alzheimer's research&therapy

DEBATE

Have we learnt all we need to know from genetic studies - is genetics over in Alzheimer's disease?

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Abstract

Background: Alzheimer's disease (AD) pathophysiology is mostly (>95%) not inherited in a Mendelian fashion. Such sporadic AD (sAD) forms do not exhibit familial aggregation and are characterized by complex genetic inheritance. Growing evidence indicates that multiple genes contribute to sAD-characteristic endophenotypes, molecular mechanisms, signaling pathways and biomarker signatures either individually or through complex gene-gene interactions, lifestyle and the environment.

Discussion: Under the hypothesis that low-prevalence variants showing moderate-to-high effect size may be associated with risk for sAD, two independent research groups have demonstrated that a rare variant (rs75932628, encoding a substitution of arginine by histidine at residue 47 (R47H), in the *TREM2* gene, which encodes the triggering receptor expressed on myeloid cells 2) is significantly associated with an increased susceptibility to sAD. Another study has provided intriguing evidence that a low-frequency variant (rs63750847) in the *APP* gene is associated with a reduced risk of developing AD and a lower likelihood of age-related cognitive decline in elderly subjects without AD.

Summary: Recent years have witnessed tremendous development in genetics technology that has allowed full individualized genome-wide or genomic screening embracing all of the risk and protective variants for sAD, both across populations and within individuals. Hopefully, the integration of neurogenetics with systems biology and high-throughput genotyping will further pave the way to decipher all of the related causes, mechanisms, and biomarkers across the spectrum of distinct AD forms. After an almost lost apprentice decade in AD therapy development, the epoch of individualized asymptomatic screening and progress in primary and secondary prevention of sAD is probably at its dawn. Even though we are more at the beginning than at the end of sAD genetics, there is some reason for optimism given the recent identification of novel risk or protective variants (such as rare *TREM2* and *APP* mutations) showing strong statistical associations with sAD.

Background

Several genetic variants have been shown to modulate the risk of developing Alzheimer's disease (AD). Large-scale, international efforts in the field of AD genetics have led to the identification of AD forms showing familial clustering, which are caused by inherited single-gene mutations. Familial AD (FAD) is generally characterized by an early (<60 years) or very early (30 to 50 years) age at onset and accounts for less than 5% of all of the AD cases [1]. A significant proportion of FAD cases is caused by autosomal dominant, highly penetrant mutations in at least three different genes, that is, amyloid precursor protein (*APP*), presenilin-1 (*PSEN1*), and presenilin-2 (*PSEN2*). At the time of writing, the Alzheimer Disease & Frontotemporal Dementia Mutation database lists a total of 231 FAD-causing pathogenic mutations (33 pathogenic variants for *APP*, 185 for *PSEN1*, and 13 for *PSEN2*) [2].

However, the great majority of AD cases (>95%) are not inherited in a Mendelian fashion. Such sporadic AD (sAD) cases do not show familial aggregation and typically have an age at onset >65 years (late-onset AD) [2]. To date, the apolipoprotein E (*APOE*) *ε4* allele is the only consistently replicated genetic risk factor for sAD and is responsible for approximately one-third of the population-attributable risk for the disease [1].

Recent progress in genomic methodology and the availability of large sample sizes have opened the era of comprehensive and unbiased genome-wide association studies (GWASs), which are not limited to the

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investigation of genetic variants of known pathophysiological significance. As a result, hundreds of genes have been tested for association with sAD. Due to a steadily increasing number of studies focusing on sAD genetics, it has become increasingly difficult to decipher and interpret the huge amount of available results. To address this issue, Bertram and colleagues [3] have established the AlzGene database with the aim of providing an updated, comprehensive, and unbiased online catalogue of all of the genetic variants associated with sAD, as well as updated meta-analyses to summarize the main findings. According to the AlzGene database, recent large-scale GWASs [4-8] have identified at least ten novel loci associated with an increased risk of developing sAD, that is, *BIN1*, *CLU*, *ABCA7*, *CR1*, *PICALM*, *MS4A6A*, *MS4A4E*, *CD33*, *CD2AP*, and *EPHA1*. The role of these genes in the pathogenesis of sAD is supported by their involvement in key pathogenetic processes in the context of neurodegeneration, including the amyloidogenic cascade, tau hyperphosphorylation, apoptotic, oxidative, cell membrane, cholesterol and lipid metabolism, and immune-inflammatory mechanisms [9].

Existing GWAS platforms are not designed to capture rare variants which, however, are assumed to have significant contributions to the heritability of sAD. It is well-known that the low frequency and the expected large number of such variants pose significant challenges for study design. In this regard, a novel testing strategy, based on a weighted-sum statistic, may be useful [10]. GWASs of larger sample size will undoubtedly identify more associations and will point to additional regions in the genome for susceptibility to sAD, although over 50,000 cases and 50,000 controls may be needed [11].

