Hampel H, Carrillo MC (eds): Alzheimer's Disease – Modernizing Concept, Biological Diagnosis and Therapy.
Adv Biol Psychiatry. Basel, Karger, 2012, vol 28, pp 15–29

The Genetics of Alzheimer's Disease

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Abstract

As the most common form of dementia, Alzheimer's disease (AD) currently affects nearly 34 million people worldwide, with a prevalence of about 5.4 million cases in the United States alone. Given the rapid expansion of the aging population in developed countries, the global prevalence of AD cases is projected to triple in 40 years. The primary risk factor for AD is age, and it is estimated that roughly 1 in 8 Americans over the age of 65 have the disease. Besides age, there are several environmental factors that appear to influence risk of AD, including diet, physical activity, cognitive activity, obesity, hypertension, diabetes and smoking. However, the disease has long been known to disproportionally affect certain family lineages, and heritability estimates for the disease range between 60 and 80%. Until recently the search for genetic influences affecting AD risk remained a largely frustrating endeavor, with the exception of a few causal variants discovered in pedigrees exhibiting rare autosomal dominant forms of the disease. Current efforts to identify genetic risk factors for AD have been complicated by both clinical heterogeneity, where multiple manifestations of dementia are currently diagnosed as AD; and locus heterogeneity, which occurs when different families have different AD risk variants. Recent genome-wide association studies (GWAS) that have enrolled tens of thousands of case-control subjects have revealed a new wave of genetic markers that may better explain the genetic influences of AD and point to new insights in pathophysiology and therapeutic development.

Early Family Studies of Alzheimer's Disease

Affecting an estimated 34 million people worldwide, Alzheimer's disease (AD) is the most common form of dementia in adults [1–2]. While risk for developing the neurodegenerative disorder increases with age, the disease has long been known to disproportionally affect certain lineages and current heritability estimates for AD range between 60 and 80% [3]. The first genetic insights into the heritability of AD came from studying families with an autosomal dominant inheritance pattern (fig. 1) [4]. In addition to

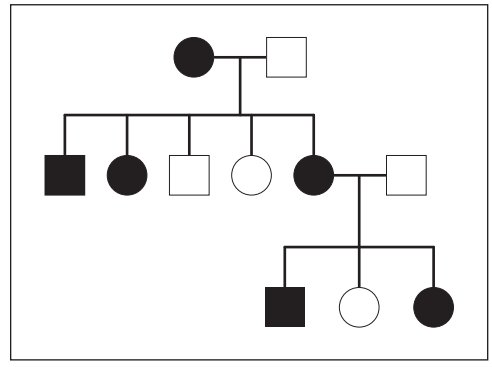

Fig. 1. In an autosomal dominant inheritance pattern the offspring of an affected parent have a 50% risk of developing the disease themselves.

having a clear mendelian inheritance pattern, affected individuals in these pedigrees were noted to manifest disease symptoms at a younger age, often before age 60, and sometimes as early as age 30 [5]. Using a technique known as linkage analysis (which identifies relatively broad chromosomal sections of DNA transmitted from parent to offspring that trend with inheritance patterns of the disease), researchers identified three genes with autosomal dominant mutations segregating with AD cases: amyloid precursor protein *(APP)*, presenilin 1 *(PSEN1)*, and presenilin 2 *(PSEN2)* [6]. Although mutations in these genes collectively account for much less than 1% of all AD cases, our understanding of basic AD pathology was substantially advanced by later studies involving these genes and their protein products [5, 7]. For example, subsequent experiments showed that certain mutations in these genes were associated with increased production of a particular isoform of the protein β-amyloid (Aβ) which has a propensity to aggregate in the intracellular space and eventually form the neuritic plaques first observed by some of the earliest neuropathologists studying AD [5, 8, 9]. The evidence from these and other functional studies surrounding *APP, PSEN1*, and *PSEN2* contributed to the development of the 'amyloid hypothesis' which postulates that the pathogenesis of AD is driven by an imbalance between the production and clearance of Aβ [4]. This theory and the biological roles of each of these genes are discussed below in further detail.

