HHS Public Access

Author manuscript

Curr Neurol Neurosci Rep. Author manuscript; available in PMC 2018 August 21.

Published in final edited form as:

Curr Neurol Neurosci Rep. ; 17(10): 78. doi:10.1007/s11910-017-0787-1.

Genetics of Alzheimer's Disease: the Importance of Polygenic and Epistatic Components

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Abstract

Purpose of Review—We aimed to summarize the recent advances in genetic findings of Alzheimer's disease (AD), focusing on traditional single-marker and gene approaches and non-traditional ones, i.e., polygenic and epistatic components.

Recent Findings—Genetic studies have progressed over the last few decades from linkage to genome-wide association studies (GWAS), and most recently studies utilizing high-throughput sequencing. So far, GWASs have identified several common variants characterized by small effect sizes (besides *APOE-ε*4). Sequencing has facilitated the study of rare variants with larger effects. Nevertheless, missing heritability for AD remains extensive; a possible explanation might lie in the existence of polygenic and epistatic components.

Summary—We review findings achieved by single-marker approaches, but also polygenic and epistatic associations. The latter two are critical, yet-underexplored mechanisms. Genes involved in complex diseases are likely regulated by mechanisms and pathways involving many other genes, an aspect potentially missed by traditional approaches.

Keywords

GWAS; Next-generation sequencing; Polygenic risk score; Epistasis

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Compliance with Ethical Standards

Conflict of Interest Neha Raghavan and Giuseppe Tosto each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Introduction

Alzheimer's disease (AD), the most common neurodegenerative disease, affects more than 5 million older adults in the USA alone [1]. Clinically, AD is characterized by decline in cognition, especially memory, although there is great heterogeneity in its clinical presentation and progression [2]. Neuropathologically, extracellular amyloid plaques and intra-cellular neurofibrillary tangles are present and neurodegeneration results from neuronal death and loss of synapses. Both environmental and genetic factors are thought to impact the disease risk profile. The genetic heritability, or impact of genetic variability on disease risk, of AD is predicted to be as high as 80% [3, 4]. Since the early 1990s, the field has had a number of successful breakthroughs shedding light on the genetics that contribute to disease risk. In this review, we provide an overview of the genetic findings in AD research, with a focus on recent advances and promising methodologies that may help researchers identify components of the heritability that are yet unknown.

Based on the age of onset, AD has been traditionally delineated as early-onset (EOAD, onset < 65 years old) or late-onset (LOAD, onset > 65 years old). The distinction is not only age-dependent as there are underlying separate but overlapping etiologies, genetics, and clinical presentations. EOAD accounts for only approximately 1–6% [5, 6] of AD cases. These forms are more likely familial and inherited in a Mendelian fashion; in the early 1990s, linkage analyses determined the loci mainly implicated in these forms, the amyloid precursor protein (*APP*), presenilin1 (*PS1*), and presenilin 2 (*PS2*) genes, which harbor highly penetrant rare variants. More than 300 variants have been identified to date ($N = 67$; 230; 39, respectively [7]. The discovery of these genetic determinants provides considerable weight to the "amyloid hypothesis," which predicts that dysregulated Aβ precipitates the development of the disease and potentially affects its progression [8].

On the other hand, the later onset form of the disease constitutes approximately 95% of AD cases [9]. LOAD is considered to be sporadic in nature, with complex genetic and environmental risk factor profile. This review will focus predominantly on this form of the disease. In 1993, genetic analysis identified *APOE* as a major genetic risk factor for LOAD [10]. The ε4 allele of *APOE* has the largest genetic effect, and has been replicated extensively across different forms of the disease (sporadic and familial LOAD [10, 11••], APP/presenilin mutation carriers [12], and across ethnic groups [13••, 14, 15••]). It has an attributable risk of approximately 25% [16], with *ε*4 homozygotes showing an odds ratio up to 20 when compared to that of *ε*3 homozygotes [17]; furthermore, one allele of *ε*4 reduces the disease onset up to 5 years, and two copies up to 10 years. For ~ 15 years, *APOE* was the only established locus for LOAD. However, with the advent of genome-wide association studies (GWAS) and whole-exome/genome sequencing, several additional loci have now been identified.

