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REVIEW

An Overview of Genome-Wide Association Studies in Alzheimer's Disease

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Abstract Genome-wide association studies (GWASs) have revealed a plethora of putative susceptibility genes for Alzheimer's disease (AD). With the sole exception of the *APOE* gene, these AD susceptibility genes have not been unequivocally validated in independent studies. No single novel functional risk genetic variant has been identified. In this review, we evaluate recent GWASs of AD, and discuss their significance, limitations, and challenges in the investigation of the genetic spectrum of AD.

Keywords Association analysis · Alzheimer's disease susceptibility genes · Apolipoprotein E · Common variant

Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive cognitive decline that ultimately results in complete incapacitation and death of the patient. As the most common form of dementia, AD has become a global public health issue. Although it has been over 100 years since the discovery of AD in 1906, clinical trials for AD medications have failed to reach the desired effect on the intended target. The relationship among various AD signal pathways has not been delineated in adequate detail. In addition, it is generally believed that a process silently progresses for many years prior to the clinical onset of AD [1]. All of these considerations have forced researchers and clinicians to use all kinds of means to re-examine AD pathogenesis for disease treatment, among which genetic studies are considered to have great strategic significance.

According to the age at onset (AAO), AD can be subdivided into early-onset AD (EOAD) (AAO < 65 years) and late-onset AD (LOAD) (AAO ≥ 65 years). Well-known pathogenic mutations for autosomal-dominant EOAD occur in the three genes presenilin-1 (*PSEN1*) [2], amyloid precursor protein (*APP*) [3], and presenilin-2 (*PSEN2*) [4, 5], all of which are rare, fully-penetrant, and probably responsible for <1% of AD cases [6]. In contrast, LOAD is far more common and is considered to be affected by highly-prevalent genetic variants with low penetrance [7], the heritability of which is predicted to be as high as 80% based on studies of twins [8]. For LOAD, *APOEε4* is the only confirmed major risk factor [9], which accounts for up to 50% of cases [10]. With relevance to neurobiological mechanisms such as neuronal apoptosis and APP trafficking, early genetic studies of LOAD have identified several candidate genes (e.g. *DAPK1* [11] and *SORL1* [12, 13]), but they are still insufficient to completely reveal the genetic factors for AD. A more thorough and efficient approach is required to study the genetic factors of complex diseases like AD.

With the development of high-throughput genotyping, the genome-wide association study (GWAS) is an emerging tool for identifying genetic risk factors for complex diseases. A GWAS typically examines single nucleotide polymorphisms (SNPs) throughout the genome to identify

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disease-associated genetic variants. Unlike linkage and candidate gene studies, a GWAS allows simultaneous assessment of thousands of genetic variants (including non-coding regions) without prior assumptions about biological pathways. This makes it a very powerful approach for genetic studies of complex disorders like AD. In this review, we examine recently-published GWASs in AD, and assess their significance, limitations, and challenges in the analysis of the genetic spectrum of AD.

Landscape of GWASs in AD

A search of PubMed using the condition "(genome-wide[Title/Abstract]) AND Alzheimer[Title/Abstract]" for publications before April 1, 2015, resulted in 135 articles, from which studies applying genome-wide association analysis were further selected. A summary of the major GWASs in AD is shown in Table 1.

Many GWASs in AD have been published since 2007, with differences in study design (case–control or family-based), population ethnicity, population size, and genotyping platform. All the GWASs, except the one conducted on two extended pedigrees [14], have confirmed *APOEε4* as the most significant risk factor. In addition, a large number of genetic risk factors for AD have been implicated in these GWASs, but with no absolute consistency in replication studies.

The Emergence of GWASs in AD

GWASs of AD started in 2007. The first one used a two-stage genotyping protocol and tested 17,343 SNPs in two pools of DNA from AD patients and controls from the USA and the UK, and revealed *APOE* to be the only gene that shows significant associations with AD [15]. This method of DNA pooling greatly reduced the cost of genotyping yet required standardization of DNA concentration in each pool to avoid bias. Nevertheless, it only covered a small proportion of the genome. Using a much denser SNP panel, a GWAS of neuropathologically-confirmed AD cases and control subjects also did not obtain positive findings other than the *APOE* region, supporting *APOE* as the major susceptibility gene for LOAD [9]. However, another GWAS using the same dataset with additional clinical cases in the replication samples demonstrated an association of *GAB2* with AD among *APOEε4* carriers [16]. This finding was suggested to be consistent with neurobiological evidence [16].