Amyloid Precursor Protein

Perhaps the most important of all the genes that were discovered from early genetic studies of autosomal dominant early-onset Alzheimer's disease (EOAD) is amyloid precursor protein (*APP*). Located on chromosome 21, *APP* encodes a ubiquitous transmembrane protein, which has been postulated to play a role in cell movement and cell adhesion [5, 9]. However, the gene is of particular importance to scientists engaged in AD research as it encodes the protein that is selectively degraded into Aβ. Degradation of APP occurs via two pathways: amyloidogenic and non-amyloidogenic

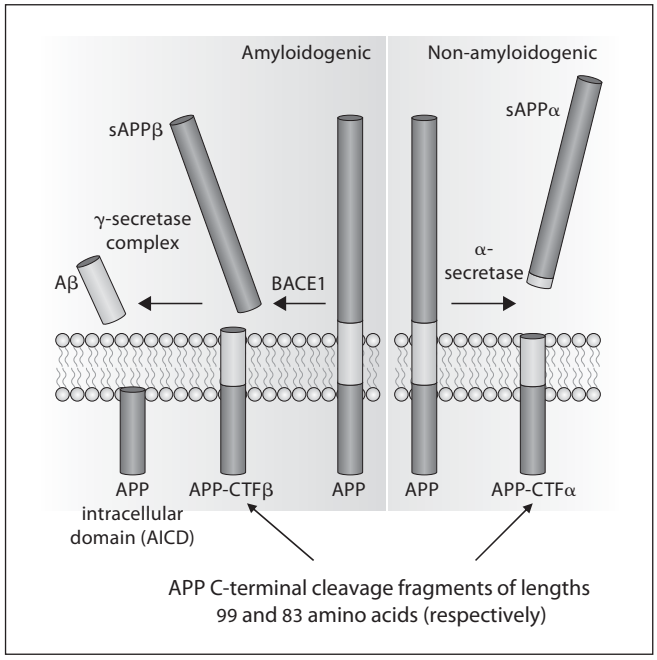

Fig. 2. APP degradation occurring via the amyloidogenic and non-amyloidogenic pathways.

(fig. 2). The amyloidogenic pathway for APP proteolysis is initiated by β-site amyloid precursor protein-cleavage enzyme 1 (BACE-1), resulting in the intermediate product sAPPβ. This segment is then further processed by the complex γ-secretase and the product of this reaction is Aβ [9]. By contrast, in non-amyloidogenic APP proteolysis, an α-secretase first cleaves APP at a different location, 83 amino acids from the C terminus. The location of this cleavage point prevents Aβ production, because it falls within the region of APP that would otherwise be processed into Aβ [9].

Other variables in the processing of APP also affect the formation and toxicity of Aβ monomers. Depending on where the γ-secretase cleaves the sAPPβ subunit, the resulting Aβ molecule will contain either 40 or 42 amino acids. While both of these molecules are present in normally functioning brain tissue, the longer isoform of Aβ is more hydrophobic than the more common $A\beta_{40}$ molecule, and consequently is more prone to aggregation [9, 10]. Autosomal dominant mutations within the *APP* gene have been shown to cause increases in net production of Aβ and elevated ratios of $A\beta_{42}$:$A\beta_{40}$, thus making it more likely for neuritic plaques to form and aggregate [10]. However, it is worth noting that while $A\beta_{42}$ molecules comprise the majority of the monomers found in amyloid plaques of AD patients, it is the small aggregates of oligomers and protofibrils, which may be comprised of either $A\beta_{40}$ or $A\beta_{42}$, that are considered the most neurotoxic forms of Aβ [9]. In particular, these more soluble aggregates of Aβ appear to be highly damaging to synapses, initiating dysfunctional events including (but not limited to) the endocytosis of N-methyl-D-aspartate (NMDA) surface receptors [11].

Table 1. Summary of EAOD attributed mutations

Gene	Mutations, n	Families, n
APP	32	89
PSEN1	185	405
PSEN2	13	22

From the Alzheimer Disease and Frontotemporal Dementia Mutation Database (www.molgen.vib-ua.be/ADMutations).