GWAS

Early Studies

In the last 15 years, GWASs have contributed to the majority of our genetic knowledge of LOAD. Over time, sample sizes have increased and biological and statistical methodologies

have improved, resulting in a steady progression of genetic findings. Significance for genetic studies is typically set to $p < 5 \times 10^{-8}$. In 2004, the first two LOAD GWASs resulting in significant findings confirmed the *APOE* locus as a significant risk factor [18, 19]. Following this discovery, subsequent GWASs were plagued by difficulty in finding novel, non-*APOE* loci, likely due to (1) small sample sizes, (2) small effect sizes of the yet-to-be-discovered markers, and (3) low coverage of genome-wide markers by the genotype chip employed. Nonetheless, 2 years later, two GWASs were published reporting genome-wide significance of *CLU* [20, 21]. In addition, these reports identified *CR1* [20] and *PICALM* [21] as additional susceptibility loci. In 2010, *CLU* and *PICALM* were identified again, while additionally identifying *BIN1* and a locus including *XOC3L2*/*MARK4*/*BLOC1S3* [22]. The next year, the Alzheimer's Disease Genetic Consortium (ADGC) newly identified additional risk loci: *MSA4A*, *CD2AP*, *CD33*, *EPHA1*, and replicated *CR1*, *CLU*, *BIN1*, and *PICALM* [23]. A companion paper found significant risk association with *ABCA7*, *MS4A6A*/*MS4A4E*, *CD33*, *CD2AP*, and replicated previous results with *EPHA1* [24].

International Genomics of Alzheimer's Project

The highest-powered GWAS to date was performed by the International Genomics of Alzheimer's Project (IGAP) in 2013 [13••]. Data were incorporated from four separate consortia: ADGC, the Cohorts for Heart and Aging Research Consortium (CHARGE), the European Alzheimer's Disease Initiative (EADI), and the Genetic and Environmental Risk in Alzheimer's Disease (GERAD) Consortium for their stage 1 meta-analysis. Together, this study included 17,008 cases and 37,154 controls. Fourteen genomic regions, in addition to the *APOE* locus, were identified in this stage. In stage 2, 11,632 single nucleotide polymorphisms (SNPs) from the genomic regions prioritized in stage 1 were genotyped in an independent sample of 8572 cases and 11,312 controls. In the end, in addition to further confirming the previous susceptibility genes (*ABCA7*, *BIN1*, *CD2AP*, *CLU*, *CR1*, *EPHA1*, *MS4A6A*, *PICALM*, *APOE4*), 11 new loci were identified: *SORL1*, *CASS4*, *FERMT2*, *HLA-DRB5-DRB1*, *INPP5D*, *MEF2C*, *CELF1*, *NME8*, *PTK2B*, *SLC2A4*, and *ZCWPW1*. Although some of these were not previously implicated in LOAD, others such as *SORL1* have been previously studied in relation to LOAD based on biological evidence, with confirmation results through target-gene genetic studies [25, 26].

Implicated Pathways

Although the functional consequences of all LOAD risk genes have not been fully resolved, many of them cluster into a few major biological pathways. The consideration of these pathways can aid our understanding of genes that may work together to affect the disease state, create a framework for the pathophysiology of the disease, and guide exploration into related targets. Proteins encoded by the identified genes tend to fall in more than one pathway: *APOE*, *CLU*, *CR1*, *PICALM*, *BIN1*, and *ABCA7* are part of the amyloid pathway; *CR1*, *EPHA1*, *ABCA7*, *MS4A4A*/*MS4A6E*, *CD33*, and *CD2AP* fall into the inflammation/immune system pathways. *APOE*, *CLU*, a *ABCA7* nd are part of lipid transport and metabolism pathways; *CLU*, *PICALM*, *BIN1*, *EPHA1*, *CD33*, and *CD2AP* in synaptic cell functioning/endocytosis pathways [27, 28]. The HLA locus, which plays a central role in the immune system, showed a strong associations at *DRB1* and *DRB5* paralogues (i.e., the genetic result of a duplication event), which encode for genes expressed in antigen-

