Review

Biological Psychiatry

Alzheimer's Disease Risk Genes and Mechanisms of Disease Pathogenesis

Celeste M. Karch and Alison M. Goate

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

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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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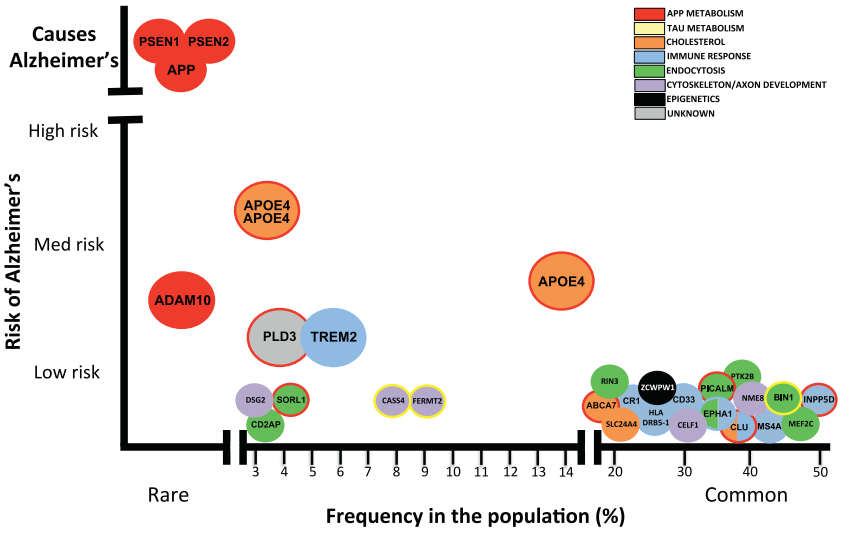

Figure 1. Rare and common variants contribute to Alzheimer's disease risk. GWAS, genome-wide associated studies. (Updated and modified with permission from Guerreiro *et al.* [149].)

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 *APOE*ε4 allele increases AD risk 3-fold, and two *APOE*ε4 alleles increase 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, 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, APOE influences the amount and structure of intraparenchymal Aβ deposits in an isoform-specific manner (38–41). Neuropathologic and neuroimaging studies demonstrate that *APOE*ε4 carriers exhibit accelerated and more abundant Aβ deposition than *APOE*ε4-negative individuals (42–44). *APOE* genotype is