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Genetic Analyses of Alzheimer's Disease in China: Achievements and Perspectives

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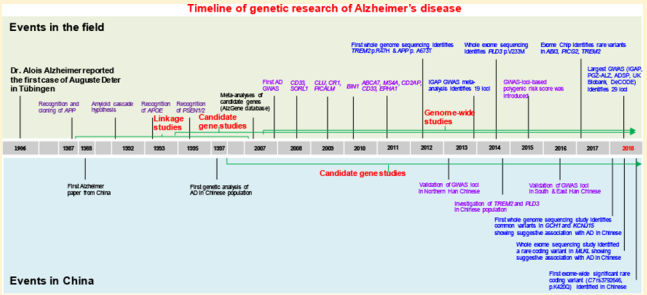
ABSTRACT: Since 2010, the Chinese have become one of the most aged populations in the world, leading to a severe burden of neurodegenerative disorders. Alzheimer's disease (AD) is the most prevalent neurodegenerative disease and has a high genetic heritability. In the past two decades, numerous genetic analyses, from linkage analyses and candidate gene studies to genome-wide association studies (GWASs) and next-generation sequencing studies, have identified dozens of AD susceptibility or causal genes. These studies have provided a comprehensive genetic view and contributed to the understanding of the pathological and molecular mechanisms of the disease. However, most of the recognized AD genetic risk factors have been reported in studies based on European populations or populations of European ancestry, and data about the genetics of AD from other populations has been very limited. As China has the largest AD population in the world and because of the remarkable genetic differences between the East and the West, deciphering the genetic basis and molecular mechanism in Chinese patients with AD may add key points to the full characterization of AD. In this review, we present an overview of the current state of AD genetic research in China, with an emphasis on genome-level studies. We also describe the challenges and opportunities for future advances, especially for in-depth collaborations, brain bank construction, and primate animal modeling. There is an urgent need to promote public awareness and increase our collaborations and data sharing.



KEYWORDS: *Alzheimer's disease, Chinese, linkage analysis, genome-wide association study, next generation sequencing, risk gene*

1. ALZHEIMER'S DISEASE IN CHINA: A HEAVY DISEASE BURDEN

Alzheimer's disease (AD, MIM no. 104300) is an irreversibly degenerative brain disorder and the most prevalent type (60−80%) of dementia in the elderly.[1] It is characterized by an accumulation of extracellular β-amyloid (Aβ) plaques and intracellular neurofibrillary (tau) tangles in the brain, leading to neuron death, brain atrophy, and memory loss.[2] The prevalence of AD ranges from 4.6% to 8.7% in people aged >60 years worldwide, and the figure increases rapidly as a population ages (prevalence up to 69.4% in people aged >90).[3] According to the World Alzheimer Report,[3,4] there were 50 million people living with dementia in 2018, of which around 35 million were AD sufferers. As the aged population grows, there will be 152 million with dementia by 2050,[4] leading to severe public health problems and very heavy social and economic burdens.[3,4]

China has been defined as a country with an aged population since 2000, with the elderly (aged >65) then making up 7% of the total population.[5] By 2010, 13.26% of the Chinese population were aged 60 or over according to the Sixth National Population Census of China (http://www.stats.gov.cn/english/NewsEvents/201104/t20110428_26449.html).[5] Previous reports have shown that there were 9.19 million dementia and 5.68 million AD patients in China in 2010.[6,7] In fact, the number could now be even larger according to the estimated prevalence of 6.61% in people aged >60 years[3] in China. This heavy disease burden is challenging the socio-economics of the country and especially the health care system. The estimated annual cost due to dementia was $47 billion in 2010 and was predicted to reach 69 billion by 2020.[8] In a recent estimation by Prof. Jianping Jia and colleagues,[9] the annual socioeconomic cost per patient was $19,144, and total

