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Alzheimer's disease risk genes and mechanisms of disease pathogenesis

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Abstract

Here, we review the genetic risk factors for late onset Alzheimer's disease (AD) and their role in AD pathogenesis. Recent advances in our understanding of the human genome, namely technological advances in methods to analyze millions of polymorphisms in thousands of subjects, have revealed new genes associated with AD risk: *ABCA7*, *BIN1*, *CASS4*, *CD33*, *CD2AP*, *CELF1*, *CLU*, *CR1*, *DSG2*, *EPHA1*, *FERMT2*, *HLA-DRB5-DBR1*, *INPP5D*, *MS4A*, *MEF2C*, *NME8*, *PICALM*, *PTK2B*, *SLC24H4 RIN3*, *SORL1*, *ZCWPW1*. Emerging technologies to analyze the entire genome in large datasets 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 neuropathological features of AD. Together, 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; genome wide association studies; endocytosis; immune response; cholesterol metabolism

Alzheimer's Disease

Alzheimer's disease is pathologically defined by extensive neuronal loss and the accumulation of intracellular neurofibrillary tangles and extracellular amyloid plaques in the brain. Genetic, biochemical, and neuropathological data suggest that A 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

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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 classical 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 our 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: *ABCA7*, *CLU*, *CR1*, *CD33*, *CD2AP*, *EPHA1*, *BIN1*, *PICALM*, *MS4A* (3-7) (Fig. 1). Additional loci were identified in a meta analysis of these large LOAD consortium datasets: *CASS4*, *CELF1*, *DSG2*, *FERMT2*, *HLA DRB5 DBR1*, *INPP5D*, *MEF2C*, *NME8*, *PTK2B*, *SLC24H4 RIN3*, *SORL1*, *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 datasets with whole genome or exome sequencing are being generated, these approaches in smaller datasets have yielded evidence of rare coding variants in two genes with moderate to large effects on LOAD risk: *PLD3* and *TREM2 (8-11)* (Fig. 1). The identification of rare variants in the population that have moderate to large effects on AD risk will 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 like AD, novel approaches to integrate genetic, expression, and epigenetic into organized molecular networks may facilitate our understanding of the underlying disease pathogenesis. AD likely arises from a complex interplay between genetic susceptibility and downstream molecular pathways. A recent study constructed gene-regulatory networks from 1,647 AD and control brain samples to demonstrate that networks involved in immune-and microglia-specific modules are disrupted in AD brains (12). *TYROBP* was identified as a key regulator in a module of genes involved in pathogen phagocytosis (12). Interestingly, TYROBP, a.k.a. DAP12, is key signaling molecule for TREM2, another recently identified AD risk gene. Thus, these methods are useful in developing integrated models of the molecular pathways disrupted in AD.

Alternative AD Phenotypes

The majority of AD risk genes affect Aβ production and clearance, highlighting the importance of this pathway in AD pathogenesis. This 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 CSF and

neuroimaging phenotypes (14-21). Using biomarkers as quantitative endophenotypes in populations who are tracked over the course of disease will give us more information regarding genes that influence disease onset and progression (14). Additional risk alleles may modify tau metabolism and impact AD progression; however, these studies are still on going.

APP, PSEN1, and PSEN2

Dominantly inherited mutations in β-amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*), and presenilin 2 (*PSEN2*) cause early onset Alzheimer's disease (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 and/or Aβ homeostasis 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). APP proteolysis by secretase results in cleavage within the Aβ domain generating non-amyloidogenic 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 suggests 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 *APOE4* carriers (27). Additionally, rare coding variants in *ADAM10*, the major α-secretase involved in shedding of the APP ectodomain (30), co-segregate 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 recent LOAD GWAS, variants in several genes were identified that are involved in cholesterol metabolism: *CLU*, *ABCA7*, *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 *APOE*ε4 allele increases AD risk 3 fold and two *APOE*ε4 alleles increases AD risk by 12 fold. *APOE*ε4 is also associated with a dose

dependent decrease in age at onset. Conversely, *APOE*ε2 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: 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, APOE influences the amount and structure of intraparenchymal Aβ deposits in an isoform specific manner (38-41). Neuropathological and neuroimaging studies demonstrate that *APOE*ε4 carriers exhibit accelerated and more abundant Aβ deposition than *APOE*ε4 negative individuals (42-44). *APOE*εgenotype is also associated with CSF Aβ42 and tau levels (15, 16, 43). Thus, 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 3 alternative transcripts (46). Several single nucleotide polymorphisms (SNPs) have been identified in CLU that confers protection against LOAD: rs11136000, rs9331888, rs2279590, rs7982, and rs7012010 (3-5, 13). Lambert et al reported an association of CLU rs9331896 with LOAD in 74,046 individuals (6). The functional impact of these polymorphisms is poorly understood. Rs9331888 is associated with expression of an alternative splice variant (36), while 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).

Prior to the identification of risk alleles in LOAD, clusterin was implicated in AD pathogenesis. Clusterin mRNA expression is elevated in AD brains (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). Thus, clusterin likely influences Aβ clearance, amyloid deposition, and neuritic toxicity. APOE-and Clusterin deficient APP transgenic mice exhibit earlier and more extensive Aβ deposition than in 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 impact 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).

