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Genetic diagnosis and prognosis of Alzheimer's disease: challenges and opportunities

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Abstract

Alzheimer's disease (AD), the most common form of dementia in western societies, is a pathologically and clinically heterogeneous disease with a strong genetic component. The recent advances in high-throughput genome technologies allowing for the rapid analysis of millions of polymorphisms in thousands of subjects has significantly advanced our understanding of the genomic underpinnings of AD susceptibility. During the last 5 years, genome-wide association and whole-exome- and whole-genome sequencing studies have mapped more than 20 disease-associated loci, providing insights into the molecular pathways involved in AD pathogenesis and hinting at potential novel therapeutic targets. This review article summarizes the challenges and opportunities of when using genomic information for diagnosis and prognosis of Alzheimer's disease.

Keywords

Alzheimer's disease; genomics; diagnosis; prognosis; therapy

EPIDEMIOLOGY OF AD

Late-onset Alzheimer disease (AD) is the most frequent form of dementia affecting 24 million persons worldwide.[1] In the US alone, five million people are affected causing a direct estimated health-care cost of $215 billion dollars per year.[1,2] The annual incidence rate of AD increases from 1% among people aged 65 years to approximately 8% for people aged 85 years and older. Based on the projected ageing of the population, these numbers will triple by the year 2050 resulting in an increase of nearly 80% in total societal costs per adult. [2]

DIAGNOSIS OF AD

Late-onset AD typically is defined by onset of symptoms after age 60 and evolves slowly from mildly impaired memory function to severe cognitive loss, terminating inevitably in

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complete incapacity and death. Although in recent years there have been significant advances in biomarkers such as plasma Aβ, CSF Aβ and tau, and amyloid imaging for AD and prediction in cognitive decline[3–5], in particular studies of plasma Aβ have produced contradictory results and to date there are no definitive diagnostic tests or biological markers of the disease. The diagnosis during life is based on a clinical examination. The pathological hallmarks in brain include deposits of extracellular β-amyloid protein (Aβ) in diffuse plaques and plaques containing elements of degenerating neurons ("neuritic plaques"). Intracellular changes include deposits of abnormally hyperphosphorylated tau protein, a microtubule assembly protein, in the form of neurofibrillary tangles. In addition, activation of microglia and loss of neurons and synapses is widespread.

DISEASE MECHANISMS IMPLICATED BY GENOMIC STUDIES

Linkage Studies—Early genetic linkage studies of numerous large pedigrees with early-onset AD (onset age: 30–50 years) led to the discovery of autosomal dominant mutations in the amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*), and presenilin 2 (*PSEN2*) genes.[6–8] These studies suggested a common pathogenic mechanism involving enhanced generation and aggregation of amyloid β protein (Aβ) ("amyloid cascade hypothesis"). According to this hypothesis, β-secretase (BACE) cleaves APP near the N terminus of the Aβ peptide; then, the membrane-bound C-terminal APP fragment is cleaved by γ-secretase leading to accumulation of Aβ40 and Aβ42.[9]

APP: APP is located at chromosome 21q21 and encodes a ubiquitously expressed type 1 transmembrane protein. The majority of APP is cleaved within the Aβ domain by α- and γ-secretases resulting in sAPPα and a C-terminal fragment (CTF), which are both non-toxic[10]. Alternatively, APP can undergo consecutive proteolytic cleavage by β- and γ-secretases generating amyloidogenic Aβ40 and 42 peptides, sAPPβ and β-CTF.

Dominant mutations in APP account for ~14% of early-onset cases of AD, with more than 30 mutations described to date (http://www.molgen.vib-ua.be/ADMutations/[11]). In addition, two recessive APP mutations (E693D, A673V) can cause early-onset AD and amyloidogenesis[12,13]. The majority of known mutations in APP cluster in the Aβ encoding region. However, early genetic sequencing studies focused on the exon 16 and 17 encoding the Aβ domain, leaving the possibility that there are pathogenic variants in other regions of the gene.