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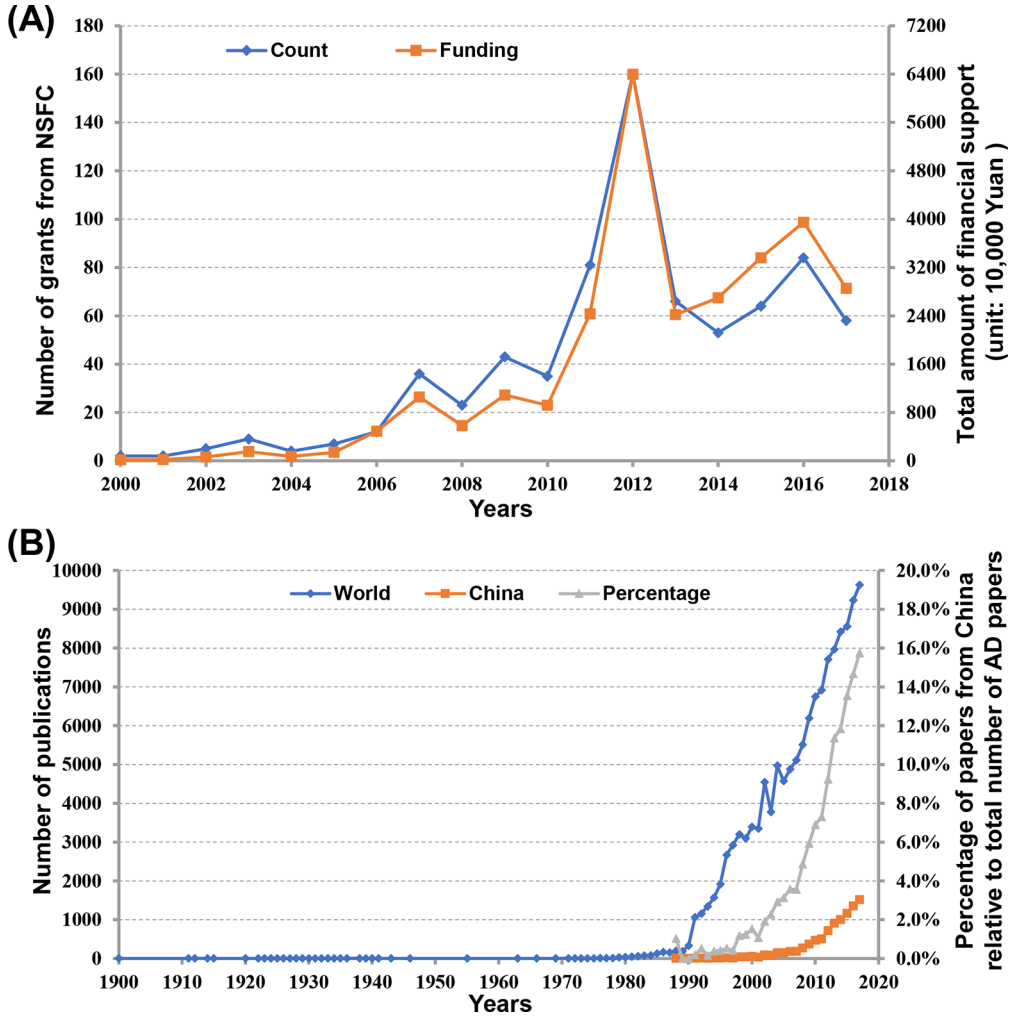

Figure 1. Increased financial support and publication records on Alzheimer's disease from China. (A) Grants from National Natural Science Foundation of China (NSFC) during 2000–2018 were retrieved from www.sciencenet.cn using "Alzheimer" or "senile dementia" as the keywords. (B) Publication records were retrieved from Web of Science, using "Alzheimer and China" as the keywords (dated in August 2018).

costs in China were $167 billion in 2015, whereas the global estimates of costs for dementia were $957 billion.

2. AD RESEARCH IN CHINA: INCREASING SUPPORT AND MORE PUBLICATIONS

Evidently, in the coming years, AD will be a major public health problem in China. More research focusing on AD and greater financial support are both needed to deal with this disease. Luckily, both the number of grants and the total amount of funding from the National Natural Science Foundation of China (NSFC) for "Alzheimer's disease" or "senile dementia" have increased over the years (Figure 1A). On average, only 16 grants for AD were supported each year before 2010, but the number increased to 81 per year between 2011 and 2017. The average amount of funding on AD per year increased from 4.18 million Yuan (RMB) before 2010 to 34.45 million Yuan after 2010, an 8-fold increase (Figure 1A). Besides NSFC, the Ministry of Science and Technology (MOST) of China is another important source of grants for investigating AD. Since 2015, dementia and other common neuropsychiatric disorders have been included in big proposals (e.g., "Precision Medicine" or "Prevention and control of major chronic non-communicable diseases") supported by the National Key R&D Program of China. To our knowledge, there were five MOST-funded grants focusing on AD from 2016 to 2018, with a total amount up to 10 million Yuan for each grant. Local funding agencies at the provincial level also have invested in this disease in recent years, with the aim to counteract the heavy aging burden. Because of increased public awareness and governmental support, focused research interest in AD also increased rapidly (Figure 1B). By searching the Web of Science database (https://apps.webofknowledge.com) using "Alzheimer" and "China" as the keywords (accessed in August 2018), we identified 10203 records and found that the first paper from China focusing on Alzheimer's disease could be traced to 1988[10] (Figure 2). In the past decade, around 766 papers on average about AD were published each year from China, whereas 7453 papers on average about AD were published each year worldwide. Although the publication number is still small, the proportion of AD publications from China in worldwide publications has increased rapidly (Figure 1B): the proportion was less than 1% before 1997, exceeded 10% in 2013, and reached 16% in 2017 (Figure 1B). With the increase of financial support and research interest, we would expect a further expansion of AD research and accumulating world influence from new Chinese discoveries.