presenting cells, and whose protein products bind antigens accessing the endocytic route whereby cells internalize extracellular matter. *SORL1* is intimately involved in the APP pathway, playing a role in the determination of APPs cleavage to Abeta [25]. *PTK2B* is a focal adhesion kinase, involved in cellular adhesion, expressed in the brain, and was also found to be an in vivo modulator of Tau toxicity [29]. *MEF2C* is also expressed in the cortex and known to be involved in the inflammation pathway; an assay of *MEF2C* binding sites was enriched in GWAS-implicated inflammation loci [30].

Differences in the Genetic Architecture of LOAD Between Ethnic Groups

African Americans and Caribbean Hispanics are approximately two to three times as likely as non-Hispanic Whites to develop LOAD [31, 32]; however, the majority of GWAS and sequencing LOAD studies have been concentrated in the non-Hispanic White population. There is evidence that the genetic architecture, or the contribution of individual genes and alleles to overall risk of the disease, differs between the groups [33]. For example, the effect of the *APOE ε4* allele on LOAD risk is considerably higher in non-Hispanic Whites than that of African Americans [32, 34]. However, heritability rates for the disease are thought to be similar across ethnic groups [35]. Thus, the variability of the genetic profile impacts the disease similarly between ethnic groups, but the weight of specific genes and their variants is likely to be different. To this effect, research thus far indicates that risk genes for LOAD, discovered primarily through research of non-Hispanic White subjects, also confer risk in African American and Caribbean Hispanic individuals [14, 36, 37••].

In a study of persons of Caribbean Hispanic descent, a novel locus on chromosome 5, *FBXL7*, met genome-wide significance [15••]. While the exact role of *FBXL7* is still unknown, F-box proteins, of which *FBXL7* is a member, are thought to be involved in cell growth, survival, and cell death [38]. This study along with a report by Lee et al. also confirmed several risk loci as nominally significant in non-Hispanic Whites: *CLU*, *PICALM*, *BIN1*, *CD33*, *FERMT2*, *CELF1*, *SLC24A4-RIN3*, and *ABCA7* [15••, 33]. Further, in a GWAS of African Americans, *ABCA7* was found to be genome-wide significant, and *CR1*, *BIN1*, *EPHA1*, and *CD33* [37••, 39] were replicated as well.

While the risk of several loci differs between ethnic groups, others show a more homogenous risk profile in genetically diverse populations. Trans-ethnic metanalyses have been employed in order to identify loci associated with LOAD across different ethnic groups. For example, a GWAS in persons of Korean, Japanese, and Caucasian descent found genome-wide significance with *SORL1* [40]. Also, a recent investigation in Europeans, African Americans, Japanese, and Israeli-Arabs found *PFDN1/HBEGF*, *USP6NL*/*ECHDC3*, and *BZEAP1-AS1* were genome-wide significant [41].

As is evidenced by the increase of genetic risk discoveries for LOAD over the years, collaboration between groups bolstering sample size is crucial to uncovering new genetic discoveries. In addition, studies with larger sample sizes in non-Caucasian populations will help increase our understanding of the genetic architecture that is shared between populations vs. specific to each ethnic group. It is important to keep in mind that standards should be set in place for every step of the research process, including diagnosis, sample collection, genotyping, and statistical analysis to help reduce spurious findings in the data.