GWAS in LOAD identified several SNPs near *ABCA7* 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). rs3764650 in *ABCA7* is associated with neuritic plaque burden in AD brains (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-eficient 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 to the singly transgenic animals (67). Thus, 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). Common variants have been identified in several genes that are associated with LOAD in GWAS: *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 4 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).

SNPs in *CR1* were identified in GWAS in LOAD (3-6, 13). The SNP rs6656401 tags several SNPs that are strongly associated with AD risk. A second SNP, rs3818361, is associated with LOAD risk in *APOEε4* carriers (13). Variants in the *CR1* locus are also associated with neuroimaging measures associated with AD (19) and neuritic plaque burden in AD brains (20). *CR1* mRNA expression in autopsy brain tissue is also associated with advanced cognitive decline (53).

CR1 is an interesting AD risk gene, as expression of complement factors are reportedly upregulated in affected regions of AD brains (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 fewer than 200 copies of CR1 per cell, while individuals who are homozygous for the high expression allele express nearly 1,400 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 monocyte inhibition via immunoreceptor tyrosine-based inhibitory motif (ITIM) domains (89). CD33 is also reported to play a role in clathrin-independent receptor-mediated endocytosis (90).

CD33 is located on chromosome 19q13.3. SNPs proximal to *CD33* (e.g. rs3865444) were identified in LOAD GWAS that reduce LOAD risk (4, 5, 7). 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). Rs3865444 failed to reach genome wide significance in the most recent study of 74,046 individuals; however, the strength of the biological findings makes CD33 an interesting player in AD (6).

CD33 mRNA expression is specifically increased in microglia and expression in autopsy brain tissue is associated with more advanced cognitive decline (53, 88). Aβ 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 Aβ42 in AD brains (88). CD33 positive immunoreactive microglia are also positively correlated with insoluble Aβ42 and plaque burden in AD brains (88). Thus, CD33 may play an important role in Aβ clearance and other neuroinflammatory pathways mediated by microglia in the brain.

MS4A

MS4A is a locus that contains several genes associated with the inflammatory response: *MS4A4A*, *MS4A4E*, *MS4A6E*. While this gene family is poorly characterized, MS4A is structurally similar to CD20 (91). CD20 regulates calcium influx following the activation of B-cell antigen receptor (92). *MS4A* genes are expressed in myeloid cells and monocytes.

GWAS in LOAD identified a SNP rs983392 (near *MS4A6A*) and rs670139 (near *MS4A4E*) as AD risk alleles (4-6). rs983392 is associated with reduced LOAD risk, while 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(s) in this region has 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 occur as 3 transcripts. The longest transcript is a transmembrane protein that is trafficked to the cell surface where it interacts with DAP12 (a.k.a. TYROBP) and binds with several ligands (94). The transmembrane domain is missing from the shorter transcripts. While 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 (FTD)-like syndrome without bone involvement (96). Recently rare, missense mutations in *TREM2* have been reported to increase LOAD risk. Gene based burden tests suggest that multiple rare, coding variants in *TREM2* make increase risk for disease. The most common variant in European-descent populations, R47H (rs75932628), is reported to increase LOAD risk approximately two fold (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 1.7-3.4-fold increased AD risk in TREM2 R47H carriers (100, 101). *TREM2* R47H is also associated with increased risk for Parkinson's disease, FTD and ALS (96, 97, 102, 103).

TREM2 mutation carriers with AD have more extensive brain atrophy than non-carriers with AD (104). Variants in the *TREM2* region are also associated with CSF tau levels (15). Interestingly, 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. Furthermore, 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: *BIN1*, *PICALM*, *CD2AP*, *EPHA1*, *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 7 major transcripts (106). BIN1 interacts with clathrin and AP2/α-adaptin (107, 108) and binds to lipid membranes and induce membrane curvature (109).

GWAS identified SNPs in *BIN1* increase risk for LOAD (3, 4). The most significant SNPs, rs744373 and rs7561528, are located more than 25kB upstream from the *BIN1* coding region. The most recent LOAD GWAS of 74,046 individuals identified rs6733839 (6).

Rs7561528 is associated with entorhinal cortical thickness and temporal pole cortical thickness (19). Rs59335482, in linkage disequilibrium with rs744373, is associated with elevated BIN1 mRNA expression and tau loads but not tangles in AD brains (110). BIN1 protein levels are altered in aged mice, AD mouse models and human AD brains (110, 111). In AD brains, 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). Thus, while 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 remains to be resolved.

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). SNPs 5’ to PICALM rs3851179 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 neurological phenotypes but display abnormal iron metabolism, which has been implicated in APP processing (124).

PICALM co-localizes 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). Thus, targeting PICALM-mediated Aβ generation and clearance may influence accumulation of Aβ in AD brains.

