Published in final edited form as:

Future Neurol. 2014 March ; 9(2): 119–122. doi:10.2217/fnl.14.1.

Genetic loci associated with Alzheimer's disease

Christiane Reitz*

*The Taub Institute for Research on Alzheimer's Disease & the Aging Brain, Columbia University, New York, NY, USA and Gertrude H Sergievsky Center, 630 West 168th Street, Columbia University, New York, NY 10032, USA and The Department of Neurology, Columbia University, New York, NY, USA Tel.: +1 212 305 0865; Fax: +1 212 305 2518; cr2101@columbia.edu

Abstract

The article by Lambert *et al.* reports the identification of 11 novel susceptibility loci for late-onset Alzheimer's disease. The observations of this study significantly enhance the field since they further disentangle the genetic causes and pathways underlying Alzheimer's disease by identifying novel disease-associated variants clustering in specific pathways. These pathways include APP processing, lipid metabolism, inflammation/immune response, intracellular trafficking/endocytosis, tau metabolism, synaptic function. All of the newly identified disease-associated variants have small effect sizes with increases in risk of 10–20%. The cumulative population attributable fraction associated with known genetic variants amounts now to approximately 80%. This article also underlines the ongoing value of genome-wide association studies for identification of causative common variants in the era of whole-exome and whole-genome sequencing studies.

Keywords

Alzheimer's disease; genes

Late-onset Alzheimer's disease (AD), the most common form of dementia in the elderly, places a considerable burden on society. In the USA alone, AD is associated with a direct estimated healthcare cost of US\$157–215 billion per year [1,2]. Under the age of 65 years, the disease is rare, but by the age of 85 years and older, 30% are affected. The incidence rate increases from 1% among people aged 65 years to approximately 8% for people aged 85 years and older. The duration of illness can be as long as 20 years, but the average duration is between 4 and 8 years [3]. It is estimated that 5 million people in the USA and 17 million worldwide have AD [2]. The aging of those born in the post-World War II era suggests that these numbers may triple by the year 2050 resulting in an increase of nearly 80% in total societal costs per adult [1]. The course is a progressive one, terminating inevitably in complete incapacity and death. The diagnosis of disease during life is based on a clinical

© 2014 Future Medicine Ltd

Financial & competing interests disclosure

The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

examination and is highly accurate. There are no definitive diagnostic tests or biological markers of the disease. At death, the most frequent pathological manifestations in brain include deposits of extracellular β -amyloid protein ($A\beta$) 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. Activation of microglia and loss of neurons and synapses is also widespread. The fundamental pathogenic mechanisms underlying these changes are unknown, but it is clear that there are significant environmental and genetic components [4–6].

Consistent with the role of a significant genetic contribution, the heritability of AD is 58–79%, and a positive family history is the strongest risk factor [7,8]. Families in which multiple members are affected with AD are at increased risk for dementia, but the distribution of secondary cases is not consistent with Mendelian inheritance. AD is more frequent among monozygotic than dizygotic twins [6,7,9], and first-degree relatives of patients with AD have approximately twice the expected lifetime risk of developing the disease.

Studies of numerous large pedigrees with early-onset AD (onset age: 30–50 years) led to the discovery of autosomal dominant mutations in the *APP*, *PSEN1* and *PSEN2* genes [10–12]. These studies suggested a common pathogenic mechanism involving enhanced generation and aggregation of $A\beta$. According to this 'amyloid hypothesis', β -secretase cleaves APP near the N terminus of the $A\beta$ peptide; then, the membrane-bound C-terminal APP fragment is cleaved by γ -secretase leading to accumulation of $A\beta_{40}$ and $A\beta_{42}$. In large multiplex pedigrees with late-onset AD, targeted exome sequencing of *APP*, *PSEN1*, *PSEN2*, *APOE*, *GRN* and *MAPT* has identified 33 missense, nonsense and splice-site variants in 60 families (13.7%), 18 of which were novel [13]. Other genes with rare variants for late-onset AD include *SORL1* [14], *ADAM10* [15], *PICALM* [16] and *TREM2* [17,18].