New Findings from Next-Generation Sequencing—Although GWAS has played an important role in the discovery of LOAD risk variants, its discovery power is limited due to the design of the study. Firstly, GWAS is primarily limited to capturing common variants, with minor allele frequencies (MAFs) in the general population greater than one/5%. These common variants fall mostly in intergenic or intronic regions with mostly unknown functional effects. Most of the identified loci are common in the population and characterized by small effect sizes (by definition, an odds ratio < 1.5) [24, 42]. Moreover, signals identified by GWAS are believed to either tag the causative common coding variants or to show "synthetic associations" [43], whereby less common causal variants that tend to occur along with one allele of a common SNP lead to overattribution of the causal role of the common SNP. It has been postulated that low-frequency (MAF < 5%) and rare (MAF < 1%) functional variants may be the missing components in the search for unaccounted heritability in a number of complex diseases, including LOAD [42, 44–47]. Although the "common-disease-common-variants" hypothesis that postulated that the heritability component of common diseases should be variants common in the population was once in strong favor, recent findings support a spectrum of variant frequencies that contribute to this common disease, with functional, rare variants falling into this continuum. While rare in the population, these variants are more likely to fall in exonic regions and produce functionally deleterious effects [48]. Next-generation sequencing methods such as whole-exome sequencing (WES) and whole-genome sequencing (WGS) allow for identification of de novo and rare variants. Recently, studies employing next-generation sequencing have identified rare genetic variants within regions prioritized by GWAS [49–51] along with novel variants in previously unidentified genes [52••, 53••, 54•, 55].

Notably, two large, independent studies concurrently reported an association of a rare variant found in *TREM2* [52••, 53••], encoding the triggering receptor expressed on myeloid cells [56]. *TREM2* is known to be involved in microglial response and inflammation. The Arg47His SNP resulted in a large OR (~ 5) in a North American/European population [52••] and an OR of 2.92 in an Icelandic population [53••]. *Trem2* showed significantly greater expression corresponding to rises in brain levels of beta amyloid in a mouse model of AD. The Arg47His SNP and others have been replicated in subsequent studies [57, 58].

In another example, by first utilizing WES data from families multiply affected with LOAD, Cruchaga et al. identified a low-frequency variant (Val232Met:MAF ~ 0.3%) in the phospholipase D3 gene (*PLD3*) segregating with the disease in two independent families. The authors subsequently validated this variant in sporadic LOAD employing more than 11,000 cases and controls [54•]. The variant was associated with AD risk (OR = 2.1) and lower age at onset. *PLD3* is highly expressed in the hippocampus and cortex, but expressed significantly less in neurons from AD brains. Knockdown of *PLD3* significantly increases extracellular Abeta42 and Abeta40. While these findings are encouraging, efforts to replicate this finding were unsuccessful [59–61], only marginally significant [62], or significant but with a smaller odds ratio [63], ultimately requiring further investigation into the causative role of the gene in AD.

While *SORL1* has been replicated as a LOAD risk gene since 2007 using GWAS, the potential deleterious mutations responsible of such association have been more elusive to

identify. In a targeted sequencing study of both families and case controls, 17 coding exonic variants were found significantly associated with LOAD [50]. Two of the rare variants identified segregated within families. Accompanying functional studies demonstrated increased Abeta40 and Abeta42 secretion when these variants were transfected into cell lines.

A recent probe into GWAS-identified LOAD risk genes found an excess of deleterious coding mutations in *ABCA7* and *BIN1* [49]. Recently, research efforts have identified additional rare variants in novel genes; these studies still need to be validated with follow-up studies. Sequencing in a multiply-affected family found a rare, missense variant in *TTC3* that was shared in all affected members of the family [64]. A rare variant in the gene *TM2D3* was enriched in Icelanders with LOAD and identified as a functionally damaging allele [65]. Two variants in tight linkage disequilibrium in *AKAP9* were found to be associated with LOAD in African Americans [66]. A rare coding mutation in the netrin receptor gene *UNC5C* was significantly associated with LOAD in a sample with European background and in vitro studies showed more cell death in human cells and rodent neurons possessing this variant [67].

Beyond the Single-Variant and Single-Gene Approach in Alzheimer's Disease—While tremendous progress has been made in the understanding of the genetic landscape of LOAD, the relationship between the genes and variants contributing to the risk of the disease remains unclear. As described earlier, a number of implicated genes fall within similar molecular pathways; however, most models of AD risk do not consider the effects of harboring multiple variants. Indeed, some of the disease's missing heritability could be explained by the additive and multiplicative effects of the associated genes with one another. The establishment of an epidemiological framework integrating these heretofore independent findings will assist in a more comprehensive understanding of genetic risk for disease. The current efforts towards this goal have focused on two main heuristics. The first is an additive model, calculating a score based on an individual's genetic profile that can help predict risk, and the second is a multiplicative model of relationships between genes ("epistasis").