Interestingly, it has recently been shown that a case control study of 5,000 cases and 5,000 controls has the power equivalent to that of a study of only 3,200 cases and 3,200 controls, or 64% of the sample size, when 20% of the case sample has been misdiagnosed [12]. Therefore, the proportion of variance explained by SNPs may be underestimated in the presence of diagnostic misclassification compared with the variance explained by SNPs of the true disorder. Moreover, some genetic variation is specific to populations with particular continental ancestry, preventing its discovery in other populations. Populations of different ancestry may be helpful in discovering new loci for sAD.

New breakthrough findings have recently provided new impetus in the clarification of the genetics mechanisms underlying the development of sAD. Under the hypothesis that low-prevalence variants showing moderate-to-high effect size may be associated with the risk for sAD, two independent research groups have demonstrated that a rare variant (rs75932628, encoding a substitution of arginine by histidine at residue 47 (R47H), in the *TREM2* gene, which encodes the triggering receptor expressed on myeloid cells 2) is significantly associated with increased susceptibility to late-onset AD [13,14]. Given the well-known anti-inflammatory role of TREM2 in the brain, it is plausible that the increased risk of late-onset AD associated with the rs75932628 variant may be due to a dysregulation of the inflammatory processes in the central nervous system. Another study has provided intriguing evidence that a low-frequency variant (rs63750847) in the *APP* gene is associated with a reduced risk of developing AD and a lower likelihood of age-related cognitive decline in elderly subjects without AD. This rare polymorphism results in an alanine-to-threonine substitution at position 673 of the APP protein (A673T) [15]. The close proximity of the A673T polymorphism to the proteolytic site of the beta-site APP-cleaving enzyme 1 (BACE1) suggests that this variant may result in impaired cleavage of APP by BACE1 in subjects bearing the A673T variant. The discovery that a genetically determined reduction in the production of the amyloid beta peptide provides dramatic protection against the development of sAD supports the clinical usefulness of the current amyloid-directed therapeutic research efforts. Therefore, these genetic findings support the hypothesis that the failures of recent phase III clinical trials targeting the amyloid beta peptide may be due, at least in part, to the late timing of intervention.

Discussion

What can we expect for the future of AD genetics? The recent development of high-throughput next-generation DNA sequencing technologies will surely play a paramount role in screening the whole genome and identifying novel genetic variants influencing the risk of sAD [16]. Important initiatives like the 1000 Genomes Project [17] - funded by the US National Human Genome Research Institute consortium - have already made important progress toward this aim. Hopefully, future technical improvements will open new horizons for improved assessment of the genetic susceptibility to sAD, a better characterization of its endophenotypes, and the study of pharmacogenomics of drug response in sAD patients [18]. Besides traditional genetics, high-throughput next-generation sequencing technologies may also be involved in novel discoveries in the field of sAD epigenetics. For example, chromatin immunoprecipitation (ChIP) combined with DNA microarray (ChIP-chip) has been successfully utilized for the study of protein-DNA interactions. In addition, ChIP followed by sequencing (ChIP-Seq) technology might allow the study of post-translational modifications of histones and the location of transcription factors at the whole-genome level. Moreover, methylated DNA immunoprecipitation (MeDIP) may be useful for unbiased detection and characterization

of DNA methylation patterns [9]. Another potential strategy to shed more light on the multifaceted complexity of sAD is systems biology, an innovative multilevel paradigm. By using systems biology, structurally and functionally different biomolecules may be simultaneously measured over time in networks of cells or even in whole organisms. This strategy can allow the characterization and integration of distinct disease endophenotypes, as well as the study of common features shared by different neurodegenerative disorders [19].

Generally, it is difficult for clinical case-control series to identify genetic risk factors for sAD based on clinical diagnosis alone. The use of objective and highly reproducible brain system endophenotypes can make it easier to identify sAD genetic risk factors and to understand their impact on brain systems. Established genetic risk factors for sAD can then subsequently be studied for their influence on the speed of disease progression.

We argue that autosomal dominantly inherited AD (ADAD) and sAD subtypes may represent distinct entities that may be different from both the genetic and pathophysiological standpoints. Such genetic differences could in turn be associated with distinct and specific multimodal biomarker signatures, possibly requiring different therapeutic strategies. In this context, the first cross-sectional biomarker study supported by the Dominantly Inherited Alzheimer Network [20] and the upcoming studies of disease-modifying therapies in asymptomatic mutation carriers may represent important hypothesis-testing and hypothesis-generating milestones that could accelerate a shift from the traditional conceptualization of monogenic FAD to the novel complex non-linear dynamic sAD model [2].

