Alzheimer’s disease risk alleles in TREM2 illuminate innate immunity in Alzheimer’s disease

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Abstract
Genetic studies have provided the best evidence for cause and effect relationships in Alzheimer’s disease (AD). Indeed, the identification of deterministic mutations in the APP, PSEN1 and PSEN2 genes and subsequent preclinical studies linking these mutations to alterations in Aβ production and aggregation have provided pivotal support for the amyloid cascade hypothesis. In addition, genetic, pathologic and biological studies of APOE have also indicated that the genetic risk for AD associated with APOE4 can be attributed, at least in part, to its pro-amyloidogenic effect on Aβ. In recent years a number of SNPs that show unequivocal genome-wide association with AD risk have implicated novel genetic loci as modifiers of AD risk. However, the functional implications of these genetic associations are largely unknown. For almost all of these associations, the functional variants have not been identified. Very recently, two large consortiums demonstrated that rare variants in the triggering receptor expressed on myeloid cells 2 (TREM2) gene confer significant risk for AD. TREM2 is a type 1 membrane receptor protein primarily expressed on microglia in the central nervous system that has been shown to regulate phagocytosis and activation of monocytes. Previously it had been shown that homozygous loss of function mutations in TREM2 cause polycystic lipomembranous osteodysplasia with sclerosis (PLOSL, Nasu Hakola disease) and also a pure form of early-onset dementia. The association of TREM2 variants with AD brings innate immune signaling into the light, affirming innate immunity’s role as a significant factor in AD pathogenesis.

Introduction: Alzheimer’s disease is not just a disease of neurons
Neurodegenerative proteinopathies are not solely diseases of neurons but brain disorders in which there is altered function of neurons, astrocytes, microglia and possibly other cells (for example, oligodendrocytes, endothelial cells, and even peripheral immune cells that survey the central nervous system) [1,2]. Indeed, invariant pathological features of Alzheimer’s disease (AD) as well as other neurodegenerative disorders are marked alterations in both astrocytes and microglia, reflecting underlying alterations in innate immune activation states within the brain. Innate immune signaling is thought to be altered early in AD, but is also skewed towards an activated state during human brain aging in the absence of a triggering proteinopathy [3,4]. Experimental studies in AD mouse models also show that manipulating innate immune pathways can have positive or negative effects on proteostasis (for example, tau and amyloid β (Aβ) pathology), cognition and neurodegeneration [5].

Despite fairly intensive investigation, the precise role of innate immunity in AD and other neurodegenerative disorders remains enigmatic. Collectively, preclinical, epidemiologic and clinical studies reveal a somewhat conflicted literature. Whereas some studies would suggest that dampening innate immunity would be beneficial, others suggest that promoting innate immune activation would be beneficial [5,6]. Moreover, from a conceptual point of view innate immunity could be placed into the AD pathological cascade at many different places: as a trigger, a consequence, a modifier of progression or some combination of these [7]. Nevertheless, as there are numerous approved therapies targeting innate immune signaling pathways (for example, anti-tumor necrosis factor-α, IL-6, IL-17 and IL-1 therapies) [8] as well as preclinical proof of concept studies for many innate immune targets, many investigators have been attracted by the potential to identify immunological targets for AD that could leverage therapies currently being developed for systemic immune disorders.
**TREM2 variants are associated with Alzheimer’s disease risk**

Recently, the unequivocal associations of SNPs within genetic loci that encode genes that function in innate immunity have added genetic support to the notion that innate immunity may have a significant role in AD. Variants in **CR1** and **CLL1**, which play roles in the complement system, repeatedly show significant genetic associations with AD [9-13] whereas other genes (**CD33, MS4A6A, MS4A4E, ABCA7, CD2AP**) with either established or likely roles in innate immune function are also implicated as AD risk loci [12-15]. In addition, there appears to be a significant overrepresentation of association within genetic loci that encode innate immune genes [16,17]. However, as with the majority of genetic associations with AD, the functional variants within these loci are unknown; thus, it is even premature to definitively conclude that such association reflects a functional variant that impacts function or expression of the encoded innate immune gene or alternatively alters a neighboring gene or non-coding RNA. In addition, the overall AD genetic risk or protection associated with these loci is small. Although if functional variants within these loci are definitively identified, it is possible that the risk associated with such rare functional variants could be much more significant.