Genetic Risk Scores Predict Alzheimer's Disease Risk and Clinical Progression—In addition to the large effect of *APOE* on LOAD risk, more than 20 GWAS loci have been shown to be associated with LOAD risk. Polygenic risk scores attempt to create a more comprehensive model by aggregating sparse information across multiple variants into a unique risk score. Genetic risk scores derived from GWAS have been utilized successfully in a number of diseases such as multiple sclerosis, height and rheumatoid arthritis, after their success was demonstrated in schizophrenia by the International Schizophrenia Consortium [68]. Scores are computed by accounting for the presence of disease-associated alleles per individual and aim to add predictive power to AD risk models. These scores may increase the predictive capabilities of genotyping, and eventually may serve as a tool for personalized disease for an individual. Table 1 describes the major findings from recent studies of LOAD polygenic risk scores.

Most LOAD risk scores developed over the last few years rely heavily on SNP effect sizes and significance values originating from the IGAP GWAS. However, varied methodologies have been employed to compute a score that will explain the greatest amount of AD risk variability. The greatest methodological difference lies in the criteria used for SNP inclusion, resulting in scores that range greatly in the number of SNPs in the model. While the computation of many of these scores counts, just the SNPs that reached genome-wide significance in the IGAP study (i.e., 21 SNPs) [71, 72, 76•], others include many more loci. One recent study, for example, included more than 87,000 SNPs, employing all SNPs with a LOAD association *p* value less than 0.05 [70•]. Although such a low threshold for inclusion may add noise within the model, the authors hypothesize that higher power can be achieved by including more SNPs that confer even low-level risk.

In addition to the confirmation of the association between such scores and AD, age of onset has also been found to consistently decrease as the polygenic score increases [71, 74, 75, 76•]. Naj et al. found that while *APOE* contributes to 3.9% of variation at age of onset, nine other IGAP SNPs together contribute to additional 1.1% variation [77]. The scores are also associated with clinical progression to AD and can predict progression from healthy controls [70•, 73, 75] or MCI [69] to AD. In addition, there is a relationship between higher score values and worsening behavioral and neuroimaging endophenotypes of the disease [73].

The predictive power of the scores is not extremely high, with values ranging between 57 and 78%. However, Escott-Price et al. posit that given the constraints of what is known about the heritability and prevalence of Alzheimer's disease, area under the curves (AUCs) near 0.78 may capture close to 90% of what can actually be predicted for LOAD risk [78]. It should be noted that the inclusion of *APOE* locus in all models increases the predictive accuracy of the scores. In two studies, the AUC increases by approximately 0.10 when *APOE4* is added to the model, this large increase is not surprising given the known high effect size of *APOE4* [70•, 71]. While it is clear that *APOE* plays a large role in the effect of these scores, nonetheless, the addition of polygenic risk further strengthens the models [72, 75, 77] by adding to the predictive power.

Polygenic risk scores, which aim to predict risk based on the risk variant profile per individual, will be important in identifying subjects at high risk for developing AD and aid in the timely diagnosis of those affected by the disease. Moving forward, it will become important for the field to converge on an established polygenic score model by testing across different cohorts to aid in reproducibility of results.

Epistasis—While polygenic scores additively account for the independent risk effects on the disease across multiple loci, epistasis measures the interactive effects between one gene/variant and one or more other genes/variants. Thus, genetic epistasis captures effects that can be observed only when two or more genes interacts, while the latters' main effects can be absent. It is well established that genes constantly interact, and that these interactions are critical for gene regulation, signal transduction, biochemical networks, etc. Thus, if a locus is examined as a single entity, without acknowledging its potential interactions, its contributions in impacting the disease might be missed. Although of great potential interest, robust identification of gene-gene interactions has been relatively unsuccessful. Studies of

epistasis remain difficult because of both false positives and false negatives, which can arise from extensive multiple comparisons and low power, respectively. Typically, the detection of epistatic relationships is initiated through biological and/or statistical methods. While the concordance of evidence from both may lead to confidence in the model, statistical epistasis does not imply biological epistasis and vice versa. For example, the presence of a statistical epistasis may occur without the presence of a physical interaction between the genes. Here, we focus on statistical epistasis, in which the interaction of genetic variants is significantly associated with the phenotype, while the details of current biological epistasis in the context of LOAD are beyond the scope of this review.