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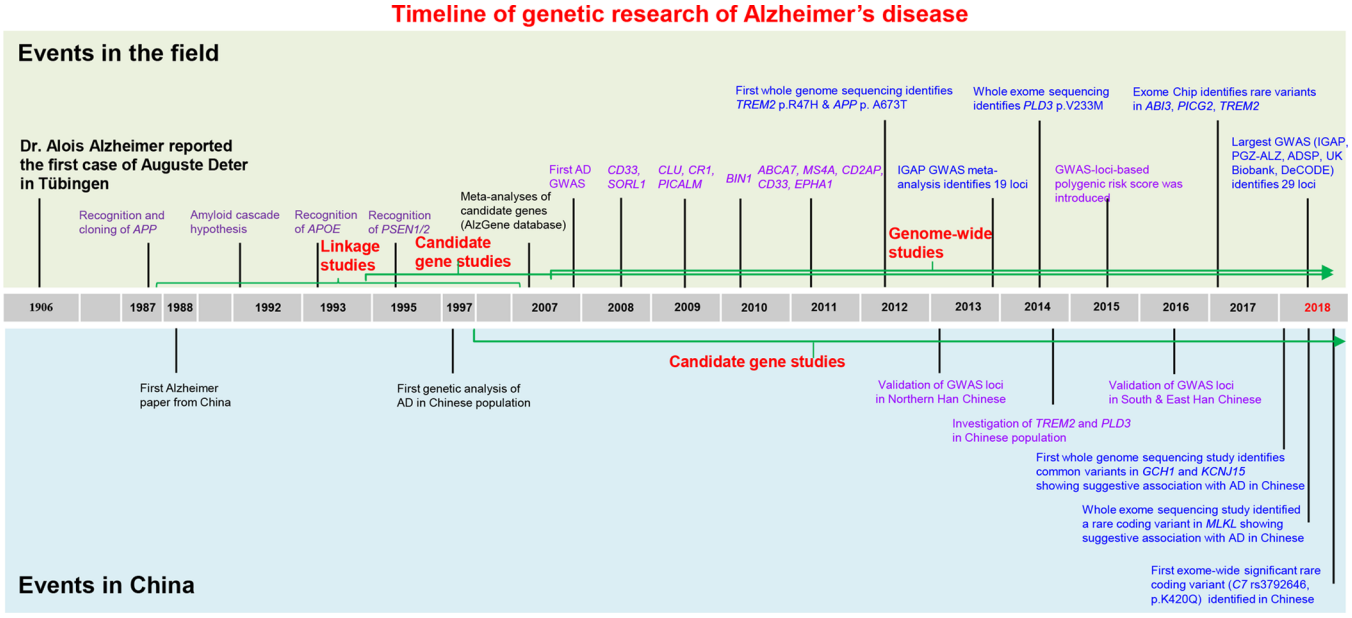

Figure 2. Time line of genetic research on Alzheimer's disease. The time line was modified from the figure showing the evolution of Alzheimer's research (https://www.alzforum.org/timeline/alzheimers-disease#2016), with permission from the Alzforum. GWAS, genome-wide association study; NGS, next-generation sequencing; time of events in Chinese groups was based on paper records in the Web of Science (dated in August 2018).