Finally, the use of polygenic risk scores may theoretically be useful for the prediction of certain complex diseases like sAD. The approach has been based on the contribution of counting multiple alleles associated with disease across independent loci. Whether polygenic risk scores may assist in the prediction of risk of sAD is unknown and should be addressed in future studies.

Summary

Recent years have been characterized by remarkable progress in genetics/epigenetics technology that enabled full, individualized genome-wide or genomic screening covering all of the risk and protective variants for sAD, both across populations and within individuals. The integration of neurogenetics with a systems biology-based approach and the use of high-throughput genotyping are expected to untangle all of the related causes, molecular mechanisms, signaling pathways and biomarkers throughout the spectrum of distinct AD forms. The era of individualized asymptomatic screening and therapy development in primary/secondary prevention of sAD is undoubtedly at its birth. Although we are more at the beginning than at the end of sAD genetics, optimism prevails given the recent important characterization of novel risk or protective variants (including rare *TREM2* and *APP* mutations) displaying significant statistical associations with sAD.

Abbreviations

AD, Alzheimer's disease; ADAD, autosomal dominantly inherited AD; APP, amyloid precursor protein; BACE1, beta-site APP-cleaving enzyme 1; ChIP, chromatin immunoprecipitation; FAD, familial AD; GWAS, genome-wide association study; PSEN, presenilin; sAD, sporadic Alzheimer's disease; SNP, single-nucleotide polymorphism; TREM2, triggering receptor expressed on myeloid cells 2.

Competing interests

The authors have no competing interests to declare.

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References

1. Bertram L, Lill CM, Tanzi RE: **The genetics of Alzheimer disease: back to the future.** *Neuron* 2010, **68:**270-281.
2. Hampel H, Lista S: **Alzheimer disease: From inherited to sporadic AD-crossing the biomarker bridge.** *Nat Rev Neurol* 2012, **8:**598-600.
3. Bertram L, McQueen MB, Mullin K, Blacker D, Tanzi RE: **Systematic meta-analyses of Alzheimer disease genetic association studies: the AlzGene database.** *Nat Genet* 2007, **39:**17-23.
4. Harold D, Abraham R, Hollingworth P, Sims R, Gerrish A, Hamshere ML, Pahwa JS, Moskvina V, Dowzell K, Williams A, Jones N, Thomas C, Stretton A, Morgan AR, Lovestone S, Powell J, Proitsi P, Lupton MK, Brayne C, Rubinsztein DC, Gill M, Lawlor B, Lynch A, Morgan K, Brown KS, Passmore PA, Craig D, McGuinness B, Todd S, Holmes C, *et al.*: **Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease.** *Nat Genet* 2009, **41:**1088-1093.
5. Lambert JC, Heath S, Even G, Campion D, Sleegers K, Hiltunen M, Combarros O, Zelenika D, Bullido MJ, Tavernier B, Letenneur L, Bettens K, Berr C, Pasquier F, Fiévet N, Barberger-Gateau P, Engelborghs S, De Deyn P, Mateo I, Franck A, Helisalmi S, Porcellini E, Hanon O; European Alzheimer's Disease Initiative Investigators, de Pancorbo MM, Lendon C, Dufouil C, Jaillard C, Leveillard T, Alvarez V, *et al.*: **Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease.** *Nat Genet* 2009, **41:**1094-1099.
6. Seshadri S, Fitzpatrick AL, Ikram MA, DeStefano AL, Gudnason V, Boada M, Bis JC, Smith AV, Carassquillo MM, Lambert JC, Harold D, Schrijvers EM, Ramirez-Lorca R, Debette S, Longstreth WT Jr, Janssens AC, Pankratz VS, Dartigues JF, Hollingworth P, Aspelund T, Hernandez I, Beiser A, Kuller LH, Koudstaal PJ, Dickson DW, Tzourio C, Abraham R, Antunez C, Du Y, Rotter JI, Aulchenko YS, *et al.*: **Genome-wide analysis of genetic loci associated with Alzheimer disease.** *JAMA* 2010, **303:**1832-1840.
7. Hollingworth P, Harold D, Sims R, Gerrish A, Lambert JC, Carrasquillo MM, Abraham R, Hamshere ML, Pahwa JS, Moskvina V, Dowzell K, Jones N, Stretton A, Thomas C, Richards A, Ivanov D, Widdowson C, Chapman J, Lovestone S, Powell J, Proitsi P, Lupton MK, Brayne C, Rubinsztein DC, Gill M, Lawlor B, Lynch A, Brown KS, Passmore PA, Craig D, *et al.*: **Common variants at ABCA7, MS4A6A/MS4A4E, EPHA1, CD33 and CD2AP are associated with Alzheimer's disease.** *Nat Genet* 2011, **43:**429-435.
8. Naj AC, Jun G, Beecham GW, Wang LS, Vardarajan BN, Buros J, Gallins PJ, Buxbaum JD, Jarvik GP, Crane PK, Larson EB, Bird TD, Boeve BF, Graff-Radford

NR, De Jager PL, Evans D, Schneider JA, Carrasquillo MM, Ertekin-Taner N, Younkin SG, Cruchaga C, Kauwe JS, Nowotny P, Kramer P, Hardy J, Huentelman MJ, Myers AJ, Barmada MM, Demirci FY, Baldwin CT, *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.

