Alzheimer’s Disease Risk Genes and Mechanisms of Disease Pathogenesis

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ABSTRACT

We review the genetic risk factors for late-onset Alzheimer’s disease (AD) and their role in AD pathogenesis. More recent advances in understanding of the human genome—technologic advances in methods to analyze millions of polymorphisms in thousands of subjects—have revealed new genes associated with AD risk, including ABCA7, BIN1, CASS4, CD33, CD2AP, CELF1, CLU, CR1, DSG2, EPHA1, FERMT2, HLA-DRB5-DBR1, INPP5D, MS4A, MEF2C, NME8, PICALM, PTK2B, SLC24H4-RIN3, SORL1, and ZCWPW1. Emerging technologies to analyze the entire genome in large data sets have also revealed coding variants that increase AD risk: PLD3 and TREM2. We review the relationship between these AD risk genes and the cellular and neuropathologic features of AD. Understanding the mechanisms underlying the association of these genes with risk for disease will provide the most meaningful targets for therapeutic development to date.

Keywords: Alzheimer’s Disease, Amyloid Precursor Protein, Cholesterol Metabolism, Endocytosis, Genome-Wide Association Studies, Immune Response

http://dx.doi.org/10.1016/j.biopsych.2014.05.006

Alzheimer’s disease (AD) is pathologically defined by extensive neuronal loss and the accumulation of intracellular neurofibrillary tangles and extracellular amyloid plaques in the brain. Genetic, biochemical, and neuropathologic data suggest that Aβ aggregation is central to initiating AD pathogenesis (1). Neurofibrillary pathology strongly correlates with neuronal dysfunction and progression of the clinical phase of AD (2). The clinical phase of AD is also marked by synaptic loss, selective neuronal death, neurotransmitter loss, and neuroinflammation (2).

EMERGING GENETICS

Dominantly inherited, early-onset AD is associated with classic mendelian patterns of inheritance with age-dependent penetrance. Late-onset AD (LOAD) also has a strong genetic component. The identification of novel loci that affect LOAD risk is critical to understanding of the underlying etiology of AD. Genome-wide associated studies (GWAS) have identified polymorphisms in or near several genes that are associated with AD risk, including ABCA7, CLU, CR1, CD33, CD2AP, EPHA1, BIN1, PICALM, and MS4A (Figure 1) (3–7). Additional loci were identified in a meta-analysis of these large LOAD consortium data sets, including CASS4, CELF1, DSG2, FERMT2, HLA-DRB5-DBR1, INPP5D, MEF2C, NME8, PTK2B, SLC24H4-RIN3, SORL1, and ZCWPW1 (6). The identification of common variants that have small effects on AD risk has begun to create a broader picture of the processes and pathways involved in AD risk. Variants in genes involved in lipid metabolism, the inflammatory response, and endocytosis have been identified through these GWAS.

Although large data sets with whole genome or exome sequencing are being generated, these approaches in smaller data sets have yielded evidence of rare coding variants in two genes with moderate to large effects on LOAD risk: PLD3 and TREM2 (Figure 1) (8–11). The identification of rare variants in the population that have moderate to large effects on AD risk would be valuable in identifying pathways that are central to disease pathogenesis. In contrast to the GWAS, sequencing studies have identified variants within the coding sequence that can be more easily examined in in vitro and in vivo model systems. These methods may provide the most meaningful targets for therapeutic development.

In complex, heterogeneous diseases such as AD, novel approaches to integrate genetic, expression, and epigenetic data information into organized molecular networks may facilitate our understanding of the underlying disease pathogenesis. It is likely that AD arises from a complex interplay between genetic susceptibility and downstream molecular pathways. A study constructed gene-regulatory networks from 1647 AD and control brain samples to demonstrate that networks involved in immune-specific and microglia-specific modules are disrupted in brains with AD (12). TYROBP was identified as a key regulator in a module of genes involved in pathogen phagocytosis (12). TYROBP, also known as DAP12, is key signaling molecule for TREM2, another more recently identified AD risk gene. These methods are useful in developing integrated models of the molecular pathways disrupted in AD.