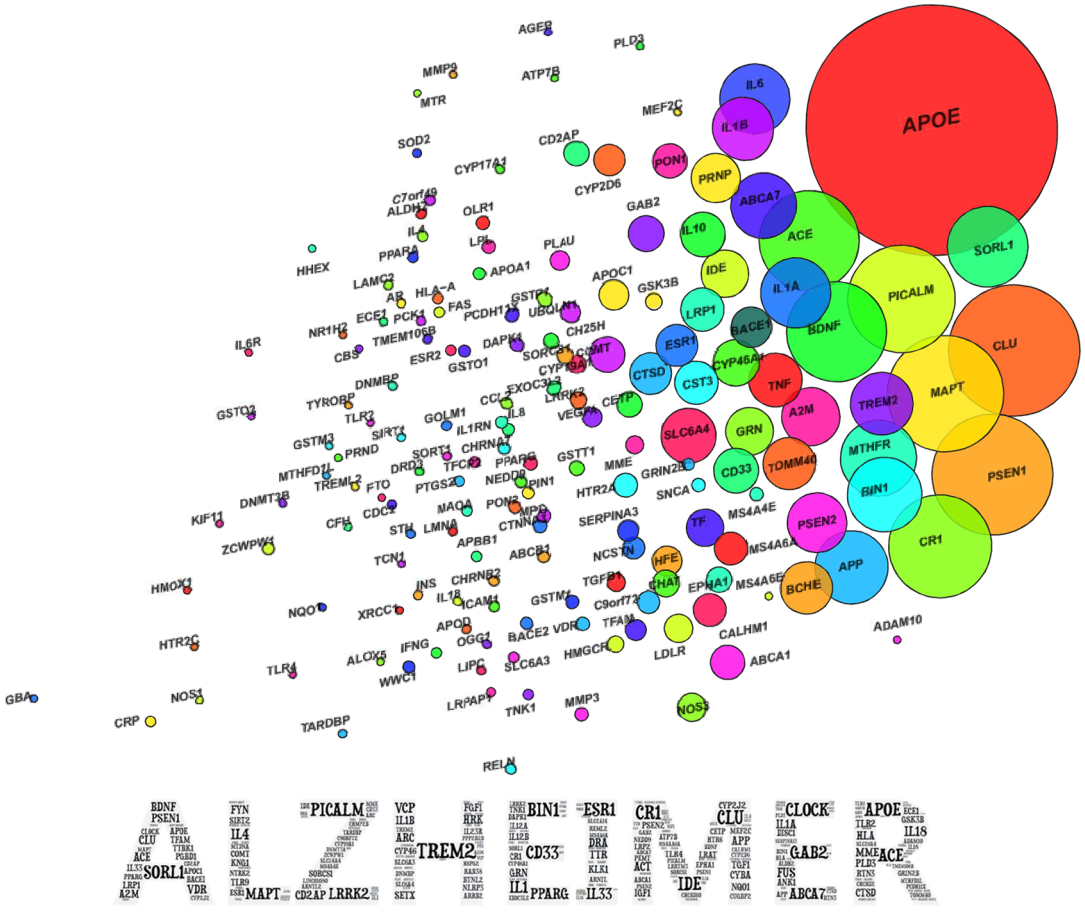

Figure 3. Risk genes presented in genetic studies of Alzheimer's disease. Numbers of publications for each gene were retrieved from the HuGE navigator (https://phgkb.cdc.gov/PHGKB/startPagePhenoPedia.action). The bubble plot was constructed by using the R package "symbols", with publication number as the radius for each circle. The Word Cloud in the bottom panel was constructed using all the genes studied in Chinese populations by using the WordArt online tool. The larger the gene name, the larger number of publications for the gene.

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3. GENETICS OF ALZHEIMER'S DISEASE: REMARKABLE ACHIEVEMENTS IN THE FIELD

Despite the complex etiological nature of AD, the disease has been considered to be a polygenic disorder with a genetic heritability of up to 79% according to twin and family studies.[11] A full understanding of the genetic factors conferring susceptibility to AD is essential for mechanism investigations, risk predictions, and effective therapies and constitutes the basis for comprehensive testing of new drugs. Three genes, *APP*,[12,13] *PSEN1*,[14,15] and *PSEN2*,[16,17] involved in the production of Aβ plaques have been recognized to be the causal genes for autosomal dominant early onset familial AD and were identified by linkage analyses in the early 1990s (cf. review papers[2,18]) (Figure 2). However, pathogenic mutations in these three genes only account for less than 5% of total AD cases.[19,20] The risk genetic component of the sporadic late-onset form, which accounts for the majority of AD cases, has been the target of most later genetic studies.