The Presenilins

Mutations within presenilin 1 and 2 (*PSEN1* and *PSEN2*) were also found to cause autosomal dominant patterns of AD transmission [12, 13]. Located on chromosomes 14 and 1, respectively, the two proteins are highly homologous, and either protein may be found (in conjunction with nicastrin, anterior pharynx defective 1, and presenilin enhancer 2) in the γ-secretase complex which enzymatically cleaves sAPPβ to produce Aβ. Mutations in either gene are also linked to an increased ratio of $A\beta_{42}$:$A\beta_{40}$ monomers [4, 5, 7, 10]. *PSEN1* mutations account for the largest proportion of autosomal dominant AD cases and functional studies associate mutations in *PSEN1* with increased production of $A\beta_{42}$. *PSEN1* has also been implicated in other processes that may be relevant to AD pathogenesis such as notch signaling [5, 7]. Pathological mutations in the *PSEN2* gene represent a much rarer portion of EAOD cases, with many *PSEN2* mutant carriers being related to a family known as the Volga Germans, a well-studied pedigree with an extensive history of AD [7, 13]. As with *PSEN1* mutations, *PSEN2* mutations are also associated with an increased ratio of $A\beta_{42}$:$A\beta_{40}$ in the brain, though mechanisms by which this change occurs are less clear [7].

It should be noted that the mutations in *APP, PSEN1*, and *PSEN2* have been documented in a relatively small number of families with a history of AD, and many mutations have only been observed in one or two pedigrees (table 1).

While the amyloid hypothesis is still at the forefront of many working models of AD, the development of Aβ aggregates is not the only conformational change that has been observed in the brains of AD patients or AD animal models. In addition to Aβ deposits, other changes in the brains of AD patients relative to those of non-demented age-matched controls include increased inflammatory response, oxidative stress, synaptic damage, neuronal death and hyperphosphorylation of tau particles leading to the development of neurofibrillary tangles [9, 11]. These observations coupled with the fact that the majority of AD cases do not follow a mendelian-dominant inheritance pattern are reminders of the need for further genetic explanations for the disease beyond *APP* and the presenilins.

Table 2. Environmental risk factors for AD (modified from Barnes and Yaffe [2])

	Population prevalence, %	Relative risk odds ratio (95% CI)
Worldwide		
Diabetes mellitus	6.4	1.39 (1.17–1.66)
Midlife hypertension	8.9	1.61 (1.16–2.24)
Midlife obesity	3.4	1.60 (1.34–1.92)
Depression	13.2	1.90 (1.55–2.33)
Physical inactivity	17.7	1.82 (1.19–2.78)
Smoking	27.4	1.59 (1.15–2.20)
Low education	40.0	1.59 (1.35–1.86)
USA		
Diabetes mellitus	8.7	1.39 (1.17–1.66)
Midlife hypertension	14.3	1.61 (1.16–2.24)
Midlife obesity	13.1	1.60 (1.34–1.92)
Depression	19.2	1.90 (1.55–2.33)
Physical inactivity	32.5	1.82 (1.19–2.78)
Smoking	20.6	1.59 (1.15–2.20)
Low education	13.3	1.59 (1.35–1.86)

Early Linkage and Candidate Studies of Late-Onset Alzheimer's Disease

Late-onset Alzheimer's disease (LOAD) is by far the more common form of AD and typically is diagnosed in patients older than 65 years of age [5]. In contrast to EOAD, LOAD follows a non-mendelian, more complex inheritance pattern, but there is still a clearly heritable component [14, 15]. There are many challenges to identifying the genetic underpinnings of this more prevalent form of the disease, including inherent clinical heterogeneity of AD, whereby multiple manifestations of dementia are currently diagnosed as the same disease, and locus heterogeneity, which occurs when different families have different AD risk variants that cause a lack of fitness within distinct biological functions but result in the same phenotype in patients. In addition, experiments that are underpowered may fail to detect alleles with small to modest risk effects and are likely to produce false negatives in follow-up analyses [6]. Moreover, epidemiological studies have revealed several well-established environmental and biological risk factors influencing AD onset including patient histories of head trauma, depression, diabetes, level of educational training, physical and cognitive leisure activities, diet, and of course the most influential risk factor, age (table 2) [2, 16, 17].

In spite of these challenges, early linkage studies performed on Caucasian families with a history of LOAD consistently identified a strong linkage peak over the *APOE* region of chromosome 19 as being associated with AD risk [6]. These early linkage studies also identified several other non-*APOE* signals of inherited genetic risk for AD with consistently replicated linkage peaks on chromosomes 6, 9, 10 and 12 that

contained many biologically plausible genes which were later proposed for follow-up in candidate gene studies. Despite the strength of some of these signals, only the *APOE* gene on chromosome 19 has been definitively established as a risk factor for LOAD from this group of risk loci identified by linkage and other studies [6, 18, 19].