Alternative AD Phenotypes

Most AD risk genes affect Aβ production and clearance, highlighting the importance of this pathway in AD pathogenesis.

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This finding is likely the result of the methods by which the genes were identified, in studies testing for association with AD case-control status (3–7,13). Using alternative AD phenotypes may reveal additional genes that modify particular aspects of the disease. Use of biomarkers as quantitative endophenotypes has led to the identification of additional genes that modify tau and Aβ metabolism in cerebrospinal fluid and neuroimaging phenotypes (14–21). Using biomarkers as quantitative endophenotypes in populations that are tracked over the course of disease can give us more information regarding genes that influence disease onset and progression (14). Additional risk alleles may modify tau metabolism and have an impact on AD progression; however, these studies are still ongoing.

**APP, PSEN1, and PSEN2**

Dominantly inherited mutations in β-amyloid precursor protein (**APP**), presenilin 1 (**PSEN1**), and presenilin 2 (**PSEN2**) cause early-onset AD (2,22). Sequential cleavage of APP, a transmembrane neuronal protein, by β-secretase and then by γ-secretase produces Aβ (23). PSEN1 and PSEN2 are critical components of the γ-secretase complex. The amyloid cascade hypothesis posits that changes in APP or Aβ homeostasis, or both, lead to the aggregation of Aβ and deposition in plaques and that these events are sufficient to initiate the cascade of pathologic abnormalities associated with AD (1). Proteolysis of APP by α-secretase results in cleavage within the Aβ domain generating nonamyloidogenic fragments that are reported to possess neurotrophic and neuroprotective properties (24,25).

Increasing evidence suggests that there are additional variants in **APP** and **APP**-modifying genes that alter AD risk in LOAD cases. Novel, rare variants in **APP**, **PSEN1**, **PSEN2**, and **ADAM10** have been identified in large LOAD families (26–28). Segregation data and bioinformatic analysis suggest that these rare variants in **APP** may increase (e.g., **APP** N660Y), decrease (e.g., **APP** A673T), or have no effect on AD risk (e.g., **APP** E599K) (26,29). A polymorphism in **PSEN1**, **PSEN1** E318G, is associated with a 10-fold increase in LOAD risk in **APOE**ε4 carriers (27). Additionally, rare coding variants in **ADAM10**, the major α-secretase involved in shedding of the **APP** ectodomain (30), cosegregate in seven LOAD families (8,31). **ADAM10** risk variants Q170H and R181G increase Aβ levels in vitro (8). In Tg2576 AD mice, **ADAM10** Q170H and R181G disrupt α-secretase activity and shift APP processing toward amyloidogenic cleavage, yielding increased plaque load (31). Together, these findings illustrate that variants in **APP** and **APP**-modifying genes (e.g., **PSEN1**, **PSEN2**, **ADAM10**) can cause early-onset AD or alter risk for LOAD.

**CHOLESTEROL METABOLISM**

**APOE** genotype is the strongest risk factor for LOAD. Its central role in cholesterol metabolism implicates this pathway in AD pathogenesis. In LOAD GWAS, variants in several genes were identified that are involved in cholesterol metabolism, including **CLU**, **ABCA7**, and **SORL1** (3–6,13).

**ApoE**

Apolipoprotein E (**APOE**) is the strongest risk factor for LOAD. **APOE** is located on chromosome 19q13.2. **APOE** encodes three common alleles (ε2, ε3, ε4). **APOE**ε4 is associated with increased AD risk (32,33): one **APOEε4** allele increases AD risk 3-fold, and two **APOEε4** alleles increase AD risk by 12-fold. **APOEε4** is also associated with a dose-dependent decrease in age at onset. Conversely, **APOEε2** is associated with decreased risk for AD and later age at onset (32,33).