Abundant Genetic Risk Factors Uncovered by GWASs

A plethora of novel AD susceptibility genes have been discovered using GWASs since 2007. A two-stage individual genotyping GWAS identified *LRAT* with genome-wide significance with AD [17], but it was not replicated in the follow-up studies [18]. Another GWAS showed an association of *GOLM1* with AD both in the discovery sample and the replication sample, though below genome-wide significance [19]. Subsequently, Beecham *et al.* [20] found *MTHFD1L* and *FAM113B* to be promising candidates in AD with a relatively small discovery sample of $\sim$500 AD cases and 500 controls. The study by Carrasquillo *et al.* was the only one to discover an AD-associated gene, *PCDH11X*, on chromosome X. However, this finding was inexplicable because this association was only significant in females but not in hemizygous males [21].

Family-based GWASs also contributed to the discovery of additional AD risk loci. *ATXN1*, *CD33*, and *APOC1* were identified in the first family-based GWAS in 2008 [22]. The second family-based GWAS by Poduslo *et al.* was performed among extended pedigrees of AD. By testing $\sim$500,000 SNPs in AD cases and unaffected family members from two extended families and unrelated controls, an association of SNPs in *TRPC4AP* with AD was revealed [14]. However, the significance of this study has been greatly inflated because it ignored the familial relationship of the unaffected family members while comparing differences between AD cases and unrelated controls [23]. Interestingly, this is also the only GWAS in AD that failed to replicate the association of *APOE* with AD, probably due to special risk factors in these pedigrees or inadequate statistical power.

To increase the power and improve the quality control, consortium efforts emerged to combine the GWAS datasets of AD since 2009. Two groups simultaneously published their results [24, 25], greatly expanding the population size to >14,000 each. Both studies found strong evidence for an association of *CLU* with AD, making *CLU* the first consistent risk gene since the identification of *APOEε4*. Association of *CR1* and *PICALM* with AD was also identified in these two studies. However, the three risk genes only account for part of the AD pathogenesis [26], not to mention the inflation of these estimates [27]. The third collaborative GWAS in AD with another large cohort included in the discovery sample was conducted in 2010 [28]. This study highlighted two additional putative AD loci, *BIN1* and *EXOC3L2*, and unsurprisingly replicated the association of *CLU* and *PICALM*, given the overlap of samples with previous GWASs implicating these two genes. Furthermore, the association of *BIN1* highlighted in this study was successfully replicated in another GWAS involving populations from the USA and Canada [29].

Besides these initial GWASs from the AD consortium database, additional GWASs in AD have been published. Naj *et al.* [30, 31] added *MTHFD1L* to the list of putative LOAD loci, which had a relatively higher odds ratio of 2.1

Table 1 Summary of genome-wide association studies of Alzheimer's disease.