Moving beyond linkage analysis studies, new insights about AD pathogenesis emerging from cell biology and neurochemistry studies forwarded the advancement of *candidate gene association studies* for AD [8]. These studies tested for disease risk associations among known variants selected from a priori knowledge of the disease by comparing the differences in their allelic frequencies between cases and controls. Because cases and controls did not need to be related, candidate genes studies had the advantage over linkage analyses of not being restricted to family-based data. While these early association studies still lacked power to detect rarer variants influencing AD risk, a few genes did emerge from these efforts that have been replicated across multiple candidate gene studies. For example, there are two loci that have been robustly identified in candidate genes studies, namely neuronal sortilin-related receptor (*SORL1*) and the angiotensin converting enzyme (*ACE*), as well as apolipoprotein E (*APOE*) which was previously identified by linkage studies.

Sortilin-Related Receptor-1

Neuronal sortilin-related receptor (*SORL1*) is a protein trafficking gene that is most likely involved in AD pathogenesis via its interaction with APP. *SORL1* regulates the trafficking of APP from the plasma membrane to the retromer recycling endosome that eventually transports the molecule to the trans-Golgi apparatus (fig. 3) [20]. This processing pathway diverts APP from the amyloidogenic pathway, which reduces the production of Aβ. Genetic variations of *SORL1* are associated with a reduction in function of this trafficking protein and an increased risk for AD. Interestingly, variants at two distinct locations in this gene have been independently shown to influence AD risk. Thus, *SORL1* illustrates that intralocus heterogeneity is another challenge for identifying specific variants of interest in AD [19, 20].

Angiotensin Converting Enzyme

The angiotensin converting enzyme (*ACE*) is responsible for the production of angiotensin II (AT_2) by cleaving angiotensin I (AT_1), and is a well-known target of many antihypertensive drugs. The complete relationship between *ACE* and AD pathogenesis is still unclear, although its association with the disease may suggest a vascular component of AD etiology. It has also been suggested that *ACE* may be capable of cleaving Aβ proteins, offering a link between *ACE* and the amyloid hypothesis. However, this cleavage has only been observed thus far in vitro [21].

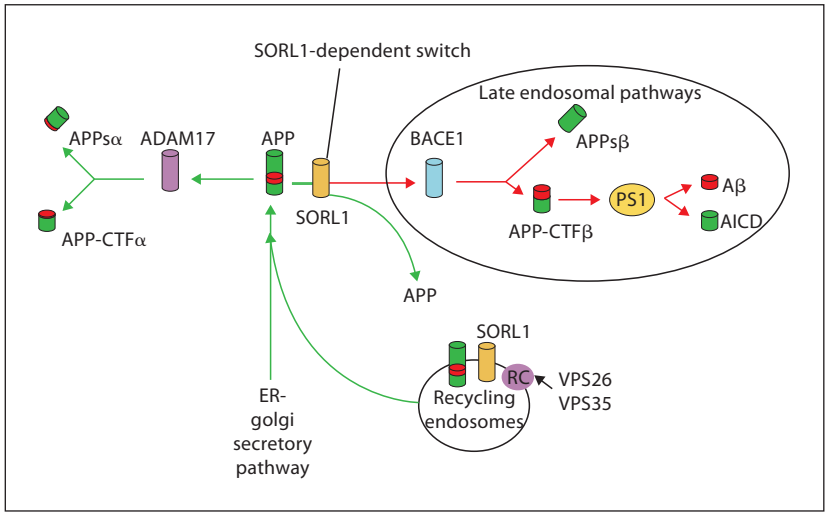

Fig. 3. *SORL1* regulates the trafficking of APP from the plasma membrane to the retromer recycling endosome that eventually transports the molecule to the trans-Golgi apparatus (from Rogaeva et al. [20]).