**APOE** is a regulator of lipoprotein metabolism (34). **APOE** plays several important roles in the central nervous system, such as cholesterol transport, neuroplasticity, and inflammation (35). **APOE** binds to Aβ and influences the clearance of soluble Aβ and the Aβ aggregation (35,36). **APOE** also regulates Aβ metabolism indirectly by interacting with receptors such as **LRP1** (37). In APP transgenic mice, **APOEε4** carriers exhibit accelerated and more abundant Aβ deposition than **APOEε4**-negative individuals (42–44). **APOE** genotype is
also associated with cerebrospinal fluid Aβ42 and tau levels (15,16,43). Genetic, cellular, animal, and human studies demonstrate that APOE is a risk factor for LOAD and modifies AD pathogenesis via an APP-dependent manner.

**CLU**

Clusterin (CLU) is an apolipoprotein. Clusterin is a stress-activated chaperone protein that functions in apoptosis, complement regulation, lipid transport, membrane protection, and cell-cell interactions (45). CLU is located on chromosome 8p21.1 and encodes three alternative transcripts (46). Several single nucleotide polymorphisms (SNPs) have been identified in CLU that confers protection against LOAD, including rs11136000, rs9331888, rs2279590, rs7982, and rs7012010 (3–5,13). An association of CLU rs9331896 with LOAD was reported in 74,046 individuals (6). The functional impact of these polymorphisms is poorly understood. The SNP rs9331888 is associated with expression of an alternative splice variant (36), whereas rs9331888 and rs11136000 are associated with plasma clusterin levels (47–49). Elevated clusterin plasma levels are also associated with brain atrophy, disease severity, and disease progression (50–52).

Before the identification of risk alleles in LOAD, clusterin was implicated in AD pathogenesis. Clusterin messenger RNA (mRNA) expression is elevated in brains with AD (53,54) and is detected in amyloid plaques (55,56). Purified clusterin interacts with Aβ and influences fibril formation in vitro (57–59). Clusterin-deficient APP transgenic mice have reduced fibril formation, fewer dystrophic neurites, and altered soluble Aβ levels (60). Clusterin likely influences Aβ clearance, amyloid deposition, and neuritic toxicity. APOE-deficient and clusterin-deficient APP transgenic mice exhibit earlier and more extensive Aβ deposition compared with control mice (61).

Clusterin is also associated with the complement system. Clusterin modulates the membrane attack complex, where it inhibits the inflammatory response associated with complement activation (45). Because neuroinflammation is a hallmark of AD, SNPs that alter clusterin expression or its functions as an amyloid response agent could affect AD pathogenesis and downstream effects.

**ABCA7**

ATP-binding cassette transporter A7 (ABCA7) is a member of the ABC transporter superfamily, where it functions to transport substrates across cell membranes (62). ABCA7 is located on chromosome 19p13.3 and can undergo alternate splicing to generate two transcripts, both of which are expressed in the brain (63).

Several SNPs near ABCA7 were identified by GWAS in LOAD as risk alleles, including rs3764650 (3–6) and rs4147929, which was identified in a meta-analysis of 74,046 individuals (6). Polymorphisms in this region increase LOAD risk. However, the impact of these polymorphisms on ABCA7 function and in AD is poorly understood (53,64).

ABCA7 is expressed in hippocampal CA1 neurons and at 10-fold higher levels in microglia (65). In brains with AD, rs3764650 in ABCA7 is associated with neuritic plaque burden (20). ABCA7 mRNA expression in autopsy brain tissue is also associated with advanced cognitive decline (53,64). ABCA7 functions in the efflux of lipids from cells into lipoprotein particles. ABCA7-deficient mice exhibit only modest effects on lipid homeostasis compared with ABCA1-deficient mice (66,67), suggesting that ABCA7 is not essential. In vitro, ABCA7 stimulates cholesterol efflux and inhibits Aβ secretion (68). ABCA7 also modulates phagocytosis of apoptotic cells by macrophages via the C1q complement pathway (69). Increasing ABCA7 expression also increases microglial phagocytosis of apoptotic cells, synthetic substrates, and Aβ (67,69–71). APP transgenic mice that are ABCA7-deficient have increased Aβ deposition compared with singly transgenic animals (67). ABCA7 may influence AD risk via cholesterol transfer to APOE or by clearing Aβ aggregates (67,68,72).