The strongest common variant for late-onset AD is the *APOE* ϵ 4 allele [19] influencing the age at onset in a dose-dependent manner. However, more than half of the patients with AD do not have the high-risk ϵ 4 allele and the population attributable risk of AD owing to APOE may be as low as 10–15% [20,21]. The first two sets of large-scale genome-wide association studies (GWAS) identified *CLU*, *PICALM*, *CRI*, *BINI*, *MS4A4A*, *ABCA7*, *CD2AP*, *CD33* and *EPHA1* as AD susceptibility loci [22–25]. The largest GWAS to date was recently performed by the International Genomics of Alzheimer's Project ($n = 74,046$). By combining all the data sets from these GWAS, identified 11 additional loci (*HLA-DRB5/HLA-DRB1*, *PTK2B*, *SORL1*, *SLC24A4*, *INPP5D*, *MEF2C*, *NME8*, *ZCWPW1*, *CELF1*, *FERMT2* and *CASS4*) [26]. This article reviews and summarizes the cumulative evidence from this recent GWAS and discusses its implications for future research.

Methods & results

The study by Lambert *et al.* consisted of a large, two-stage meta-analysis of the major GWAS of individuals of European ancestry that included a total of 74,046 subjects. In stage 1, 7,055,881 single nucleotide polymorphisms genotyped or imputed in at least 40% of AD

cases and 40% of control samples were used to perform a fixed-effects inverse variance-weighted meta-analysis on four previously published GWAS data sets consisting a total of 17,008 AD cases and 37,154 controls. In total, 11,632 single nucleotide polymorphisms associated with AD risk, exhibiting a p-value of $<1 \times 10^{-3}$, were genotyped and tested for association in stage 2 in an independent set of 8572 AD cases and 11,312 controls.

In addition to the *APOE* locus, 19 loci reached genome-wide significance defined as $p < 5 \times 10^{-8}$ in the combined stage 1 and 2 analysis (*CR1*, *BIN1*, *CD2AP*, *EPHA1*, *CLU*, *MS4A6A*, *PICALM*, *ABCA7*, *HLA-DRB5/HLA-DRB1*, *PTK2B*, *SORL1*, *SLC24A4/RIN3*, *INPP5D*, *MEF2C*, *NME8*, *ZCWPW1*, *CELF1*, *FERMT2* and *CASS4*). Out of these 11 (*HLA-DRB5/HLA-DRB1*, *PTK2B*, *SORL1*, *SLC24A4/RIN3*, *INPP5D*, *MEF2C*, *NME8*, *ZCWPW1*, *CELF1*, *FERMT2* and *CASS4*) were novel. The odds ratios ranged from 1.08 to 1.29; examining the genetic effect attributable to all the associated loci, the most strongly associated single nucleotide polymorphisms at each locus other than *APOE* had population-attributable fractions or preventive fractions between 1.0 and 8.0% in the stage 2 sample. The cumulative population attributable fraction was 89.4%.

The results from the combined stage 1 and 2 data sets also identified 13 suggestive loci with association p-values of $<1 \times 10^{-6}$ (an intergenic locus at chr1q31.2, *HS3ST1*, *NDUFA6*, *ECHDC3*, *AP2A2*, *ADAMST20*, *IGH@*, *SPPL2A*, *TRIP4*, *SCIMP* and *ACE*). The TREML2/TREML2 locus was recently reported to carry a rare variant (R47H) associated with a three- to four-fold increased risk of developing AD [17,18].

Discussion & significance

In conclusion, this meta-analysis of major AD GWAS identified 11 new susceptibility loci. These novel loci underline the significance of specific pathways already shown to be enriched for association signal in AD GWAS, such as immune response and inflammation (*HLA-DRB5/DRB1*, *INPP5D* and *MEF2C*), cell migration (*PTK2B*) and lipid transport and endocytosis (*SORL1*), and strengthen the importance of some additional previously suggested pathways including APP (*SORL1* and *CASS4*), tau (*CASS4* and *FERMT2*) pathology, hippocampal synaptic function (*MEF2C* and *PTK2B*), cytoskeletal function and axonal transport (*CELF1*, *NME8* and *CASS4*), regulation of gene expression and post-translational modification of proteins, and microglial and myeloid cell function (*INPP5D*).