Apolipoprotein E

Apolipoprotein E (*APOE*) is the most widely studied and robust genetic risk factor for AD. First identified in linkage analysis peaks and then again in subsequent candidate gene studies, it is now known that there are three common isoforms of the gene that differ from each other at amino acid residues 112 and 158. The variants, labeled as ε2, ε3, and ε4 alleles, contain cysteine/cysteine, cysteine/arginine, and arginine/arginine residues and are found in the population at frequencies of 8, 77 and 15% respectively [22]. These substitutions affect both the charge and three-dimensional structure of the ApoE protein, and consequently many of its binding properties with other molecules. ApoE is a major determinant of lipid transport and is expressed throughout the body, though primarily in the liver and brain [22, 23]. Genetic association studies show roughly a 2- to 3-fold increased risk of AD associated with the presence of one ε4 allele and at least a 12-fold increased risk of AD for ε4 homozygotes, though these risk effects appear to vary in different ethnicities [18, 23]. In addition, other studies have shown that ε4 carriers have an earlier age of onset for the disease [24, 25]. Meanwhile, the rarer ε2 allele is thought to be protective for AD [26]. *APOE* genotype is among the more robust of susceptibility variants for common complex diseases and thus *APOE* disclosure has been a valuable model for examining the impact of disclosing such risk variants as described in more detail below [27–32].

The ε4 variant of *APOE* has been associated with nearly every major pathway important to AD pathology, including neurodegeneration and synaptic dysfunction (table 3), although many of these associations have not been consistently observed

Table 3. Effect of APOE genotype in AD pathology (modified from Leoni [22])

Events correlated with APOE genotype	Direction of effect in ε4 carriers
APP expression and production	+
Aβ aggregation and deposition	+
Tangle formation	+
Abnormal tau phosphorylation	+
Neuronal toxicity (by proteinase fragments)	+
Cholesterol efflux and uptake from astrocyte and neurons	–
Aβ processing and elimination	–
LRP1 and LDLR mediated Aβ clearance	–
Cholesterol transport and delivery	–
Anti-inflammatory action	–
Synaptic repair	–
Synaptic plasticity	–
Neurite outgrowth	–

(+) = Event/process is observed to increase in the presence of the ε4 allele.
(–) = Event/process is observed to decrease in the presence of the ε4 allele.

across experiments. However, some of the most robust findings are suggestive of ApoE's involvement in Aβ aggregation and clearance [22, 23]. Supportive evidence comes from studies showing that the ε3 variant has a higher affinity for Aβ than ε4 thereby better facilitating its removal from the extracellular space [33, 34]. While the accumulation of data from follow-up studies presents a highly convincing argument for ApoE's importance in AD pathogenesis, the protein's involvement in a wide variety of brain functions has the unfortunate affect of making its precise mechanistic role in AD more elusive. Furthermore, the ε4 variant of the gene is neither necessary nor sufficient for the development of AD. Thus, while the importance of *APOE* as a risk factor for AD is irrefutable, there are clearly heritable features beyond *APOE* and it does not come close to completely explaining the full genetic heritability of the disease [35].

Genome-Wide Association Studies and Consortia Efforts

While candidate gene studies have used a priori information to investigate hundreds of gene variations that might explain the inherited risk of AD, recent technology has facilitated the development of a more unbiased method to the search for novel genetic loci explaining AD risk. Microarray platforms can now assay over 5 million single nucleotide polymorphisms (SNPs) or genetic variants in each subject, and compare cases and controls in large genome-wide association studies (GWAS). Even given the impressive number of SNPs tested, the expectation of GWAS is not that researchers will directly identify the causal variant(s) behind AD pathology, but rather that the

coverage of the chip allows a researcher to detect a signal from SNPs that are in linkage disequilibrium with the causal variants. It is important to note this distinction, as it explains why the results of a GWAS do not provide detailed functional information about a particular variant. Instead, positive results from a GWAS tell us which variants occur at significantly different allelic frequencies between cases and controls, and may point us to the genes surrounding or near these variants.

Simultaneously testing millions of SNPs at a time is a huge technological achievement, but given that most studies enroll *only* a few thousand individuals, the interpretation of GWAS results presents a statistical challenge. To protect against false positive associations that might result from multiple testing, researchers typically impose a highly conservative threshold to declare genome-wide significance for a particular hit (typically a value of less than 5.0×10^{-8}). In recent years, approximately 15 large GWA studies exploring genetic associations for AD risks have been published [19]. While the *APOE* variant was found to be genome-wide significant in all but one of these studies, most of the other genome-wide significant findings were not consistently replicated across these analyses. The lack of fully replicable findings in any particular variant besides *APOE* in GWA studies suggests heterogeneous genetic influences are responsible for a large portion of AD cases [5].