The search for disease-related genetic factors (susceptibility loci) focused mainly on the study of candidate genes in the early 2000s (Figure 2). In the past few decades, a total of 1760 genes have been reported in AD based on records retrieved from the Phenopedia tool in the Public Health Genomics Knowledge Base (https://phgkb.cdc.gov/PHGKB/startPagePhenoPedia.action, accessed in August 2018).[21] Most of these studies analyzed only a few variants in selected gene(s) in small sample sets. Among the 1760 genes, 72.5% (1276 genes) were reported only once, resulting in a high possibility of false positive reports as discussed by Guerreiro and colleagues.[19] Although many of these "risk" genes could not be validated in independent populations even of similar ancestry, several hundreds of positive associations have been reported and validated by independent studies. For instance, 220 of the 1760 genes were reported by at least 4 publications (Figure 3). The apolipoprotein E (*APOE*) was the most commonly found gene associated with sporadic AD, being reported by 1544 publications (dated in August 2018 according to Phenopedia). For other candidate associations, the AlzGene database (http://www.alzgene.org/) has systematically collected, summarized, and meta-analyzed the reports of 695 genes from 1395 studies.[22] Their list of top associations has helped the field considerably in the pre-GWAS era. Note that in the current "big data" era, candidate studies will be less important; however, intensive analyses of target genes still have practical value, as we showed recently with an integrative analysis approach looking for candidate genes.[23]

Although many genes have been suggested as being involved in AD (albeit at different levels of certainty), the success of the candidate gene approach relies in an in-depth understanding of the disease pathways. Unbiased genome-wide screening in large sample sets may give such insights. With the development of high throughput genotyping technologies, GWAS has been used widely in the genetic research of complex diseases since 2007.[24] Instead of studying a few genetic variants, GWAS has tested millions of common variants in the whole genome for association with a disease. The first GWAS of AD was published in February 2007 based on 380 cases and 396 controls.[19,25,26] Thereafter there was a rapid increase in GWAS over the following decade (Figure 2), identifying several genome-wide significant loci associated with AD such as *CLU*, *CR1*, and *PICALM*,[27,28] which could be validated in different populations (Figure 2). In 2013, the International Genomics of Alzheimer's Project (IGAP) conducted a comprehensive meta-analysis of four reported GWAS studies with 17008 AD cases and 37154 controls,[29] leading to the identification of 19 common loci reaching genome-wide significance. The 19 loci acted as the most reliable hits for AD genetics for 5 years,[29] before the three even larger GWAS studies that were initially released on bioRxiv recently.[30−32] In the latest GWAS, Jansen et al.[32,33] meta-analyzed data from three cohorts: the IGAP,[29] the Psychiatric Genomic Consortium (PGZ-ALZ), and the Alzheimer's Disease Sequencing Project (ADSP),[34,35] with a total of 24000 AD cases and 55000 controls. They validated the results using the UK Biobank (which included 74793 AD-by-proxy cases and 328320 controls) and DeCODE (an independent Icelandic cohort with more than 6500 AD cases and 174000 controls) data.[32,33] Based on this extremely large sample set of more than 100000 cases and 500000 controls, they identified 29 AD risk genome-wide significant loci,[33] of which 19 had been reported in the 2013 IGAP study.[29] This milestone work has suggested robust AD GWAS loci for further functional assays.

There is no doubt that candidate gene association analyses and GWASs are successful in uncovering AD-associated common variants within susceptibility genes. However, most of the AD-associated loci have been shown to be noncoding common variants with unknown functions and weak effect sizes.[24,36] A functional variant that has a high effect size (odds ratio >1.2) but is rare in a population is difficult to be identified by GWAS because of the technical limit of the chip being used.[24] This was partially addressed by the recent whole-exome-microarray-based study of the IGAP cohort with 85133 subjects,[37] which identified rare functional variants in *PLCG2*, *ABI3*, and *TREM2*. However, the exome-microarray only analyzed known variants in the chip. The discovery of most rare functional variants relies on next-generation sequencing (NGS) technologies. The first NGS-based hit was *TREM2* p.R47H (rs75932628), identified in the Icelandic cohort by whole genome sequencing.[38] In this cohort, the authors also identified a protective mutation p.A673T in the *APP* gene.[39] Another NGS hit was the *PLD3* p.V233M (rs145999145), identified by whole exome sequencing in a large family.[36] Alongside these top hits from a large-scale NGS analysis, another NGS study reported a rare coding variant, p.T835M (rs137875858), in *UNC5C*.[40] These rare variants had an effect size close to that of the *APOE* ε4 allele (OR > 3). Note that the association of *TREM2* p.R47H with AD was well validated in several independent association studies,[41−43] but *PLD3* was questioned by subsequent studies,[44−47] and *UNC5C* was less well validated.[43] Compared to GWAS, NGS studies yield fewer hits, simply because NGS costs much more money and requires a larger sample size for achieving a reasonably high statistical power. The ADSP was the largest whole-exome sequencing project in AD research so far.[35] It highlighted rare coding variants in the *SORL1* gene identified by previous GWAS[48] and identified several novel genes (*IGHG3*, *STAG3*, and *AC099552.4*) harboring functional variants.[35] In total, around 10 genes with rare functional variants were identified by NGS studies so far, providing promising targets for further mechanism studies and therapeutic treatments.