Year	Authors (*et al.*)	Participant recruitment site(s)	Case number/control number (discovery stage; replication stage)	Number of SNPs	Genes identified
2007	Grupe [15]	UK, USA*	380/396; 1428/1666	17,343	*APOE*
2007	Coon [9]	USA, the Netherlands*	664/422	502,627	*APOE*
2007	Reiman [16]	USA, the Netherlands*	446/290; 415/260	312,316	*GAB2*
2008	Abraham [17]	UK*	1082/1239; 0/1400	561,464	*APOE*, *LRAT*
2008	Li [19]	UK, Canada*	753/736; 418/249	469,438	*APOE*, *GOLM1*
2008	Bertram [22]	USA**	941/404; 1767/838	484,522	*APOE*, *APOC1*, *ATXN1*, *CD33*, *GWA_14q31*
2009	Beecham [20]	USA*	492/496; 238/220	532,000	*APOE*, *FAM113B*, *MTHFD1L*
2009	Carrasquillo [21]	USA*	844/1255; 1547/1209	313,504	*APOE*, *PCDH11X*
2009	Poduslo [14]	European ancestry**	11/79; 199/85	500,000	*TRPC4AP*
2009	Lambert [24]	Europe*	2032/5328; 3978/3297	537,029	*APOE*, *CR1*, *CLU*
2009	Harold [25]	USA, Europe*	3941/7848; 2023/2340	529,205	*APOE*, *CLU*, *PICALM*
2010	Seshadri [28]	USA, Europe*	3006/14642; 2032/5328; 3333/6995	2,500,000	*APOE*, *BIN1*, *CLU*, *EXOC3L2*, *PICALM*
2010	Hu [29]	USA, Canada*	1034/1186; 1831/1764	509,376	*APOE*, *BIN1*
2010	Naj [30]	USA, Europe*	931/1104; 1338/2003	483,399	*APOE*, *MTHFD1L*
2011	Hollingworth [32]	European ancestry (meta-analysis)*	6688/13685; 4896/4903; 8286/21258	496,763	*ABCA7*, *MS4A6A/MS4A4E*, *EPHA1*, *CD33*, *CD2AP*
2011	Naj [33]	USA*	8309/7366; 3531/3565; 7650/25839	2,324,889	*APOE*, *BIN1*, *CD2AP*, *CD33*, *CLU*, *CR1*, *EPHA1*, *MS4A4A*, *PICALM*
2011	Sherva [38]	Israel*	124/142; 5509/7254	286,316	*AGPAT1*, *ATP6V0A4*, *GLOD4*, *RGS6*, *TMEM132C*
2011	Wijaman [36]	USA**	1848/1991; 549/544	592,532	*APOE*, *BIN1*, *CLU*, *CUGBP2*
2012	Lee [40]	USA*	549/544; 116/70	658,610	*DGKB*, *GWA-10q23.1*, *GWA-18q23*, *GWA-3q25.2*, *HPCAL1*, *CLU*, *PICALM*, *BIN1*
2012	Gaj [41]	Poland*	141/141	NA	*GWA-9q21.33*
2013	Miyashita [42]	Japan, Korea, with Caucasian datasets*	1008/1016; 885/985; 339/1129; 11840/10931	5,877,918	*SORL1*, *PICALM*, *BIN1*
2013	Reitz [43]	African American*	1968/3928	17,332,474	*ABCA7*, *HMHA1*, *GRIN3B*, *APOE*, *CR1*, *BIN1*, *EPHA1*, *CD33*
2013	Lambert [37]	European ancestry (meta-analysis)*	17008/37154; 8572/11312	7,055,881	*CR1*, *BIN1*, *CD2AP*, *EPHA1*, *CLU*, *MS4A6A*, *PICALM*, *ABCA7*, *APOE*, *HLA-DRB5/HLA-DRB1*, *PTK2B*, *SORL1*, *SLC24A4/RIN3*, *INPP5D*, *MEF2C*, *NME8*, *ZCWPW1*, *CELF1*, *FERMT2*, *CASS4*
2014	Jun [62]	European ancestry, African American, Japanese**	61/2530; 14195/15235	341,492	*PLXNA4*

* Case-control approach, ** Family-based approach

NA data not available

than other common variants identified by GWASs. In 2011, a meta-analysis of GWASs in participants of European ancestry identified *ABCA7*, *MS4A6A/MS4A4E*, *EPHA1*, *CD33*, and *CD2AP* as AD-associated genes [32]. Meanwhile, another combined GWAS identified *MS4A4A*, *CD2AP*, *EPHA1*, and *CD33* as AD-associated genes [33]. These results together with the study by Bertram *et al.* [22] in 2008 made *CD33* the only gene (except for *APOE*) with significance in GWASs in AD with both case–control and family-based approaches [34]. Using GWAS datasets, Jun *et al.* [35] looked into the *APOE* region and found no association of SNPs in this region with AD or AAO after adjusting for *APOE* status, suggesting that *APOE* could explain all the genetic risk in the *APOE* region. Wijsman *et al.* conducted the largest combined GWAS among familial LOAD pedigrees so far, in which *CUGBP2*

reached genome-wide significance among *APOEε4* homozygotes and the association of *BIN1* and *CLU* was successfully replicated [36].

Eventually, there was a meta-analysis on GWASs with the huge population size of 74,046 individuals with European ancestry. Using the raw data of GWASs, this meta-analysis increased the power of detecting variants with minor effects, and confirmed 19 AD susceptibility loci (other than *APOE*) [37] with modest odds ratios of 0.73–1.22.

Finding Genetic Risk Factors in Diverse Ethnic Groups

Because of the possibility of ethnic-specific LOAD susceptibility variants, GWASs examining AD associations in multiple ethnic populations have been reported recently.

In 2011, a GWAS was conducted in a unique Israeli-Arab population [38], which was characterized as being highly inbred with an unusually high prevalence of AD despite having a lower *APOEε4* allele frequency than other Caucasian populations [39]. This study revealed several candidate genes for further study, although none of them showed statistical significance after multiple test corrections, nor did they account for the increased AD prevalence in this population.