Families carrying APP duplications exhibit classic AD with cerebral amyloid angiopathy (CAA).[12,14–16] In addition, individuals with three copies of chromosome 21 (ie. trisomy 21, Down Syndrome) develop AD neuropathology.[12] In contrast, subjects with partial trisomy of chromosome 21 that does not include the APP gene do not develop clinical or neuropathological AD.[12] The Swedish mutation (KM670/671NL) leading to clinical and neuropathological AD, shows 2–3-fold increased plasma Aβ levels caused by altered β-secretase activity [17]. APP mutations clustering at the C-terminal ending of the Aβ domain alter γ-secretase function, shifting APP processing towards an increase in the highly amyloidogenic Aβ42 fragment and reduction in the less toxic Aβ40 fragment. The Dutch APP mutation (E693Q) occurs in the Aβ domain and results in accelerated Aβ aggregation.

[12] Individuals carrying this variant develop hereditary cerebral hemorrhage with amyloidosis characterized by predominant vascular Aβ deposition with diffuse plaques in the parenchymal tissue.[12] The E693Delta (Osaka) mutation identified in Japanese pedigree enhances Aβ oligomerization.[18] The Arctic mutation (E693G) also occurring within the Aβ domain[12] does not modify absolute Aβ levels or the Aβ42/Aβ40 ratio but is believed to increase the propensity of the Aβ peptide to aggregate[19]. These findings strongly support the notion that Aβ aggregation is critical to AD pathogenesis in these cases.

PSEN1 and PSEN2: PSEN1 and PSEN2, localizing in the endoplasmic reticulum and Golgi apparatus, form together with nicastrin, presenilin enhancer 2 (PEN2) and anterior pharynx-defective-1 (APH-1) the γ-secretase complex. Kinetic studies have demonstrated that familial AD mutations in PSEN1 and PSEN2 can exert their effect by various mechanisms: they can affect γ-secretase function by inhibiting the initial endoproteolytic cleavage releasing the intracellular domain of APP; they can lead to a premature release of intermediary substrates of APP during γ-secretase processing leading to the generation of longer Aβ peptides; and they can exert an effect on the cleavage site leading to preferential cleavage of APP at position 49–50 or 51–50[20]. In PSEN1 located at 14q24.3, 185 dominant pathogenic mutations have been identified, accounting for approximately 80% of early-onset familial AD cases (http://www.molgen.vib-ua.be/ADMutations/).[11] One of these mutations, the PSEN1 E280A mutation[21–23] causing early-onset familial Alzheimer's disease (EOFAD) at a mean age of 49 years and showing brain imaging and CSF evidence of Aβ plaque accumulation, was identified in the world's largest known autosomal dominant AD kindred residing in Antioquia, Colombia[21].

In its homolog PSEN2 located at 1q31-q42, 13 dominant pathogenic mutations have been identified accounting for approximately 5% of early-onset AD cases (http://www.molgen.ua.ac.be/admutations/).[12] In addition, variants with unclear pathogenicity have been described in both genes. There is evidence that some of these mutations, such as PSEN1 E318G[24] and PSEN2 R62H[25] may be risk factors for AD. Finally, also in late-onset AD cases with a strong family history of disease dominantly inherited mutations in PSEN1 and APP have been identified. These families may carry additional genetic variants that delay age at onset of the normally fully penetrant disease mutation.

ADAM10: Further support for the hypothesis that alteration of APP processing and Aβ generation is sufficient to cause AD comes from the identification of rare coding variants in ADAM10 in seven late-onset AD families.[26] ADAM10, located at 15q22, encodes the major α-secretase involved in cleavage of the APP ectodomain [26]. The ADAM10 risk variants R181G and Q170H increase Aβ levels *in vitro*[26] and disrupt α-secretase activity and shift APP processing toward amyloidogenic cleavage in Tg2576 mice, resulting in increased plaque load[27].

Role of rare and common variants in late-onset AD—For several decades, the main hypothesis advocated for complex diseases such as the late-onset form of AD was the "common disease-common variant hypothesis' suggesting that the genetic factors underlying common diseases such as late-onset AD will be alleles that are themselves quite common in the population at large.[28] In line with this notion, over the past several years,

the most common strategy for finding novel gene candidates for late-onset AD has been the genome-wide association study (GWAS), in which as many as several million genetic markers (single nucleotide polymorphisms, SNPs) are simultaneously tested for genetic association with disease risk and/or disease endophenotypes such as age-of-onset, biomarkers, brain imaging measures or neuropathological endpoints. Overall, these studies have identified loci accounting for only part of the heritability of most complex diseases. Although some of this 'missing heritability' may be ascribed to a large number of common variants with weak effect that are only detectable in larger studies, it is now clear that there is a substantial contribution from rare variants with large effect that are not readily identifiable by SNP-based methods.[29,30] To address this issue, recent and ongoing work has focused on targeted resequencing of known risk loci and whole genome (WGS) and whole exome (WES) sequencing to reveal rare variants explaining part of the "missing heritability".