GWAS Consortia

The majority of recently discovered gene associations were derived from large GWAS consortium efforts, where many collaborators studying the genetic influences of AD pooled their data and used meta-analysis of allele frequency patterns to amass greater statistical evidence for these genes' relevance to AD risk. Table 4 lists the top genetic variants (outside of *APOE*), which were described by these consortium efforts [36–41].

Even when a specific gene is identified through consortium efforts, the gene's direct involvement in disease pathology can be difficult to ascertain without functional data available for the protein it encodes. For example, it is suggested that bridging integrator 1 (*BIN1*) may be indirectly linked to AD pathology via its binding partner, dynamin 2, which has previously been associated with AD risk [8, 42]. However, it has also been hypothesized that the products of *BIN1* are involved in receptor-mediated endocytosis and thereby might play a role in the production and/or clearance of Aβ [8]. Similarly, the roles of two membrane-spanning domain proteins, *MS4A4A* and *MS4A6E*, are not clearly understood. However, it is posited that these genes affect signal transduction in the brain given their membership in the multimeric receptor complex [40]. Sometimes there are surprising findings. For example, ephrin type-A receptor 1 (*EPHA1*) has never been linked to a neurodegenerative disorder, but it has been previously implicated in brain cancers, suggesting a role in neuronal growth and development. In addition, a ligand of *EPHA1* (Ephrin-A2) has been associated with the non-amyloidogenic proteolytic pathway of APP [40].

Table 4. Top results from AD consortia

Gene symbol	Non-APOE genes identified	Large AD consortia studies	
CLU	clusterin	• Harold et al. [36] • Seshadri et al. [38] • Hollingworth et al. [39]	• Lambert et al. [37] • Naj et al. [40] • Jun et al. [41]
PICALM	phosphatidylinositol-binding clathrin assembly protein	• Harold et al. [36] • Hollingworth et al. [39] • Jun et al. [41]	• Seshadri et al. [38] • Naj et al. [40]
CR1	complement component receptor 1	• Lambert et al. [37] • Hollingworth et al. [39]	• Naj et al. [40] • Jun et al. [41]
BIN1	bridging integrator 1	• Seshadri et al. [38] • Hollingworth et al. [39]	• Naj et al. [40]
MS4A4A/ MS4A4E6	membrane-spanning 4-domains subfamily A members 4A and E6	• Hollingworth et al. [39]	• Naj et al. [40]
EPHA1	ephrin type-A receptor 1	• Naj et al. [40]	• Seshadri et al. [38]
CD33	myeloid cell surface antigen CD33	• Naj et al. [40]	
CD2AP	CD2-associated protein	• Naj et al. [40]	
ABCA7	ATP-binding cassette transporter-A7	• Hollingworth et al. [39]	

Pathways Consistently Implicated in AD Risk

The majority of the AD-associated genes that have been identified thus far through consortia efforts build upon previous hypotheses regarding AD pathogenesis and add to the body of evidence further implicating pathways such as inflammation, oxidative stress, protein trafficking and Aβ processing with the progression of AD. For example, clusterin (*CLU*) encodes an apolipoprotein which is expressed in the brain, and variants of the gene have been predicted to have pleotropic effects. Rat model experiments show *CLU* co-localizing in neuritic amyloid plaques, and other functional studies reveal evidence that *CLU* may be protective against oxidative stress, damage to cell membranes resulting from inflammation response, apoptosis, and the aggregation of hydrophobic unfolded proteins, like $A\beta_{42}$, all of which have been linked to AD progression [43].

Several of the consortia-identified genes, particularly *CR1* and *CD33*, support evidence of the immune system's involvement in AD. Mouse model studies have shown evidence that complement component receptor 1 (*CR1*) may play a role in clearance of Aβ via the complement system [44]. Meanwhile, the myeloid

cell surface antigen *CD33* has been reported to be involved in immune response-induced apoptosis [45].