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4. CANDIDATE GENE STUDIES OF AD IN CHINESE POPULATIONS: VALIDATION OF THE TOP HITS AND DISCOVERY OF CHINESE-SPECIFIC RISK VARIANTS

While the worldwide genetic research was being fruitful, genetic study of AD in China was still at a preliminary stage. The first genetic analysis of AD in a Chinese population was reported in 1997, focusing on the effect of *APOE* ε4.[49] Beginning with candidate gene association analysis using low throughput genotyping technologies, there was only a hundred or so genes ever reported in Chinese with around 200 genetic reports so far (Figures 2 and 3). Only two dozen genes were reported by at least two papers. The most consensus genes were the European-based GWAS and NGS hits, such as *APOE*, *TREM2*, *PICALM*, *CLU*, *SORL1*, and *ACE* (Figure 3) or important neuronal genes such as *MME*,[50] *BDNF*,[51,52] *Arc*,[53] and *TTR*.[54] Nevertheless, the majority of the hypothesis-driven candidate genes in Chinese subjects were made in the scattered reports of small-scale studies.

Validating the associations of the European-based top loci with AD risk in different populations such as the Han Chinese was essential work in genetic research of AD. The research group from Qingdao University, led by Prof. Lan Tan and Dr. Jin-Tai Yu, investigated the associations of GWAS-linked loci with late-onset AD in northern Han Chinese populations.[55,56] They validated the associations between common variants of *APOE*, *CLU*, *CD33*, and *MS4A6A* and AD but failed to validate the associations of *ABCA7*, *CD2AP*, and *EPHA1* with AD in northern Chinese.[55,56] The association of these European-GWAS loci with AD in Han Chinese populations from Southwest and East China were investigated by our group.[57] We verified the associations between *PICALM*, *CLU*, *MS4A4E*, and *BIN1* and AD in Han Chinese populations, whereas the remaining GWAS genes, such as *CD33* and *ABCA7*, might not play major roles in etiology of AD in our populations under study.[57] Despite the successful validation of most GWAS hits in the Chinese, there were exceptions. For instance, we analyzed single nucleotide polymorphisms (SNPs) within the AD-associated top immune genes (*CR1*, *CR2*, *CLU*, *CD33*, and *TREM2*) in Chinese populations from Southwest and East China and found that the Europeans hits *CR1*, *CLU* and *CD33* showed no association with AD in the Han Chinese samples, while in Chinese, it is the *CFH* gene that shows a strong association with AD risk.[58]

In addition to performing genotyping of the GWAS SNPs, some of the GWAS top genes were screened using Sanger sequencing with an attempt to map the potentially functional variants.[59,60] Missense variants in *CR1* were observed influencing the risk of AD in northern Chinese.[61] The mutation pattern of European-based NGS genes in Chinese populations was also investigated in recent studies. Among the limited list of NGS hits, *TREM2* received the most attention.[38] Screening for the p.R47H mutation in a small Chinese sample showed the absence of this mutation in Chinese AD patients.[43] Complete Sanger sequencing of the full sequence of *TREM2* revealed that another rare coding variant, p.H157Y, influenced the risk of AD in Chinese, rather than the NGS hits seen in Europeans.[42] For another important NGS hit, *PLD3*,[36] we and other groups screened variants in this gene in Chinese individuals and found a weak effect of the hit p.V232M (rs145999145).[43,47] Most recently, Tan and colleagues identified a potential association of rare variants p.I163M and c.1020-8G>A in *PLD3* with late-onset AD in Han Chinese.[62]

As may be expected, the limited quantity and small sample sizes of these validation studies carried out in Chinese populations have yielded few definitive results. The main reason for the inability to validate the associations has been the small sample sizes, which have insufficient statistical power to detect the associations. However, genetic and phenotypic heterogeneity might be another reason. For instance, we observed a coding variant p.Y402H in the *CFH* gene conferring AD risk in Chinese with a relatively strong effect size (OR = 1.7), whereas this variant showed no association with AD in European populations due to population heterogeneity.[58] The identification of *TREM2* p.H157Y in Chinese patients with AD, rather than the European hit p.R47H, was another population-specific case.[42]