**IMMUNE RESPONSE**

Neuroinflammation and dysregulation of the immune response is a central feature of AD (2). In GWAS, common variants have been identified in several genes that are associated with LOAD, including CR1, CD33, MS4A, CLU, ABCA7, and EPHA1 (3–7,13). Additionally, rare coding variants were identified in TREM2 in sequencing studies of LOAD cohorts (9,10).

**CR1**

Complement receptor 1 (CR1) encodes the CR1 protein. CR1 is a component of the complement response. CR1 is located on chromosome 1q32 in a cluster of complement-related proteins. CR1 encodes four isoforms that differ based on genetic duplication and deletions (73). CR1 expression on phagocytic cells, such as erythrocytes, results in the ingestion and removal of complement-activated particles (74).

In GWAS, SNPs in CR1 were identified in LOAD (3–6,13). The SNP rs6656401 tags several SNPs that are strongly associated with AD risk. A second SNP, rs3813861, is associated with LOAD risk in APOEε4 carriers (13). Variants in the CR1 locus are also associated with neuroimaging measures in AD (19) and neuritic plaque burden in brains with AD (20). CR1 mRNA expression in autopsy brain tissue is also associated with advanced cognitive decline (53).

CR1 is an interesting AD risk gene because expression of complement factors is reportedly upregulated in affected regions of brains with AD (75,76). Neurons and glia are sources of complement in the brain (77–79). Additionally, material isolated from neurofibrillary tangles and amyloid plaques activates the complement system (80,81).

CR1 encodes high-expression and low-expression alleles (74). Individuals who are homozygous for the low-expression CR1 allele have <200 copies of CR1 per cell, whereas individuals who are homozygous for the high-expression allele express nearly 1400 copies per cell (73). Higher CR1 protein expression is associated with a higher clearance rate of immune complexes (82,83). Clearance of plasma Aβ42 is dependent on C3b binding to CR1 (84). It is also hypothesized that Aβ42 activates the complement system (85). Because elevated complement cascade activity could exacerbate AD pathology, individuals with CR1 variants that dampen the complement response may be at lower risk of developing AD pathology.
CD33

CD33 is a member of the sialic acid-binding Ig-like lectin family of receptors and is expressed on myeloid cells and microglia (86–88). Sialic acid binding activates CD33, leading to mono-ocyte inhibition via immunoreceptor tyrosin-based inhibitory motif domains (89). CD33 is also reported to play a role in clathrin-independent receptor-mediated endocytosis (90).

CD33 is located on chromosome 19q13.3. In LOAD GWAS, SNPs proximal to CD33 (e.g., rs3865444) were identified that reduce LOAD risk (4, 5, 7). The SNP rs3865444 is associated with an increase in CD33 lacking exon 2 (87), and rs12459419 modulates exon 2 splicing efficiency (87). Splicing of CD33 influences microglial activation (87). In the most recent study of 74,046 individuals, rs3865444 failed to reach genome-wide significance; however, the strength of the biological findings suggests that CD33 may play a role in AD (6).

CD33 mRNA expression is specifically increased in microglia, and expression in autopsied brain tissue is associated with more advanced cognitive decline (53, 88). ApJ phagocytosis is inhibited in immortalized microglial cells expressing CD33, and this effect is abolished in cells expressing CD33 lacking exon 2 (88). The minor allele of rs3865444 is associated with reduced CD33 mRNA expression and insoluble Ap42 in brains with AD (88). CD33-positive immunoreactive microglia are also positively correlated with insoluble Ap42 and plaque burden in brains with AD (88). CD33 may play an important role in ApJ clearance and other neuroinflammatory pathways mediated by microglia in the brain.