Apolipoprotein E (APOE) region—For more than a decade, only one genetic risk factor, the *APOEε*4 allele, located on chromosome 19q13, was an unequivocally established "susceptibility" gene in non-Hispanic whites of European ancestry. APOE is a lipid-binding protein and is expressed in humans as three common isoforms coded for by three alleles, APOEε2, ε3, and ε4. A single *APOE-ε4* allele is associated with a 2- to 3-fold increased risk, having two copies is associated with a five-fold or more increase.[31] In addition, each inherited APOEε4 allele lowers the age-at-onset by 6–7 years.[32–39] APOEε4 is also associated with lower cognitive performance, in particular the memory domain, is associated with mild cognitive impairment (MCI) [40–43] and with progression from MCI to dementia [40–50]. While the population attributable risk for APOEε4 is estimated at 20–50%, [51] the presence of ε4 is neither necessary nor sufficient for developing the disease [52]. In ethnic groups other than non-Hispanic whites, the association between *APOE* and LOAD is largely inconsistent across studies.

Findings from candidate gene and GWA studies—Due to a paucity of data in other ethnic groups, most genetic association studies have restricted their efforts to non-Hispanic white populations. In addition, there are differences in linkage disequilibrium (LD) and allele frequencies between ethnic groups, which can lead to genetic background noise and the likelihood of false-positive findings due to confounding in combined analyses. Consequently, the largest GWAS to date which included up to 75,000 subjects were performed in individuals of European ancestry. These GWAS studies identified *CR1, BIN1, CD2AP, EPHA1, CLU, MS4A6A, PICALM, ABCA7, HLA-DRB5/HLA-DRB1, PTK2B, SORL1, SLC24A4/RIN3, INPP5D, MEF2C, NME8, ZCWPW1, CELF1, FERMT2, CASS4, CD33* and *EPHA1* as AD susceptibility loci.[53–58] The majority of these genes cluster into three pathways: inflammation and immune response, lipid metabolism and endocytosis/ intracellular trafficking. The *SORL1* (sortilin-related receptor, L(DLR class) 1) gene had previously been demonstrated to modulate intracellular trafficking and processing of APP in a candidate gene approach.[59,60] CLU, also known as apolipoprotein J (ApoJ), is a lipoprotein highly expressed in both the periphery and the brain.[61] Like ApoE, it is involved in lipid transport.[62] CLU is also hypothesized to act as an extracellular chaperone that influences Aβ-aggregation and receptor-mediated Aβ clearance by