5. GENOME-WIDE ANALYSES OF CHINESE WITH AD: A START IN 2018

Despite the above candidate gene studies, the Chinese population has been extremely under-represented in genome-wide studies for AD. Since 2008, about 50 GWAS were published on AD or related traits primarily in patients from Europe and the United States, while no GWAS of individuals of Chinese descent were published before 2018. In fact, there was only one GWAS report in East Asians (with a Japanese population) in 2015, although no significant risk loci was identified from this study with the exception of the well-known hit *APOE4*.[63] Luckily, genome-wide studies from China have come at last, albeit a little late. A recent study led by Prof. Nancy Ip and colleagues performed a low-coverage whole genome sequencing of 477 AD patients from East China and identified two novel common variants (rs72713460 in *GCH1* and rs928771 in *KCNJ15*) conferring AD risk in the Chinese population, serving as the first genome-wide analyses of AD in Han Chinese.[64] In another study, Wang et al.[65] conducted whole-exome sequencing for 246 *APOE* ε4 negative AD patients from Hong Kong and identified a suggestively significant rare stop-gain variant (p.Q48X) in the *MLKL* gene to be associated with AD. We started whole-exome sequencing in a small AD cohort by using an extreme-phenotype strategy, namely, working on a sample set with extremely early onset age (younger than 55 years old) or with familial history or both in early 2015 and identified an exome-wide significant rare functional variant p.K420Q (rs3792646) in the complement *C7* gene conferring risk to AD with a considerable effect size.[66] The association was validated by independent Han Chinese cohorts and appeared to be an important rare variant in Chinese or East Asians.[66] We provided further functional evidence to show that C7 mutant p.K420Q disturbed cell viability, immune activation, β-amyloid processing, and excitatory synaptic transmission.[66] In addition to these three NGS studies, there are other small-scale whole-genome or exome sequencing or GWAS projects from Chinese research groups on the way. Genome-wide studies in Chinese and other populations are promising for the identification of more novel risk genes and may add more knowledge to our understanding of the genetic basis of AD. However, it should be noted that larger samples are needed in future studies to achieve a sufficient statistical power. Moreover, to carry out functional assays for these risk genes identified from genome-wide studies is essential to provide a final proof for their potential pathogenicity.

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6. KEY ADVANCES IN MECHANISTIC RESEARCH OF AD IN CHINA

In addition to the progress of genetic studies of AD and the successful elucidation of the underpinnings, there have been several remarkable advances in mechanistic research of AD in China in the context of the available hypotheses of Aβ plaques and tau phosphorylation. To name a few, the team led by Prof. Yigong Shi has determined the crystal structure and biochemical characterizations of γ-secretase,[67−72] serving as an important reference to the mechanistic understanding of AD and the pathogenicity of γ-secretase mutants. The research teams mainly led by Prof. Jianzhi Wang and Prof. Ke-Qiang Ye have established a new research direction in APP processing regarding δ-secretase.[73−76] In particular, they revealed the abnormal regulation of pathways concerning tau accumulation and tauopathies.[77,78] Prof. Yan-Jiang Wang and his team have provided a novel perspective regarding the peripheral clearance of Aβ[79−83] and tau[84] on AD therapy. The list here is by no means exhaustive, and there are obviously other remarkable advances that have been made in China though not mentioned in this review due to space limitation. Together, these mechanistic and therapeutic studies show an increase in the quality of AD studies in China, and no doubt there will be more valuable work yet to come from Chinese researchers. The identification of novel AD-risk genes would provide more targets for these dedicated mechanistic efforts, besides potential clinical diagnostic usage.

7. WHAT IS NEXT FOR AD GENETICS IN CHINA: PERSPECTIVES AND CHALLENGES

As mentioned above, AD is gaining more and more attention from researchers around the world, and both genetic and mechanistic studies have made some striking advances in the past century. Worldwide, there were dozens of GWAS and NGS hits showing robust association evidence in AD susceptibility. The daunting task is to decipher the causal variants and their molecular mechanisms behind the risk hits.[24,85] However, until recently the situation was far different in China, as the genetic research was at the preliminary stage of validating the European-based top hits in relatively small samples[42,43,55−57,59−61] and starting to screen for population-specific loci at the genome-wide level.[64−66] We and others did validate some of the top hits in Chinese populations and also observed several population-specific variants such as *CFH*,[58] *C7*,[66] and *TREM2*.[42] There is still a long way to go before the European-based variants are confirmed in the Chinese population, and comprehensive genome-wide analyses with a large size are still required. In the near future, the increasing number of genome-wide studies of AD in the Chinese is predicted, together with increased public awareness and focus on fundamental AD research, to yield reliable results.