MS4A

MS4A4A is a locus that contains several genes associated with the inflammatory response: MS4A4A, MS4A4E, and MS4A6E. Although this gene family is poorly characterized, MS4A4A is structurally similar to CD20 (91). CD20 regulates calcium influx after activation of B-cell antigen receptor (92). MS4A4 genes are expressed in myeloid cells and monocytes.

The SNPs rs9833932 (near MS4A6A) and rs670139 (near MS4A4E) were identified as AD risk alleles in GWAS in LOAD (4–6). The SNP rs9833932 is associated with reduced LOAD risk, whereas rs670139 is associated with increased LOAD risk. MS4A6E mRNA expression and rs670139 are associated with more advanced Braak tangle and plaque stages in AD brain tissue (53). However, the functional SNP or SNPs in this region have yet to be identified.

TREM2

TREM2 is a receptor expressed on microglia that stimulates phagocytosis and suppresses inflammation (93). TREM2 is located on chromosome 6q21.1 and occurs as three transcripts. The longest transcript encodes a transmembrane protein that is trafficked to the cell surface where it interacts with DAP12 (also known as TYROBP) and binds with several ligands (94). The transmembrane domain is missing from the shorter transcripts. Although these transcripts have not been experimentally verified, they are predicted to be secreted.

Homozygous mutations in TREM2 are associated with autosomal recessive forms of dementia with bone cysts and fractures (95). Autosomal recessive mutations in TREM2 were also identified in a family with frontotemporal dementia–like syndrome without bone involvement (96). Rare, missense mutations in TREM2 have been reported to increase LOAD risk. Gene-based burden tests suggest that multiple rare, coding variants in TREM2 increase risk for disease. The most common variant in populations of European descent, R47H (rs75932628), is reported to increase LOAD risk approximately twofold (9, 10, 97–99). However, there is some debate regarding the degree to which carrying TREM2 R47H increases AD risk; studies report a range of 1.7-fold to 3.4-fold increased AD risk in TREM2 R47H carriers (100, 101). TREM2 R47H is also associated with increased risk for Parkinson’s disease, frontotemporal dementia, and amyotrophic lateral sclerosis (96, 97, 102, 103).

TREM2 mutation carriers with AD have more extensive brain atrophy than noncarriers with AD (104). Variants in the TREM2 region are also associated with cerebrospinal fluid tau levels (15). After trafficking to the cell surface, TREM2 is cleaved by γ-secretase (105). TREM2 may play an important role in neurodegeneration, possibly in clearance of protein aggregates or in neuroinflammatory mechanisms.

ENDOCYTOSIS

Endocytosis is critical for normal processing of APP, which is central to AD pathogenesis. Synaptic activity and neurotransmitter release is disrupted in AD (2). Genes associated with endocytosis and synaptic function were identified in several GWAS of LOAD risk, including BIN1, PICALM, CD2AP, EPHA1, and SORL1 (3–6, 13).

BIN1

Bridging integrator 1 (BIN1) is involved in regulating endocytosis and trafficking, immune response, calcium homeostasis, and apoptosis. BIN1 is located on chromosome 2q14.3 and is differentially spliced to seven major transcripts (106). BIN1 interacts with clathrin and AP2/α-adaptin (107, 108) and binds to lipid membranes and induces membrane curvature (109).

The SNPs in BIN1 that increase risk for LOAD were identified by GWAS (3, 4). The most significant SNPs, rs744373 and rs7561528, are located >25 kB upstream from the BIN1 coding region. The most recent LOAD GWAS of 74,046 individuals identified rs6733839 (6). The SNP rs7561528 is associated with entorhinal cortical thickness and temporal pole cortical thickness (19). The SNP rs59335482, in linkage disequilibrium with rs744373, is associated with elevated BIN1 mRNA expression and tau loads, but not tangles, in brains with AD (110). Alterations in BIN1 protein levels are found in aged mice, AD mouse models, and human brains with AD (110, 111). In brains with AD, elevated BIN1 mRNA expression levels are associated with delayed disease onset and shorter disease duration (53).