endocytosis.[61] *BIN1* (amphiphysin II) is a member of the Bin1/amphiphysin/RVS167 (BAR) family of genes that are involved in diverse cellular processes, including actin dynamics, membrane trafficking and clathrin-mediated endocytosis[63] which affect APP processing and Aβ production or Aβ clearance from brain. PICALM is also involved in clathrin-mediated endocytosis and recruits clathrin and adaptor protein complex 2 to sites of vesicle assembly[64]. CD33 encodes a type I transmembrane protein belonging to the sialic acid-binding immunoglobulin-like lectins, mediating the cell-cell interaction and inhibiting normal functions of immune cells. In the periphery, CD33 is expressed on myeloid cells and monocytes. In the brain, CD33 is mainly expressed on microglial cells and is involved in microglia-mediated clearance of Aβ. CR1 is part of the complement system and a cell-surface receptor that is involved in clearing immune-complexes containing C3b and C4b. C3b can bind Aβ oligomers; consequently it is possible CR1 is involved in Aβ clearance. CR1 may also play a role in AD through neuroinflammation.[65] Of note, in this process CLU may play a role as an inhibitor[66]. The *MS4A4A/MS4A4E/MS4A6E* locus is on chromosome 11 and part of a cluster of 15 *MS4A* genes. Like CD33, MS4A4A is expressed on myeloid cells and monocytes and likely has an immune-related function. *EPHA1* belongs to the ephrin receptor subfamily of the protein-tyrosine kinase family. Members of this family of cell surface receptors interact with ephrin ligands on adjacent cells to modulate cell adhesion, migration, axon guidance, synapse formation and plasticity. Like other ephrin receptors, EPHA1 regulates cell morphology and motility[67]. In humans, EPHA1 is expressed by intestinal epithelium, colon but also CD4-positive T lymphocytes[68] and monocytes[69]. This may suggest that, like CD33, CR1, and MS4A4/MS4A6E, the role of the *EPHA1* gene product in AD may be mediated through the immune system. CD2AP encodes a scaffolding protein binding directly to actin, nephrin and other proteins involved in cytoskeletal organization[70]. It is implicated in dynamic actin remodeling and membrane trafficking that occurs during receptor endocytosis and cytokinesis. In the immune system, CD2AP is required for synapse formation.[71] ABCA7 is a member of the superfamily of ATP-binding cassette (ABC) transporters. ABC proteins transport various molecules across extra- and intra-cellular membranes. ABCA7 binds APOA-I and functions in apolipoprotein-mediated phospholipid and cholesterol efflux from cells.[72] In addition, *ABCA7* affects the transport of other important proteins, including amyloid precursor protein, [72] through the cell membrane and is involved in host defense through effects on phagocytosis by macrophages of apoptotic cells.[73] The largest GWAS performed in African Americans confirmed this gene as a susceptibility locus.[74] A recent study indicates that the common variants identified in these GWAS genes explain 33% of the total phenotypic variance out of which *APOE* alone explains 6% and other known markers 2%, leaving more than 25% of phenotypic variance to be identified[75].

RECENT SEQUENCING STUDIES

TREM2 and TREML2—Two whole-exome and whole-genome sequencing studies performed in persons of European ancestry identified simultaneously a rare disease-associated variant (rs75932628, R47H) increasing the risk 3–4-fold in the gene encoding triggering receptor expressed on myeloid cells 2 (TREM2).[76,77] A study in African Americans confirmed this association.[78] TREM2 is a receptor of the innate immune system expressed on microglia, macrophages, dendritic cells and osteoclasts, and a member

of the immunoglobulin superfamily. [79] Endogenous ligands of this receptor are unknown but when triggered, it signals through the transmembrane adapter protein TYROBP/DAP12 to activate phagocytosis of pathogens and cellular debris. In addition, TREM2 suppresses expression and secretion of inflammatory cytokines in macrophages and microglia. Autosomal recessive mutations in TREM2 cause Nasu-Hakola disease, a rare genetic disorder characterized by bone cysts and progressive early-onset dementia fatal by mid-life. [80] In addition to R47H, several additional rare variants in TREM2 were observed more frequently in cases than controls, [76,81], and a common protective variant (p.S144G (rs3747742)) has been identified in TREML2[82] suggesting that there may be multiple rare or common disease-associated variants in this gene family. There is also evidence that TREM2 R47H could be associated with Parkinson's disease, frontotemporal dementia, and amyotrophic lateral sclerosis[83–85]. The identification of coding variants in TREM2 and TREML2 that increase risk for AD supports the role of the immune response and inflammation in AD pathogenesis.

PLD3—Whole-exome sequencing (WES) in 14 large families densely affected by late-onset AD combined with consecutive analyses in several large case-control data sets identified a rare disease-associated variant in PLD3 (phospholipase D3; Val232Met).[75] Subsequent gene-based analyses of PLD3 sequence data in 4,387 cases and controls of European descent and 302 African American cases and controls, suggested that in both ethnic groups numerous variants in this gene increase risk for AD.[75] PLD3 is highly expressed in brain regions affected by the AD process including the cortex and hippocampus and is significantly lower expressed in neurons from AD brains compared to control brains. Overexpression of PLD3 leads to a significant decrease in intracellular APP and extracellular Aβ42 and Aβ40, and knockdown of PLD3 leads to a significant increase in extracellular Aβ42 and Aβ40.[75] For both TREM2/TREML2 and PLD3 as well as most genes identified by GWAS, the specific mechanisms by which they affect AD pathogenesis need to be disentangled.