Endocytosis is a critical process in synaptic transmission and response to neuronal damage, and lack of fitness in cellular endosomal protein trafficking has been linked to several neurodegenerative diseases [40]. Two genes from the collective work of the AD consortia provide strong supporting evidence for the importance of synaptic endocytosis relative to AD progression. The first gene, CD2-associated protein (*CD2AP*), is a scaffold adaptor protein that assists in the regulation of receptor-mediated endocytosis [39]. The second, phosphatidylinositol-binding clathrin assembly protein (*PICALM*), is involved in clathrin-mediated endocytosis, a process whereby several molecules including lipids, growth factors and neurotransmitters are shipped to various parts of the cell for further processing, secretion or degradation. It should also be noted that the associations of *BIN1, CD33* and *SORL1* with AD also support the importance of protein trafficking pathways in AD progression [5, 20].

Finally, the association with ATP-binding cassette transporter A7 (*ABCA7*) appears to strongly support the amyloid hypothesis. *ABCA7* is a transmembrane transporter protein that is highly expressed in the brain. Among other roles, it is involved with APP trafficking and inhibits Aβ production. It is also involved in the clearance of lipids from the cell and has been hypothesized to interact (either directly or indirectly) with *CLU* and *APOE* [39].

Conclusions and Future Directions of Genetic Research

Even with all of the exciting results from recent GWAS collaborations, there is a need for new methods to detect novel risk loci. Investigators have had some early success in applying gene-gene interaction models to tease out epistatic effects between known risk loci and AD progression [41]. Ongoing research regarding the gene-environment interactions that lead to AD progression also promises to elucidate more of the missing heritability thus far unexplained by markers implicated from previous genetic AD association studies [46]. Meanwhile, statistical tools that test for pathway enrichment in lists of the most prominently associated SNPs from GWA results are being developed and tested in other neurological disease datasets and may one day help to decipher broader pathway associations with AD risk [47, 48]. Such pathway insights, along with the discovery of recently identified risk genes, could be influential in the developments in AD treatment by suggesting new targets for drug therapies [49]. Beyond SNP data, researchers are also employing gene expression based technologies to advance our understanding of AD pathogenesis, as evidenced by data published from recent microarray experiments in human neuronal tissue [50] and siRNA knockdown experiments in animal models [51]. In addition, advances in next generation sequence technology (NGS) continue to

make whole-exome, whole-genome, and targeted deep sequence screens increasingly more affordable, which will expedite the discovery of the functional variants implicated by known risk markers identified in GWAS and other association studies [8]. Finally, new research investigating the epigenetics of AD promises to elucidate the role which structural changes in the neuronal DNA (i.e. via histone modification or methylation) play in promoting or inhibiting the manifestation of AD given an individual's genotype [52, 53].

Future progress in unraveling the genetic heterogeneity of the AD will likely allow neurologists and other clinicians to offer more effective therapies tailored to the specific genetic profiles of their patients. In fact, some studies have already raised the possibility of different therapeutic effects or side effects based on *APOE* genotype [54–56]. Popular interest in genetic tests for a wide variety of disease risks, including risk of AD, has stimulated the growth of direct-to-consumer genetic testing [57] and a tremendous interest in the impact of receiving genetic risk information. The Risk Evaluation and Education for Alzheimer's Disease Study (REVEAL) is a series of four separate multi-center randomized clinical trials that have collectively enrolled over 1,100 individuals in order to explore emerging themes in the disclosure of genetic information and health outcomes. This work has used the relationship between *APOE* and risk of AD to explore the quantitative development of risk estimates from epidemiological studies and in different ethnic groups [15, 58–60], the emotional impact of disclosing risk information about AD [28, 61, 62], the reasons individuals seek genetic risk information [63, 64], issues in self-perception of genetic risk for AD and how these change with genetic testing [30, 65–67], the degree to which participants recall and value their AD risk assessment results and discuss them with others [68–71], the degree to which genetic testing affects insurance purchasing [27, 72], and the degree to which genetic testing alters health behaviors [29, 73]. In summary, while GWAS consortia have recently interrogated multiple large datasets capable of detecting genes that could have a more subtle effect on AD risk, a genetic explanation for a sizable portion of the heritability of this disease remains to be discovered. However, even at this decidedly incomplete stage, the story of the genetics of AD is already affecting the way in which we understand and respond to this disorder, and pointing the way to new insights and new therapies in the future.

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