9. Zetzsche T, Rujescu D, Hardy J, Hampel H: **Advances and perspectives from genetic research: development of biological markers in Alzheimer's disease.** *Expert Rev Mol Diagn* 2010, **10:**667-6990.
10. Ionita-Laza I, Buxbaum JD, Laird NM, Lange C: **A new testing strategy to identify rare variants with either risk or protective effect on disease.** *PLoS Genet* 2011, **7:**e1001289.
11. Wray NR, Purcell SM, Visscher PM: **Synthetic associations created by rare variants do not explain most GWAS results.** *PLoS Biol* 2011, **9:**e1000579.
12. Wray NR, Lee SH, Kendler KS: **Impact of diagnostic misclassification on estimation of genetic correlations using genome-wide genotypes.** *Eur J Hum Genet* 2012, **20:**668-674.
13. Jonsson T, Stefansson H, Steinberg S, Jonsdottir I, Jonsson PV, Snaedal J, Bjornsson S, Huttenlocher J, Levey AI, Lah JJ, Rujescu D, Hampel H, Giegling I, Andreassen OA, Engedal K, Ulstein I, Djurovic S, Ibrahim-Verbaas C, Hofman A, Ikram MA, van Duijn CM, Thorsteinsdottir U, Kong A, Stefansson K: **Variant of TREM2 associated with the risk of Alzheimer's disease.** *N Engl J Med* 2013, **368:**107-116.
14. Guerreiro R, Wojtas A, Bras J, Carrasquillo M, Rogaeva E, Majounie E, Cruchaga C, Sassi C, Kauwe JS, Younkin S, Hazrati L, Collinge J, Pocock J, Lashley T, Williams J, Lambert JC, Amouyel P, Goate A, Rademakers R, Morgan K, Powell J, St George-Hyslop P, Singleton A, Hardy J; Alzheimer Genetic Analysis Group: **TREM2 variants in Alzheimer's disease.** *N Engl J Med* 2013, **368:**117-127.
15. Jonsson T, Atwal JK, Steinberg S, Snaedal J, Jonsson PV, Bjornsson S, Stefansson H, Sulem P, Gudbjartsson D, Maloney J, Hoyte K, Gustafson A, Liu Y, Lu Y, Bhangale T, Graham RR, Huttenlocher J, Bjornsdottir G, Andreassen OA, Jönsson EG, Palotie A, Behrens TW, Magnusson OT, Kong A, Thorsteinsdottir U, Watts RJ, Stefansson K: **A mutation in APP protects against Alzheimer's disease and age-related cognitive decline.** *Nature* 2012, **488:**96-99.
16. Bertram L, Hampel H: **The role of genetics for biomarker development in neurodegeneration.** *Prog Neurobiol* 2011, **95:**501-504.
17. 1000 Genomes Project Consortium, Abecasis GR, Altshuler D, Auton A, Brooks LD, Durbin RM, Gibbs RA, Hurles ME, McVean GA: **A map of human genome variation from population-scale sequencing.** *Nature* 2010, **467:**1061-1073.
18. Hampel H, Frank R, Broich K, Teipel SJ, Katz RG, Hardy J, Herholz K, Bokde AL, Jessen F, Hoessler YC, Sanhai WR, Zetterberg H, Woodcock J, Blennow K: **Biomarkers for Alzheimer's disease: academic, industry and regulatory perspectives.** *Nat Rev Drug Discov* 2010, **9:**560-574.
19. Hampel H, Lista S, Khachaturian ZS: **Development of biomarkers to chart all Alzheimer's disease stages: the royal road to cutting the therapeutic Gordian Knot.** *Alzheimers Dement* 2012, **8:**312-336.
20. Bateman RJ, Xiong C, Benzinger TL, Fagan AM, Goate A, Fox NC, Marcus DS, Cairns NJ, Xie X, Blazey TM, Holtzman DM, Santacruz A, Buckles V, Oliver A, Moulder K, Aisen PS, Ghetti B, Klunk WE, McDade E, Martins RN, Masters CL, Mayeux R, Ringman JM, Rossor MN, Schofield PR, Sperling RA, Salloway S, Morris JC; Dominantly Inherited Alzheimer Network: **Clinical and biomarker changes in dominantly inherited Alzheimer's disease.** *N Engl J Med* 2012, **367:**795-804.

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