USE OF GENOMIC INFORMATION FOR DISEASE DIAGNOSIS AND PROGNOSIS

In addition to pointing to mechanisms involved in the disease pathogenesis, identification of genetic risk factors could theoretically improve patient care by incorporation into a diagnostic or predictive test for AD allowing more targeted medical intervention (ie. 'genetic profiling'). While the level of discriminative accuracy considered acceptable is clearly dependent on the invasive nature of the treatment, to date, the feasibility of genetic risk profiling for AD diagnosis and prognosis is limited because the currently identified genes only explain a small proportion of the heritability of AD.[12,86] This limited diagnostic utility for AD diagnosis and prognosis is in line with similar observations in other common complex diseases and traits. A 54-locus genetic profile for the highly heritable trait height predicted only 5.6% of variation compared with 40% achieved by traditional predictions based on parental height[87]. In a large metaanalysis of 22,720 initially stroke-free subjects, a 324 SNP risk score for stroke led only to a marginal improvement in risk prediction compared with the classical epidemiological risk factors for stroke, and genetic risk profiling alone was inferior in predictive power to clinical risk profiling alone.[88] Similar observations have been made for diabetes[89,90] and hypertension[91]. A

simulation study of genetic profiles for coronary heart disease suggests that 50 variants with ORs of 1.2 and genotype frequencies of 50% are needed to reach a discriminative accuracy of ~70% [92]. At allele frequencies of 30% this number doubles to 100 variants.[92] Also, because of the strength of association between *APOE* and AD, for prediction of AD a weighted or log-odds risk score seems more appropriate than an unweighted approach [93]. Ideally, genetic profiling would also need to be complemented with information on environmental risk exposures.

As opposed to genetic profiling using only the established genome-wide significant risk variants, a genomic profiling approach includes all nominally associated SNPs in a genome-wide association study. To date, this method still has limited discriminative accuracy for complex diseases with no known strong genetic risk determinants, reaching only discriminative values of 55–60% for diseases such as type 2 diabetes, bipolar disorder or coronary heart disease [93]. It is expected that the current large-scale collaborative studies including GWAS, whole-genome and whole-exome sequencing studies, whole-genome copy number variant analysis, epistasis and pathway analyses as well as analyses in ethnic groups other than non-Hispanic whites will identify additional rare and common disease-associated variants and improve the predictive power of genetic or genomic profiling.

USE OF GENETIC INFORMATION FOR TREATMENT

Over the past two decades, drugs and potential druggable targets have not been successfully translated from animal models into effective therapies for humans. The failure of the conducted Phase 3 clinical trials targeting amyloid beta may be to some extent explained by their study design [94,95]. Most of these trials were based on subjects with mild to moderate dementia and a clinical diagnosis of late-onset AD, not taking into account the degree of brain amyloid load. However, as expected from a heterogeneous disease, recent studies have shown that a significant subset of the subjects in these trials were amyloid negative on neuroimaging; thus, they were *a priori* unlikely to respond to antiamyloid treatment.[96] Also, Aβ deposition predominantly occurs in the preclinical phase of the disease, and drug-related reversal of Aβ deposition may have no impact on disease progression after clinical symptoms have manifested and synapse loss and neurodegeneration have taken place.

Use of a genetic profile can advance drug development by identifying participants eligible for, most likely to benefit from or least likely to experience adverse effects of a targeted therapeutic approach. In line with this notion, two clinical trials launched in 2013 that are targeting Aβ, make use of genetic information focusing on dominantly inherited AD cases in the preclinical stage of disease who are known to develop AD at a certain age and carry mutations causing disease by increasing Aβ production (ie. APP, PSEN1, PSEN2 mutations). The Dominantly Inherited Alzheimer Network (DIAN) study[97,98] is testing Gantenerumab and Solanezumab in families carrying various *APP*, *PSEN1* and *PSEN2* mutations. The Alzheimer's disease Prevention Initiative (API)[99,100] is testing Crenezumab in presymptomatic individuals from the extended Colombian kindred carrying the *PSEN1* E280A mutation. A third trial, the A4 study[101] by the Alzheimer's Disease Cooperative Study (ADCS), is testing Solanezumab on asymptomatic elderly aged 65–85 years whose AD mutation carrier status is unknown but who have a high Aβ burden on brain

imaging. Initial outcomes in all these trials will be a change in plasma, CSF and imaging biomarkers of AD, follow-up studies will assess several clinical and cognitive outcomes.[95]