In 2012, Lee *et al.* [40] conducted a GWAS among Caribbean Hispanic individuals and successfully replicated the association of AD with *CLU*, *PICALM*, and *BIN1*, and other 5 SNPs. Gaj *et al.* [41] pooled DNA samples from female-only patient groups from Poland and identified *rs7856774* at *9q21.33* as a novel LOAD candidate risk variant, independent of the effect of *APOE*.

In 2013, a GWAS among AD cases and controls was performed in Korean and Japanese populations with replication samples including Caucasians [42]. This study demonstrated for the first time the genome-wide significance of LOAD with *SORL1*, and confirmed the role of other known loci including *PICALM* and *BIN1* for LOAD in the Japanese population.

In the same year, a GWAS in LOAD using African-American cohorts was reported [43]. As noted by Robert L. Nussbaum, this study adopted the best practices of GWAS including quality control of genotyping, testing for population stratification, and merging genotyping data performed on different platforms with different sets of variants [44, 45]. This report revealed that *ABCA7* increased the risk for LOAD $\sim$1.8-fold in African Americans compared to a more modest increased risk of 1.1-fold to 1.2-fold in individuals with European ancestry [45]. In addition, this study confirmed that *APOEε4*, *CR1*, *BIN1*, *EPHA1*, and *CD33* were associated with LOAD in African Americans as previously confirmed in Caucasians, highlighting the importance of these variants in disease risk by replicating the associations in multiple ethnically diverse populations. These studies demonstrate that some AD risk loci appear to have similar effects among different populations while others seem to be population-specific [46].

GWASs on Phenotypes Associated with Diagnosis and Clinical Presentation of AD

Although most of the GWASs in AD may choose disease status as the phenotype for investigation, GWASs using intermediate phenotypes of AD have been reported due to the findings by Shulman *et al.* [47]. These intermediate phenotypes include biomarkers (e.g. from neuroimaging and from cerebrospinal fluid), clinical features, and neuropathological features of AD.

AD Biomarkers from Neuroimaging and in Fluids as the Phenotype

Neuroimaging and AD biomarkers in fluids have been chosen as phenotypes in GWASs in AD. By using hippocampal atrophy from neuroimaging as a quantitative phenotype, Potkin *et al.* [48] revealed *TOMM40* as a novel AD-associated gene. The well-replicated association of *CR1* and *PICALM* among AD cases and controls has also been confirmed in a multi-center GWAS using phenotypes of AD-related neuroimaging changes such as hippocampal volume [49]. Stein *et al.* [50] conducted the first voxel-wise GWAS and suggested *CSMD2* and *CADPS2* as candidate genes for future investigation. Ramanan *et al.* [51] used florbetapir (^{18}F) positron emission tomography (PET) to evaluate the cortical load of amyloid β, which revealed an association of *APOE* and *BCHE* with this load. Carrasquillo *et al*. [52] revealed the association of *IDE* with amyloid β40 and total amyloid β levels in plasma. Han *et al.* [53] found *CYP19A1* and *NCAM2* to be associated with AD biomarkers in cerebrospinal fluid (CSF) including β-amyloid peptide ($A\beta_{1\text{-}42}$), total tau protein, and phosphorylated tau ($P\text{-}tau_{181P}$). Using the same AD biomarkers in CSF as Han *et al.*, Kim *et al.* [54] showed that *APOE*, *LOC100129500*, *TOMM40*, and *EPC2* had genome-wide significance. By performing so far the largest GWAS using AD biomarkers in CSF, Cruchaga *et al.* [55] revealed the association of *GLIS3* and *TREM* with AD.

Clinical Features as the Phenotype

Clinical features have also been used as phenotypes in GWASs to uncover genetic risk variants for AD. AD patients with psychotic symptoms are associated with more rapid cognitive decline. By conducting the first GWAS in AD with psychotic symptoms, Hollingworth *et al.* [56] revealed the strongest evidence for an association of *APOE*

and an intergenic region on chromosome 4 for AD. Moreover, AAO has also been used as the phenotype in large-scale GWASs, which revealed the association of *CR1*, *BIN1*, and *PICALM* with AAO among patients with LOAD. However, the effect of these genes in AD did not exceed that of *APOE* [57].

Neuropathological Features as the Phenotype

The underlying pathology of AD has also been used in GWAS investigations. For example, by performing a GWAS of neuritic plaque pathology, Shulman *et al.* [58] discovered that *APOE*, *CR1*, *ABCA7*, *CD2AP*, and a variant near *APP* were associated with the neuritic plaque burden of AD.