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. SNPs in CD2AP rs9296559 and rs9349407 are associated with increased LOAD risk (4, 5). CD2AP rs9349407 is associated with neuritic plaque burden in AD brains (20). 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 AD brains (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, enodophilin, and synaptojanin. 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. A SNP near *EPHA1*, rs11767557, is associated with reduced LOAD risk (4, 5). 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 AD brains (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 thus 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 comprised 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 recent 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 AD brains (140 142). SORL1 is also a receptor that binds lipoproteins, including APOE-containing particles, and mediates their uptake via endocytotic pathways (134). Thus, 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 phophatidylcholine 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*, co-expression of PLD3 with APP produces significantly lower extracellular Aβ levels by a mechanism that remains unknown (11).

New LOAD Risk Genes

Additional loci were identified in the largest LOAD GWAS to-date: *CASS4*, *CELF1*, *DSG2*, *FERMT2*, *HLA-DRB5-DBR1*, *INPP5D*, *MEF2C*, *NME8*, *PTK2B*, *SLC24H4-RIN3*, *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. *MEF2C* 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). Importantly, several of these susceptibility loci occur in gene-dense regions; so, 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. The majority of the genes recently identified affect Aβ production and clearance, highlighting the importance of this pathway in AD pathogenesis. As whole genome and exome sequencing studies in large datasets are completed, it is very likely that many more genes will 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.

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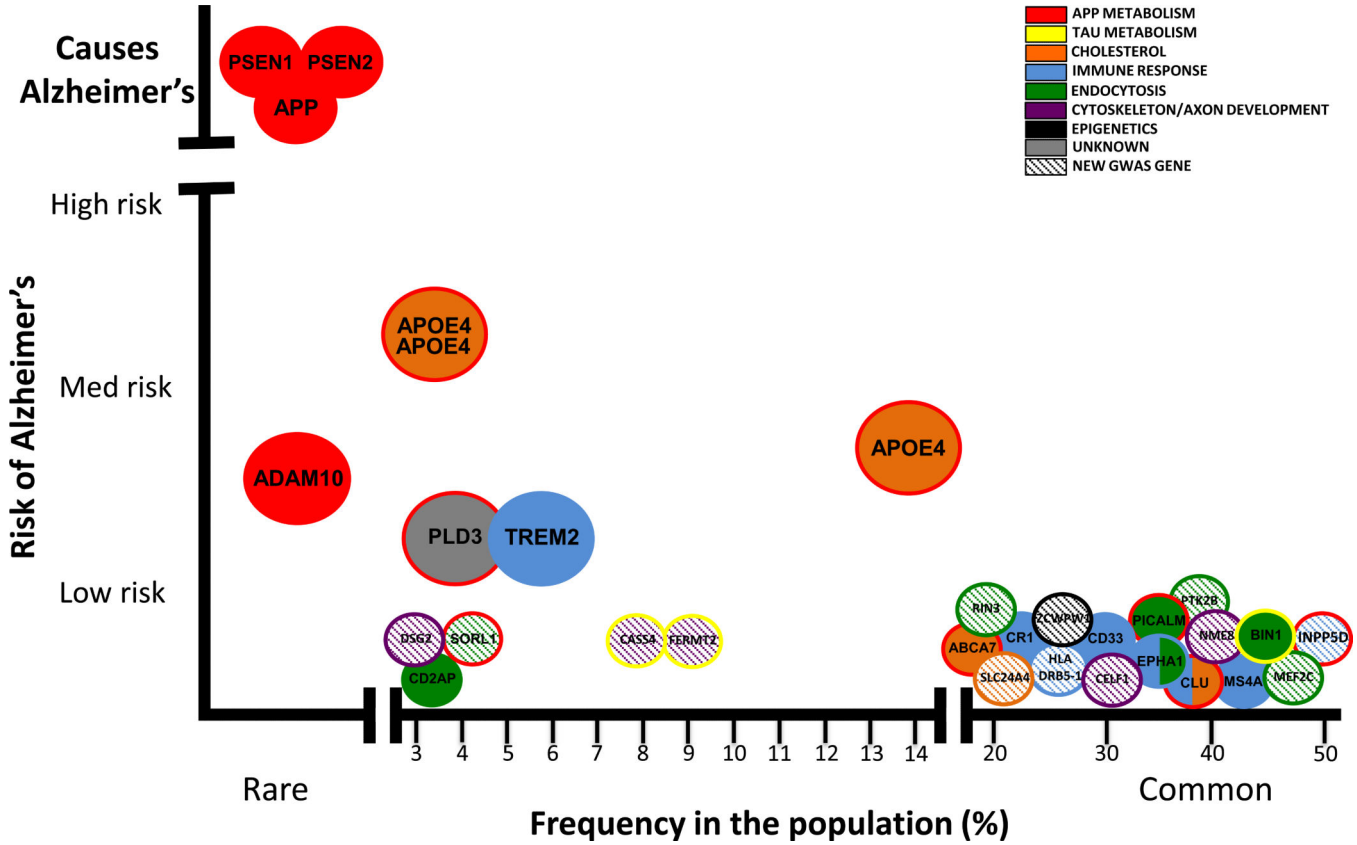

Figure 1. Rare and common variants contribute to Alzheimer's disease risk
Figure updated and modified from (149).