Conclusion & future perspective

Overall, this clarification and identification of pathways underlying AD etiology bears a strong potential for the development of therapeutic targets. However, before this information can be used in clinical settings, large-scale sequencing and functional analyses are required that fully characterize the candidate genes and functional variants responsible for the association of these GWAS loci with the disease and clarify their exact roles in its pathophysiology.

Acknowledgments

C Reitz was supported by a Paul B Beeson Career Development Award (K23AG034550).

References

1. Alzheimer's Association. 2010 Alzheimer's disease facts and figures. *Alzheimers Dement.* 2010; 6:158–194. [PubMed: 20298981]
2. Hurd MD, Martorell P, Delavande A, Mullen KJ, Langa KM. Monetary costs of dementia in the United States. *N. Engl. J. Med.* 2013; 368:1326–1334. [PubMed: 23550670]
3. Mayeux R. Epidemiology of neurodegeneration. *Annu. Rev. Neurosci.* 2003; 26:81–104. [PubMed: 12574495]
4. Alsop DC, Detre JA. Reduced transit-time sensitivity in noninvasive magnetic resonance imaging of human cerebral blood flow. *J. Cereb. Blood Flow Metab.* 1996; 16:1236–1249. [PubMed: 8898697]
5. Gatz M, Pedersen NL, Berg S, et al. Heritability for Alzheimer's disease: the study of dementia in Swedish twins. *J. Gerontol. A Biol. Sci. Med. Sci.* 1997; 52:M117–M125. [PubMed: 9060980]
6. Gatz M, Reynolds CA, Fratiglioni L, et al. Role of genes and environments for explaining Alzheimer disease. *Arch. Gen. Psychiatry.* 2006; 63:168–174. [PubMed: 16461860]
7. Lautenschlager NT, Cupples LA, Rao VS, et al. Risk of dementia among relatives of Alzheimer's disease patients in the MIRAGE study: what is in store for the oldest old? *Neurology.* 1996; 46:641–650. [PubMed: 8618660]
8. Mayeux R, Sano M, Chen J, Tatemichi T, Stern Y. Risk of dementia in first-degree relatives of patients with Alzheimer's disease and related disorders. *Arch. Neurol.* 1991; 48:269–273. [PubMed: 2001183]
9. Bergem AL, Lannfelt L. Apolipoprotein E type epsilon4 allele, heritability and age at onset in twins with Alzheimer disease and vascular dementia. *Clin. Genet.* 1997; 52:408–413. [PubMed: 9520135]
10. Goate A, Chartier-Harlin MC, Mullan M, et al. Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. *Nature.* 1991; 349:704–706. [PubMed: 1671712]
11. Levy-Lahad E, Wasco W, Poorkaj P, et al. Candidate gene for the chromosome 1 familial Alzheimer's disease locus. *Science.* 1995; 269:973–977. [PubMed: 7638622]
12. Sherrington R, Rogaev EI, Liang Y, et al. Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease. *Nature.* 1995; 375:754–760. [PubMed: 7596406]
13. Cruchaga C, Haller G, Chakraverty S, et al. Rare variants in APP, PSEN1 and PSEN2 increase risk for AD in late-onset Alzheimer's disease families. *PLoS ONE.* 2012; 7:e31039. [PubMed: 22312439]
14. Pottier C, Hannequin D, Coutant S, et al. High frequency of potentially pathogenic *SORL1* mutations in autosomal dominant early-onset Alzheimer disease. *Mol. Psychiatry.* 2012; 17:875–879. [PubMed: 22472873]
15. Kim M, Suh J, Romano D, et al. Potential late-onset Alzheimer's disease-associated mutations in the *ADAM10* gene attenuate {alpha}-secretase activity. *Hum. Mol. Genet.* 2009; 18:3987–3996. [PubMed: 19608551]
16. Schnetz-Boutaud NC, Hoffman J, Coe JE, Murdock DG, Pericak-Vance MA, Haines JL. Identification and confirmation of an exonic splicing enhancer variation in exon 5 of the Alzheimer disease associated *PICALM* gene. *Ann. Hum. Genet.* 2012; 76:448–453. [PubMed: 22943764]
17. Jonsson T, Stefansson H, Steinberg S, et al. Variant of *TREM2* associated with the risk of Alzheimer's disease. *N. Engl. J. Med.* 2013; 368:107–116. [PubMed: 23150908]
18. Guerreiro R, Wojtas A, Bras J, et al. *TREM2* variants in Alzheimer's disease. *N. Engl. J. Med.* 2013; 368:117–127. [PubMed: 23150934]
19. Pericak-Vance MA, Bebout JL, Gaskell PC Jr, et al. Linkage studies in familial Alzheimer disease: evidence for chromosome 19 linkage. *Am. J. Hum. Genet.* 1991; 48:1034–1050. [PubMed: 2035524]
20. Daw EW, Payami H, Nemens EJ, et al. The number of trait loci in late-onset Alzheimer's disease. *Am. J. Hum. Genet.* 2000; 66:196–204. [PubMed: 10631151]