Other Forms of GWASs in AD

Other forms of GWASs in AD have also been conducted. To explore personalized treatment for AD, GWAS of AD pharmacogenomics was performed on a cohort of AD patients responding and not responding to treatment with cholinesterase inhibitors (ChEIs) [59]. One SNP in *PRKCE*, and one SNP in an intergenic region that acts as a *cis*-regulator of *NBEA*, were associated with response to treatment. This study helped to identify common genetic variants predictive of response to ChEI treatment in AD patients. Also, there was a GWAS on AD and Parkinson's disease, which revealed no common genetic risk factors shared by these two diseases [60]. In addition, a GWAS using DNA-methylation markers was performed, which revealed that brain DNA methylation in multiple AD loci including *SORL1*, *ABCA7*, *HLA-DRB5*, *SLC24A4*, and *BIN1* was associated with AD pathologies [61].

Recently, researchers have come up with updated protocols for the wider utilization of GWAS datasets. A novel method of incorporating the entire family structure to reduce bias was used in a family-based GWAS, which generated strong evidence for a novel association of *PLXNA4* with AD [62]. The first genome-wide epistasis study for AD was performed using GWAS data with a protocol for exhaustive epistasis screening, which revealed an AD-associated interacting SNP-pair of the *KHDRBS2* and the *CRYL1* genes [63].

Perspective of GWASs in AD

GWAS has advantages over conventional genetic approaches for studying the genetics of complex diseases like AD due to its independence of disease pathways, precision of gene searches, high-throughput, and whole-genome screening range. GWAS has well-replicated the association of *APOE* with AD. In addition, it has identified numerous AD-associated genes with success rates much higher than in the pre-GWAS era. The top 10 candidate genes in AlzGene (www.alzgene.org) from meta-analysis are also findings from GWASs. Subsequent biological pathway analysis has confirmed the potential pathogenic role of some genes previously identified by GWASs, validating their value in guiding future research into the mechanisms underlying AD. However, the lack of consistent results among GWASs implies genetic heterogeneity of AD. The major ethnic group in GWASs is Caucasian; no GWAS results have been published using the Chinese population, and GWASs for various ethnic groups need to be examined in the future.

Admittedly, GWAS has some limitations. First, it can only reveal genes "associated" with a disease without directly validating them as causing the disease, because the disease-associated genes might be in linkage disequilibrium with the specific disease-causing genes [64]. Thus, functional analysis is needed to validate the GWAS-discovered candidate AD risk genes. Second, this approach is based on the "common disease-common variants" hypothesis rather than the "common disease-multiple rare variants" hypothesis [65–67], which addresses the coverage of GWAS as one of its pitfalls.

Although GWASs in AD have successfully revealed numerous associated SNPs, the odds ratios of common variants are generally modest (ranging from 1.1 to 2.0), accounting for only a small proportion of the estimated heritability when calculated using a simple additive model [68, 69]. Several reasons may contribute to the unexplained heritability. One is that the effects of some causal variants are too small to reach statistical significance in GWASs, unless a much larger sample size is acquired [70]. In addition, some genetic variance might be undetected because the causal variants are not in complete linkage disequilibrium with the genotyped SNPs [70]. Furthermore, GWAS misses rare variants with a minor allele frequency of <0.01, which might have relatively large effects for developing complex diseases [71]. To illustrate this point in particular, Kim *et al.* [72] discovered rare variants in *ADAM10* to be highly pathogenic in 7 of 1,000 LOAD pedigrees, which challenges the idea that LOAD is only associated with common variants like *APOEε4*. This is a good example of the contributions of rare variants to common diseases like LOAD, which have not been revealed readily by GWAS.

To reinforce and complement the GWAS results of AD, genetic variant searches in multiplex families, correlation studies focusing on specific variants, and other detection methods including sequence-based association studies for detecting rare and structural variants are warranted in the future. In addition, the functional effects of the AD risk genes identified by GWASs remain to be elucidated. In any event, GWAS is still widely used in current AD genetic

studies. In the future, we expect the emergence of GWASs with multi-ethnic populations that should provide novel insights into the genetic spectrum and pathogenesis of AD, and reveal useful clues for designing effective treatment and prevention strategies.

Conclusion

A number of GWASs for AD-associated candidate genes have been reported worldwide. These reports vary in study design, population ethnicity, sample size, and genotyping platform. As a mechanism-free approach, the GWAS has identified numerous putative genes for AD, and has greatly enriched our knowledge of the AD genetic spectrum. Once the pathophysiological basis of these AD-associated genes is established, these findings will finally lead to clinical applications for the earlier prediction, diagnosis, and better therapy for AD.

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