BIN1 may play a role in tau processing. BIN1 interacts with another microtubule-associated protein (CLIP-170) (112). BIN1 and tau interact in neuroblastoma cells and mouse brains (110). BIN1 knockdown suppresses tau-induced toxicity in a Drosophila model of AD (110).

BIN1 is also implicated in clathrin-mediated endocytosis and intracellular endosome trafficking, where it could modify APP trafficking (23, 113). BIN1 binds to GTPase dynamin (114). BIN1-deficient mice have impaired endocytic protein scaffolds and synaptic vesicle recycling (115).
BIN1 also plays an important role in senescence and apoptosis (116,117). BIN1 is implicated in phagocytosis by macrophages and binds α-integrins, which regulate the immune response (118). Although BIN1 has functions relevant to several aspects of disease pathogenesis, the exact role of BIN1 in disease and the functional variant associated with disease risk is unresolved.

**PICALM**

Phosphatidylinositol binding clathrin assembly protein (PICALM) encodes a protein involved in clathrin assembly. PICALM is located on chromosome 11q14 and results in 23 alternative transcripts. PICALM is predominantly expressed in neurons (119). The SNPs 5’ to PICALM rs3651179 and rs541458 are associated with reduced LOAD risk (3,6,13). However, the functional effects of these SNPs remain to be determined.

PICALM recruits clathrin and adaptor protein complex 2 (AP2) to the cell membrane, where it plays a role in determining the amount of membrane to be recycled by regulating clathrin cage size (120). PICALM also plays an essential role in synaptic vesicle fusion to the presynaptic membrane via VAMP2 trafficking (121). Deletion of the PICALM homolog AP180 in Drosophila and yeast result in impaired clathrin-mediated endocytosis (122,123). PICALM-deficient mice have no overt neurologic phenotypes but display abnormal iron metabolism, which has been implicated in APP processing (124).

PICALM colocalizes with APP in vitro and in vivo (119). Disrupting PICALM expression alters APP trafficking in vitro, and overexpression of PICALM in vivo increases plaque deposition in AD transgenic mice (119). PICALM modulates Aβ-induced toxicity in a yeast model (125). PICALM binds to autophagosomes, suggesting that PICALM may also play a role in autophagy-mediated Aβ clearance (126). Targeting PICALM-mediated Aβ generation and clearance may influence accumulation of Aβ in brains with AD.

**CD2AP**

CD2-associated protein (CD2AP) is a scaffolding protein that is involved in cytoskeletal reorganization and intracellular trafficking (127). CD2AP is located on chromosome 6q12. In CD2AP, SNPs rs9296559 and rs9349407 are associated with increased LOAD risk (4,5). CD2AP rs9349407 is associated with neuritic plaque burden in brains with AD (20). The SNP rs10948363 was most recently identified in a meta-analysis of 74,046 individuals (6). However, the putative functional SNP remains undetermined, and CD2AP mRNA expression is not altered in brains with AD (53). Knockdown of a CD2AP fly ortholog in a Drosophila model of AD enhances tau neurotoxicity (128).

CD2AP is required for synapse formation (127), where it associates with Cbl, endophilin, and synaptotagmin. Lysosomal function is also impaired in cells from CD2AP-deficient mice, suggesting that CD2AP is a critical regulator of vesicular trafficking to the lysosome (129).

**EPHA1**

EPHA1 is a member of the ephrins family of tyrosine kinase receptors that binds to membrane-bound ephrins-A ligands on adjacent cells. This interaction leads to contact-dependent, bidirectional signaling to adjacent cells (130). EPHA1 is located on chromosome 7q34. The SNP rs11767557, near EPHA1, is associated with reduced LOAD risk (4,5). The SNP rs11771145 was associated with reduced LOAD risk in the largest GWAS study to date (6). However, there is no evidence that EPHA1 mRNA expression is altered in brains with AD (53).