21. Evans DA, Hebert LE, Beckett LA, et al. Education and other measures of socioeconomic status and risk of incident Alzheimer disease in a defined population of older persons. *Arch. Neurol.* 1997; 54:1399–1405. [PubMed: 9362989]
22. Harold D, Abraham R, Hollingworth P, et al. Genome-wide association study identifies variants at *CLU* and *PICALM* associated with Alzheimer's disease. *Nat Genet.* 2009; 41:1088–1093. [PubMed: 19734902]
23. Naj AC, Jun G, Beecham GW, et al. Common variants at *MS4A4/MS4A6E*, *CD2AP*, *CD33* and *EPHA1* are associated with late-onset Alzheimer's disease. *Nat. Genet.* 2011; 43:436–441. [PubMed: 21460841]
24. Seshadri S, Fitzpatrick AL, Ikram MA, et al. Genome-wide analysis of genetic loci associated with Alzheimer disease. *JAMA.* 2010; 303:1832–1840. [PubMed: 20460622]
25. Lambert JC, Heath S, Even G, et al. Genome-wide association study identifies variants at *CLU* and *CR1* associated with Alzheimer's disease. *Nat. Genet.* 2009; 41:1094–1099. [PubMed: 19734903]
26. Lambert JC, Ibrahim-Verbaas CA, Harold D, et al. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. *Nat. Genet.* 2013; 45(12):1452–1458. [PubMed: 24162737]

EXECUTIVE SUMMARY

Background

- The previously identified genetic susceptibility loci for Alzheimer's disease left a large part of the genetic contribution to the disease unexplained.

Methods & results

- The study by Lambert *et al.* consisted of a large, two-stage meta-analysis of the major genome-wide association studies of individuals of European ancestry that included 74,046 subjects in total.
- This mega-metaanalysis identified 11 novel susceptibility loci (*HLA-DRB5/HLA-DRB1*, *PTK2B*, *SORL1*, *SLC24A4/RIN3*, *INPP5D*, *MEF2C*, *NME8*, *ZCWPW1*, *CELF1*, *FERMT2* and *CASS4*).

Discussion & significance

- The identified novel loci underline specific pathways already shown to be enriched for association signal in Alzheimer's disease genome-wide association studies (immune response/inflammation, cell migration, lipid transport and endocytosis) and strengthen the importance of additional previously suggested pathways including APP and tau pathology, hippocampal synaptic function, cytoskeletal function and axonal transport, regulation of gene expression and post-translational modification of proteins, and microglial and myeloid cell function.

Conclusion & future perspective

- Overall, this clarification/identification of pathways underlying Alzheimer's disease etiology bears a strong potential for the development of therapeutic targets.
- However, before this information can be used in clinical settings, large-scale sequencing and functional analyses are required that fully characterize the candidate genes and functional variants responsible for the association of these genome-wide association studies loci with the disease and clarify their exact roles in its pathophysiology.