Beginning in the early 2000s, two primary studies of epistatic relationships were reported. These showed an interactive effect in LOAD between genes falling in the interleukin pathway (*IL6* and *IL10*) [79], and another study reported significant findings between genes that are part of the iron transport pathway (*TF* and *HFE*) [80]. Both of these molecular mechanisms had been previously reported to be involved in LOAD, and later work replicated these interactions in independent samples [81, 82].

More recent epistastic findings between LOAD loci are shown in Table 2. Ebbert et al. reported significant interactions between variants within GWAS-identified LOAD genes: *CLU-MS4A4E* and *CD33-MS4A4E* [85] although only the CLU-MS4AE interaction was later replicated by an independent research group [88]. Searching for epistatic effects within known LOAD loci has uncovered genetic relationships associated with the disease's endophenotypes, or intermediate traits associated with the disease, such as amyloid deposition [84] and brain atrophy [87] as surrogated for AD. Other studies have restricted their investigation to specific sets of genes beyond those identified by GWAS. For example, when considering the vacuolar protein sorting 10 (VPS10) domain receptor family of genes, a set of loci extensively implicated in LOAD by functional and genetic investigations including sortilin, SorL1, SorCS1, SorCS2, and SorCS3, interactions were detected between *SORCS1*, *SORCS2*, and *SORCS3* [83].

Genome-wide exploration for epistatic effects has resulted in conflicting and rarely replicated results. Employing 13 data sets from the ADGC, Hohman et al. found a number of interactive effects including *SIRT1* × *ABCB1*, *PSAP* × *PEBP4*, and *GRIN2B* × *ADRA1A* [89]. However, the most validated epistatic finding in LOAD also came from a genome-wide interaction search in a large French cohort ($N \sim 9000$). An interacting SNP pair was found within the *KHDRBS2* and the *CRYL1* genes and was further replicated in an independent German cohort [86••]. These genes did not show any main effects, significant associations with AD on their own, and have not been previously associated with LOAD. Transcriptome analysis also revealed negative correlation between both genes' expression in the temporal cortex and cerebellum.

These studies have shown interactive effects in both genes widely known to be associated with LOAD and also in genes not previously shown to be associated with the disease. This latter group of genes is only significantly associated with AD as a part of an interaction gene pair, and therefore does not show any effect when analyzed singularly. Thus, epistatic effects

may explain both why some gene effects examined in isolation do not replicate, and also may explain a portion of the missing heritability of AD.

Conclusions

Alzheimer's disease research has advanced significantly over the last 25 years, and has benefitted from modern scientific advances, most recently including high-throughput sequencing of both the exome and the whole genome. In parallel, sample sizes have increased, and in turn, the power of studies has improved, allowing for new findings in GWAS. Importantly, continued collaborations between research groups and access to data will ensure consistency, replicability, and increased scientific findings. Novel methodologies will promote the discovery of polygenic and epistasis interactions and associations that explain what is yet unknown of the genetic heritability of Alzheimer's disease.

Acknowledgments

Dr. Tosto is supported by NIH grant R21AG054832

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Table 1

Recent studies of AD polygenic risk/hazard scores (PRS/PHS)