The major challenge for both candidate studies and genome-wide studies in China is limited sample size for each study. The success of the IGAP[29] and recent large GWAS meta-analyses[30−33] clearly demonstrates the importance of collaboration to get large sample sizes. There are currently limited collaborations between Chinese research groups and the leading groups in Europe and America, nor among the Chinese groups themselves according to information in the literature. Creative solutions are needed to explore the possibilities for increased domestic and international collaborations. Consortiums established by the main research groups might help to achieve larger sample size in future studies. In addition, successful genetic studies require careful phenotyping of the AD patients and healthy controls with matched ages, which are dependent on medical conditions in hospitals and public awareness. In addition to direct collaborations of samples, data sharing would be another way to boost productivity.[86] As data sharing is becoming the culture in the genetic research community, we would expect that there will be more and more data sharing in China. For instance, we released the data of our whole-exome sequencing for early onset and familial AD patients at the AlzData Web server (http://www.alzdata.org/exome.html),[87] as a way of allowing for easy access to the bulk data. Moreover, with the dedicated team work of large groups of Chinese scientists, we are not only making more science and technology innovations to the field[88] but also infusing an element of traditional Chinese culture of team work into the global scientific community, as proposed by Professor Mu-ming Poo.[89]

Another challenge for AD genetic research in China has been the limited genome-level attempts in the "omics" era. Transcriptomic, proteomic, and epigenomic data of brain tissues, in addition to genomic data, are rapidly becoming indispensable for AD genetic research worldwide,[87,90] but studies on Chinese populations have been absent. Availability of post-mortem brain tissues has been a challenging task worldwide, even more so in China for cultural reasons. To our knowledge, the first Brain Bank was established in Hefei, Anhui Province, in 2002 initiated by Prof. Jiang-Ning Zhou and enhanced by Prof. Yong Shen; then the Wuhan Institute for Neuroscience and Neuroengineering of the South-Central University for Nationalities established the China Brain Bank Center (CBBC, http://cbbc.scuec.edu.cn) in 2007. To date, both banks have made limited progress due to limited public and governmental support. Hopefully, we now have the China Human Brain Banking Consortium initiated on May 27, 2016 based on 10 brain banks from leading universities (http://anatomy.sbm.pumc.edu.cn:88/). Clearly, these resources might benefit from the screening of *de novo* mutations in AD brain and contribute to the transcriptomic and proteomic analyses. The combination of genomic data from large sample sets with brain-bank-based epigenetics and functional genomic profiles will be a crucial step toward developing personalized precision medicine for AD in China and the world.

Despite the immature status and challenges for AD genetics in the Chinese population, China has its own specific resources for AD research. The first resource is the use of non-human primates. China is currently the leading producer and major supplier of experimental primates.[91] Researchers from China have established a number of primate animal models for AD[92] and other brain disorders.[93−96] Leading primate research facilities in China, such as the Kunming Primate Research Center of the Chinese Academy of Sciences, Kunming Institute of Zoology, have received international recognition.[91,97,98] The recent successful cloning of a monkey by the research team led by Prof. Qiang Sun and colleagues at the CAS Center for Excellence in Brain Science and Intelligence Technology and Institute of Neuroscience, Chinese Academy of Sciences, provided a fast way to create genetically modify monkeys with uniform genetic background.[99,100] In addition to the monkey, our group is trying to establishing a novel AD model using the Chinese tree shrew,[101] which is a promising animal for research into brain disorders.[102] Another special advantage China may have is the consideration of therapy with

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herbal preparations for the treatment of AD,[103] as traditional Chinese medicine has not been extensively studied in Western countries,[90] and there are impressive advances in biosynthesis of bioactive compounds in traditional Chinese medicinal plants in recent years.[104] Recently, a new AD drug from China, sodium oligo-mannurarate (GV-971), extracted from brown algae, completed a phase 3 trial (https://clinicaltrials.gov/ct2/show/NCT02293915) and shows some promise of being a therapy for the treatment of AD.

8. CONCLUSION

In summary, China has the largest number of AD suffers in the world and genetic research looking at the Chinese population is indispensable for a full understanding of the etiology of AD. Although we are still in the initial stages, we predict major advances will be made in the coming years as basic research, governmental support, and public awareness are increased. Also, China may be able to make a special contribution toward resolving the mechanisms underlying AD and developing effective treatments, in part based on studies using Chinese non-human primates and herbal resources.

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D.F.Z. and Y.G.Y. designed the work and wrote the manuscript. D.F.Z. analyzed the data and generated the figures. M.X. and R.B. collected some materials for the content and revised the manuscript.

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Notes

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