted from Chouraki and Seshadri (2014) and Guerreiro and colleagues (2013a))

Locus	Variant	Chr	Position (bp) (hg19)	Effect/Alt Alleles	Effect Allele Freq	OR (95% CI)	Potential Biological Process or Pathways Affected	References
Common risk loci identified through linkage								
APOE	rs429358/C112R	19	45411941	ε4/(ε3/ε2)	0.14	~2 to 5	Cholesterol/lipid metabolism	(Corder et al., 1993; Saunders et al., 1993; Strittmatter et al., 1993)
	rs7412/C158R	19	45412079					
Common risk loci identified through GWAS								
CR1	rs6656401	1	207692049	A/G	0.20	1.18 (1.14–1.22)	Immune and complement systems/ inflammatory response	(Lambert et al., 2009)
BIN1	rs6733839	2	127892810	T/C	0.41	1.22 (1.18–1.25)	Synaptic vesicle endocytosis	(Seshadri et al., 2010)
INPP5D	rs35349669	2	234068476	T/C	0.49	1.08 (1.05–1.11)	Immune response and inflammation; APP metabolism	(Lambert et al., 2013b)
MEF2C	rs190982	5	88223420	G/A	0.41	0.93 (0.90–0.95)	Immune response and inflammation; Hippocampal synaptic function	(Lambert et al., 2013b)
HLA-DRB1/5	rs9271192	6	32578530	C/A	0.28	1.11 (1.08–1.15)	Immune response and inflammation	(Lambert et al., 2013b)
CD2AP	rs10948363	6	47487762	G/A	0.27	1.10 (1.07–1.13)	Receptor endocytosis and cytokinesis	(Hollingworth et al., 2011; Naj et al., 2011)
NME8	rs2718058	7	37841534	G/A	0.37	0.93 (0.90–0.95)	Cytoskeletal function and axonal transport	(Lambert et al., 2013b)
ZCWPW1	rs1476679	7	100004446	C/T	0.29	0.91 (0.89–0.94)	Epigenetic regulation	(Lambert et al., 2013b)
EPHA1	rs11771145	7	143110762	A/G	0.34	0.90 (0.88–0.93)	Immune and complement systems/ inflammatory response	(Hollingworth et al., 2011; Naj et al., 2011)
PTK2B	rs28834970	8	27195121	C/T	0.37	1.10 (1.08–1.13)	Hippocampal synaptic function; cell migration	(Lambert et al., 2013b)
CLU	rs9331896	8	27467686	C/T	0.38	0.86 (0.84-0.89)	Immune and complement systems/ inflammatory response; cholesterol/lipid metabolism	(Harold et al., 2009; Lambert et al., 2009)

Locus	Variant	Chr	Position (bp) (hg19)	Effect/Alt Alleles	Effect Allele Freq	OR (95% CI)	Potential Biological Process or Pathways Affected	References
CELF1	rs10838725	11	47557871	C/T	0.32	1.08 (1.05–1.11)	Cytoskeletal function and axonal transport	(Lambert et al., 2013b)
MS4A (gene cluster)	rs983392	11	59923508	G/A	0.40	0.90 (0.87-0.92)	Immune and complement systems/ inflammatory response	(Hollingworth et al., 2011; Naj et al., 2011)
PICALM	rs10792832	11	85867875	A/G	0.36	0.87 (0.85–0.89)	Clathrin-mediated endocytosis	(Harold et al., 2009)
SORL1	rs11218343	11	121435587	C/T	0.039	0.77 (0.72–0.82)	Endocytosis and cargo sorting (trafficking and metabolism of APP), lipid transport	(Lambert et al., 2013b)
FERMT2	rs17125944	14	53400629	C/T	0.092	1.14 (1.09–1.19)	Angiogenesis, Tau pathology	(Lambert et al., 2013b)
SLC24A4- RIN3	rs10498633	14	92926952	T/G	0.22	0.91 (0.88–0.94)	Possible cardiovascular link	(Lambert et al., 2013b)
ABCA7	rs4147929	19	1063443	A/G	0.19	1.15 (1.11–1.19)	Cholesterol/lipid metabolism; Immune and complement systems/inflammatory response	(Hollingworth et al., 2011; Naj et al., 2011)
CASS4	rs7274581	20	55018260	C/T	0.083	0.88 (0.84–0.92)	APP and Tau pathology; Cytoskeletal function and axonal transport	(Lambert et al., 2013b)
Rare Variant Risk Loci								
APP	rs63750847/A673T	21	27269932	A/G	0.0045	21	Neuronal Differentiation/Amyloid cascade	(Jonsson et al., 2012)
TREM2	rs75932628/R47H	6	41129252	T/C	0.0063	2.26 (1.71–2.98)	Immune response; chronic inflammation	(Guerreiro et al., 2013b; Jonsson et al., 2013)
Risk loci from GWAS independently replicated								
TREML2	rs9381040	6	41154650	C/T	0.30.	0.93 (0.91–0.96)	Inflammation regulation	(Benitez et al., 2013)
TRIP4	rs74615166	15	64725490	C/T	0.02	1.31 (1.17–1.42)	Immune response; endocrine processes	(Ruiz et al., 2014)
Potential AD loci from GWAS not yet replicated								
ACE	rs138190086	17	61538148	A/G	0.011	1.34 (1.20–1.50)	Regulates blood pressure; part of the renin-angiotensins system	(Lambert et al., 2013b)
Potential AD loci with inconsistent associations								
CD33	rs3865444	19	51727962	A/C	0.31	0.94 (0.91–0.96)	Immune and complement systems/ inflammatory response	(Hollingworth et al., 2011; Naj et al., 2011)

Locus	Variant	Chr	Position (bp) (hg19)	Effect/Alt Alleles	Effect Allele Freq	OR (95% CI)	Potential Biological Process or Pathways Affected	References
DSG2	rs8093731	18	29088958	C/T	0.017	0.73 (0.62–0.86)	Mediates cell-cell junctions between multiple cell types	(Lambert et al., 2013b)
PLD3	rs145999145	19	40877595	A/G	0.060	2.75 (2.05–3.68)	Hydrolysis of membrane phospholipids; APP processing	(Cruchaga et al., 2014)