Study	No. of SNPs	Samples and/or methods used to create score	Main findings
Rodriguez-Rodriguez et al. (2013) [69]	8	• N/A[a]	• Score not associated with conversion from MCI to AD. • Score associated with more rapid rate of conversion in those who progressed from MCI to AD.
Escott-Price et al. (2015) [70•]	87,605	• SNPs w/AD association $p < 0.5$ within IGAP samples excluding GERAD	• AUC after inclusion of ε4, ε2, age, sex, 20 IGAP GWAS SNPs, and SNPs w/AD association $p < 0.5$ is 0.78
Sleegers et al. (2015) [71]	22	• IGAP meta-analysis loci excluding *DSG2* plus *APOE*, *TREM2*	• Score significantly associated with AD risk, (OR = 2.32, $p < 0.001$). • Greatest AUC 0.70, increasing to 0.78 in those with family predisposition
Chouraki et al. (2016) [72]	19	• IGAP meta-analysis loci, excluding *APOE*, *DSG2*, and *CD33*	• Score significantly associated with AD risk, especially in those with *APOE* ε4 (HR = 1.17, $p < 0.0001$) • Risk prediction showed improvement when score added to model of age, sex education, and *APOE* ε4
Mormino et al. (2016) [73]	16,123	Stage I IGAP SNPs $p < 0.01$ (this threshold was chosen due to its ability to discriminate between AD and controls on ADNI sample.)	• Score significantly associated with longitudinal memory and executive function. • Score significantly associated with progression to MCI or AD. • No significance found in these domains when restricting to IGAP loci only.
Marden et al. (2016) [74]	22	• IGAP meta-analysis loci plus APOE	• Score was significantly associated with memory decline.
Desikan et al. (2017) [75]	31	• Stepwise regression used to select SNPs within ADGC Phase 1 cohort	• Subjects in highest score quartile had lowest AAO and highest yearly incidence rate. • Score associated with neuropathology and biomarkers
Tosto et al. (2017) [76•]	21	• IGAP meta-analysis loci	• Score significantly conferred greater AD risk, best model (OR = 1.31, $p < 0.001$ White, OR = 1.73, $p < 0.001$ Hispanic). • AAO significantly associated with score. • Greatest AUC 0.59

ADNI Alzheimer's Disease Neuroimaging Initiative, *ADGC* Alzheimer's Disease Genetics Consortium, *IGAP* International Genomics of Alzheimer's Project, *GERAD* Genetic and Environmental Risk in Alzheimer's Disease, *AAO* age at onset, *AUC* area under the curve, *OR* odds ratio, *HR* hazard ratio

[a] SNPs chosen based on past studies, rationale not provided

Table 2

Recent studies involving epistastic relationship between genetic loci that contribute to AD or AD endophenotype risk

Study	Phenotype	Epistatic relationship	Statistics
Reitz et al. (2013) [83]	AD	4 LD blocks within *SORCS1*, *SORCS2*, and *SORCS3* demonstrate epistasis.	No epistasis met correction for multiple comparisons, but few interactions were higher than chance.
Hohman et al. (2013) [84]	Amyloid deposition	*BIN1* (rs744373)-*PICALM* (rs3851179)[a]	$p = 0.0252$
		BIN1 (*rs7561528*)-*PICALM* (*rs3851179*)	$p = 0.005$
Ebbert et al. (2014) [85]	LOAD	*CLU-MS4AE*	SF = 3.81; $p < 0.016$
		CD33-MS4AE	SF = 5.31, $p < 0.003$
Gusareva et al. (2014) [86••]	AD	KHDRBS2-CRYL1	$p = 0.006$; replication $p = 0.036$
Koran et al. (2014) [87]	Inferior lateral ventricle size, bilateral	SYNJ2-PI4KA	Right: $p = 9.13 \times 10^{-12}$ Left: $p = 8.17 \times 10^{-13}$
Ebbert et al. (2016) [88]	LOAD	*CLU-MS4AE*	SF = 2.23, $p = 0.0004$
Hohman et al. (2016) [89]	LOAD	SIRT1 × ABCB1	OR = 1.36, $p = 2.7 \times 10^{-9}$
		PSAP × PEBP4	OR = 1.25, $p = 1.1 \times 10^{-9}$
		GRIN2B × ADRA1A	OR = 0.77, $p = 6.67 \times 10^{-9}$

SF synergy factor, a metric of the strength of allelic interactions, *OR* odds ratio

[a] Interactions between 2 SNP sets in *BIN1-PICALM*