Plasma biomarkers of AD include Aβ40 and Aβ42[102] whose brain level is under physiological conditions balanced by the peripheral production by platelets and production and deposition of Aβ in the brain. In non-demented persons, plasma Aβ concentrations reflect brain Aβ levels. In familial AD[103] and Down syndrome with *APP* triplication[104], total plasma Aβ levels and $A\beta_{1–42}$ levels are increased. The usefulness of plasma Aβ as a risk biomarker for sporadic AD remains controversial [105,106] but there is evidence that elevated plasma $A\beta_{1–42}$ is an antecedent risk factor for sporadic AD, while decreasing levels or a decline in the $A\beta_{1–42}/A\beta_{1–40}$ ratio indicate disease onset.

CSF biomarkers of AD include levels of $A\beta_{1–42}$, total tau (t-tau) and p-tau.[107] In MCI or AD CSF levels of $A\beta_{1–42}$ are decreased while t-tau or p-tau are increased compared to non-demented subjects. The combined assessment of $A\beta_{1–37}$, $A\beta_{1–38}$, $A\beta_{1–39}$, $A\beta_{1–40}$ and $A\beta_{1–42}$ may further increase sensitivity and specificity in predicting progression from early cognitive impairment to AD[109].

Typical changes on structural MRI include atrophy in the medial temporal lobe in particular in the hippocampus and the amygdala.[110] In addition, white matter changes may be present. Atrophy in the hippocampus and entorhinal cortex is associated with a decline in memory function, progression of memory impairment[111] and an increased risk of AD[110,112]. On functional MRI (fMRI) AD is characterized by a decreased BOLD signal in the medial temporal lobe, parietal lobe and hippocampus during a cognitive task.[113] On positron emission tomography (PET) the amyloid specific imaging probe Pittsburgh compound B (PIB) binds selectively to cortical and striatal Aβ plaques, shows a strong positive correlation with AD diagnosis, fibrillary amyloid plaques at autopsy [114] and is inversely correlated with CSF Aβ42 levels in the presence of clinical AD[115]. Florbetaben (^{18}F-BAY94-9172) and Florbetapir (^{18}F AV-45) are amyloid imaging agents with similar binding profiles but longer half-life than PIB which can also differentiate AD from controls and other dementias [116,117] On ^{18}F-fluorodeoxyglucose (FDG)-PET imaging cerebral metabolism is decreased in AD, in particular in the parietal lobe.[118]

Newly identified risk genes can also advance drug development for AD by identifying novel therapeutic targets such as the complement, chaperone or cholesterol pathways. Whether these strategies are worth pursuing in AD not only depends on the potential of the compounds to cross the blood–brain barrier and the underlying mechanisms through which these genes are involved in AD. Sequencing studies are expected to uncover functional variants shedding light on these mechanisms by their nature (gain or loss of function) and/or location in specific functional domains, splice sites or regulatory regions.

EXPERT COMMENTARY

GWAS have identified more than 20 genomic susceptibility loci modifying AD risk. Common variants explain ~33% of the total phenotypic variance leaving a significant part of the phenotypic variance to be identified [75]. Ongoing studies using even larger sample sizes will likely identify additional loci with smaller effect sizes or allele frequencies. In

addition, gene-based and pathway-based analyses of genes not genome-wide significant but overrepresented among the SNPs with low p values are expected to identify additional genes and biological pathways. While extensive sample sizes of tens or hundreds of thousands of subjects are being used for populations of European descent, large-scale studies on other ethnic groups are lacking. Due to differences in allele frequencies and linkage disequilibrium between ethnic groups, studies in other ethnic groups need to be performed as they may identify genes and pathways not detected in Europeans. In addition, other AD outcomes such as age of onset of AD, rate of progression of AD and rate of cognitive decline, as well as the variants associated with AD-related disorders such as metabolic syndrome or cardiovascular disease need to be examined in large sample sizes and different ethnic groups. While common variants identified by GWAS identify pathways involved in the disease etiology, it is unlikely that they will be used to predict individual risk for AD.