EPHA1 plays roles in cell and axonal guidance and synaptic plasticity (131,132). EPHA1 is expressed by CD4-positive T lymphocytes and monocytes (133). Although the most strongly associated SNP is close to EPHA1, there are several other genes within the region of linkage disequilibrium defined by this SNP, and the functional SNP could be in or affect expression of one of these neighboring genes.

**SORL1**

Sortilin-related receptor L (SORL1) is involved in vesicle trafficking from the cell surface to the Golgi-endoplasmic reticulum. SORL1 is a member of the Vsp10p domain receptor family and is composed of five type I transmembrane receptors.

SORL1 is located on chromosome 11q23.2. SORL1 was originally identified as an AD risk gene in candidate-based approaches (134,135). A GWAS in 74,046 individuals revealed that rs11218343 near SORL1 is associated with reduced AD risk (6).

SORL1 directs APP to endocytic pathways for recycling (134) and plays an important role in Aβ generation (136–138). SORL1-deficient mice have elevated Aβ levels (139). SORL1 mRNA expression is reduced in brains with AD (140–142). SORL1 is also a receptor that binds lipoproteins, including APOE-containing particles, and mediates their uptake via endocytic pathways (134). The role of SORL1 in controlling APP cleavage and APOE uptake may be critical to maintaining signaling functions in the brain.

**UNKNOWN**

**PLD3**

Phospholipase D3 (PLD3) is a poorly characterized “non-classical” member of the PLD protein family with no reported catalytic activity (143). PLD3 is located at chromosome 19q13.2 and is alternatively spliced into 25 predicted transcripts. Whole exome sequencing in LOAD families was coupled with genotyping in large case-control series to identify PLD3 V232M as an AD risk factor (11).

Classical PLD proteins catalyze the hydrolysis of phosphatidylcholine to generate phosphatidic acid, which acts as an effector for clathrin-mediated endocytosis (144), and have been implicated in AD pathogenesis (145–148). PLD3 is highly expressed in neurons in the hippocampus, entorhinal cortex, and frontal cortex. In vitro, coexpression of PLD3 with APP produces significantly lower extracellular Aβ levels by an unknown mechanism (11).

**NEW LOAD RISK GENES**

Additional loci were identified in the largest LOAD GWAS to date, including CASS4, CELF1, DSG2, FERMT2, HLA-DRB5-DBR1, INPP5D, MEF2C, NME8, PTK2B, SLC24H4-RIN3, and...
ZCWPW1 (6). Much less is known of the role of these genes in AD; however, many of these genes fit into known pathways that are altered in AD. HLA-DRB5-DRB1 and INPP5D are involved in the immune response. MEFC2 is involved in the immune response and in synaptic function. PTK2B is involved in cell migration and synaptic function. CELF1, NME8, and CASS4 are involved in cytoskeletal function and axonal transport. CASS4 is implicated in APP and tau metabolism. FERMT2 is also implicated in tau metabolism (6). Several of these susceptibility loci occur in gene-dense regions; it remains unclear which gene is responsible for the association.

CONCLUSIONS
The identification of common and rare variants that contribute to AD risk has provided new opportunities to understand the mechanisms underlying AD. Most of the genes identified more recently affect Aβ production and clearance, highlighting the importance of this pathway in AD pathogenesis. As whole genome and exome sequencing studies in large data sets are completed, many more genes are likely to be added to this list. It remains to be seen whether additional pathways are identified or whether most genes will fall into the already identified pathways and cellular mechanisms.

ACKNOWLEDGMENT AND DISCLOSURES
The authors report no biomedical financial interests or potential conflicts of interest.

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Received Nov 12, 2013; revised Apr 30, 2014; accepted May 5, 2014.

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Genetic Risk in Alzheimer’s Disease


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