Not yet completed is the follow-up of identified GWAS loci to map the specific underlying mutations. It is expected that several of these variants underlying GWAS signals will be identified through the ongoing large-scale sequencing projects performing whole-exome sequencing or whole-genome sequencing in more than 20,000 unrelated AD cases and controls and families multiply-affected by AD such as the Alzheimer's Disease Sequencing Project (ADSP) and Alzheimer's Disease Neuroimaging Initiative (ADNI). Previous studies in smaller sequencing sets have identified several disease-associated mutations modifying AD risk 2–3-fold in genes previously identified in candidate gene analyses and GWAS including PLD3 and TREM2 [75–77] Similar to the GWAS data, the sequencing data of these large-scale sequencing projects will be available to the research community through public repositories such as the NIA Genetics of Alzheimer's Disease Data Storage Site (NIAGADS, https://www.niagads.org/) and the database of Genotypes and Phenotypes (dbGaP, http://www.ncbi.nlm.nih.gov/gap), national genetics data repositories that facilitate access of genomic data to qualified investigators. Combining this data with functional analyses will provide further insight into the disease pathways and potentially druggable targets for therapeutic measures.

FIVE YEAR VIEW

The identification of common and rare variants that contribute to AD risk has provided significant insight into the molecular pathways underlying AD. GWASs and next-generation sequencing studies have identified genes that fall into specific common pathways in particular inflammation and immune response, lipid metabolism, and endocytosis/synaptic function. Ongoing targeted sequencing and functional studies of these identified genes are likely to clarify within the next few years some of the mechanisms involved in AD etiology. The ongoing large-scale whole-genome and whole-exome sequencing studies coupled with functional follow-up experiments are expected to identify numerous additional susceptibility loci. This more complete mapping of the genes and pathways dysregulated in AD, will enable us to improve genomic profiling for AD diagnosis and prognosis, and to develop more targeted - and thereby more effective- therapeutic measures.

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KEY ISSUES

- Late-onset AD is the most frequent form of dementia affecting 24 million persons worldwide
- The etiology of AD is largely unclear and there is no effective therapy for prevention or treatment
- AD is a pathologically and clinically heterogeneous disease with a strong genetic component to which both common and rare genetic variants contribute
- Mapping of the genes and pathways dysregulated in AD, will allow to improve genomic profiling for AD diagnosis and prognosis, and to develop more targeted and more effective therapeutic measures
- During the last 5 years, genome-wide association studies have mapped more than 20 common disease-associated variants
- Targeted sequencing and whole exome and whole genome sequencing studies have in addition identified rare disease-associated variants in *SORL1*, *PLD3* and *TREM2*
- The identified genetic variants hint to specific pathways involved in AD etiology including inflammation and immune response, lipid metabolism, endocytosis/synaptic function, amyloid processing, tau pathology and synaptic function
- The ongoing large-scale whole-genome and whole-exome sequencing studies are expected to identify numerous additional susceptibility loci within the near future

Table 1

Major pathways identified by genomic studies

Pathway	***Gene***
Amyloid pathway	*APOE, SORL1, CLU, CR1, PICALM, BIN1, ABCA7, CASS4, PLD3*
Immune system/inflammation	*CLU, CR1, EPHA1, ABCA7, MS4A4A/MS4A6E, CD33, CD2AP, HLA-DRB5/DRB1, INPP5D, MEF2C, TREM2/TREML2*
Lipid transport and metabolism	*APOE, CLU, ABCA7, SORL1*
Synaptic cell functioning/endocytosis	*CLU, PICALM, BIN1, EPHA1, MS4A4A/MS4A6E, CD33, CD2AP, PTK2B, SORL1, SLC24A4/RIN3, MEF2C*
Tau pathology	*BIN1, CASS4, FERMT2*
Cell migration	*PTK2B*
Hippocampal synaptic function	*MEF2C, PTK2B*
Cytoskeletal function and axonal transport	*CELF1, NME8, CASS4*
microglial and myeloid cell function	*INPPD5*