Because of these issues, it has been challenging to experimentally assess the biological underpinnings of the potential genetic link between these novel loci and AD. However, recent studies have demonstrated that rare coding variants in triggering receptor expressed on myeloid cells 2 (**TREM2**), a known regulator of microglial activation and phagocytosis, confer substantial risk for AD [18,19]. **TREM2** is highly expressed on microglia, as well as osteoclasts, dendritic cells and macrophages. It is a type 1 transmembrane glycoprotein that binds poorly well as osteoclasts, dendritic cells and macrophages. It is a type 1 transmembrane glycoprotein that binds poorly characterized ligands (for example, bacteria, cell debris, and an astrocytoma cell-line), and, upon ligand binding, signals through DAP12 (**TYROBP**), an immunoreceptor tyrosine-based activation motif (ITAM)-containing transmembrane adaptor protein, and the SYK kinases that interact with the ITAM domain of DAP12 [20-22]. Since the cytoplasmic domain of **TREM2** by itself has no intrinsic signaling capacity, it relies on DAP12 for signal transduction [23]. Homozygous, loss of function mutations in both **TREM2** and DAP12 are known causes of polycystic lipomembranous osteodysplasia with sclerosing leuкоencephalopathy (**PLOSL**), which is also known as Nasu Hakola disease [24-27]. By inference, one would expect that variants that reduce DAP12 function (and possibly other downstream signaling molecules) might also confer risk for AD if they result in partial but not complete loss of function. Notably, other homozygous mutations in **TREM2** (**T66M, Y38C, Q33X**) have been associated with dementia without bone cysts [19,28]. Though the clinical presentation of these subjects is consistent with PLOSL without bone involvement, postmortem brain pathology has not been reported.

Association of **TREM2** with AD was initially shown using whole exome sequencing and whole genome sequencing [18,19]. In these studies, the most definitive risk for AD was associated with the heterozygous R47H variant (rs75932628-T) of **TREM2**. Notably, the risk associated with this allele was strong with odds ratios in the initial two studies of 2.9 (95% confidence interval 2.16 to 3.91) [18] and 4.5 (95% confidence interval 1.7 to 11.9) [19]; thus, roughly equivalent to the risk associated with one **APOE4** allele [29]. In addition, a number of other variants in **TREM2** were present in AD patients but not controls, with one variant (**D87N**) showing significant association with disease [30]. Since these initial publications, two other publications have confirmed the risk associated with the R47H variant to other populations and even early onset AD [31,32]. Thus, **TREM2** represents the first gene within the innate immune signaling pathway for which functional variants show association with AD risk.

On the surface these exciting genetic findings appear to provide the first rapidly tractable genetic association between a gene that is known to regulate innate immunity and AD. However, some caution is warranted, as inferring both functional effects of these variants on **TREM2** and the relationship to the AD pathological cascade is, at this point, largely speculative. The **TREM2** R47H and other variants more tentatively associated with AD risk are all located within the extracellular immunoglobulin-like domain of **TREM2**. Thus, similar to the mutations in the same region that cause PLOSL, it is hypothesized that the variants in **TREM2** associated with AD cause loss of function or partial loss of function, reducing ligand binding and downstream signaling [18,30]. It is also possible that they result in nonsense-mediated RNA decay and reduce **TREM2** levels. A soluble form of **TREM2** and other variants have also been identified that could influence the function, level, or both of **TREM2** [33,34]. Thus, **TREM2** could have non-cell autonomous actions. In addition, as the **TREM2** ectodomain can be shed [34], it has been speculated that **TREM2** may undergo regulated intramembrane proteolysis with the membrane stub being further processed by γ-secretase, and it is possible that these cleavages could be altered by these mutations. Finally, although the initial focus of **TREM2** in AD will likely focus on its role in microglial activation, it is important to consider other possible functional roles of **TREM2** on cells other than microglia within the central nervous system and also in regulating peripheral immune cell entry and activity in the brain.
Given that Trem2 activation has been shown to enhance phagocytosis and suppress cytokine production in mice [22,35], TREM2 could have very complex biological effects relevant to regulation of Aβ deposition as well as innate immune responses triggered by Aβ accumulation, such as regulation of cell-to-cell transmigration of tau, induction of other intracellular proteinopathies and neurodegeneration. Trem2 has been shown to be present in plaque-associated microglia in young and aged APP transgenic mice, presumably as a response to Aβ pathology [19,36,37]. Thus, TREM2 variants could influence age of onset, progression of disease, or both. However, at this point much more data are needed to understand how AD-associated variants influence TREM2 function, and how that variation in function alters factors relevant to AD pathogenesis. Notably, postmortem pathological phenotypes of brains from D87N and R47H carriers were well within the normal spectrum of pathologies noted in typical AD [19]. To date, there have been no reports of distinguishing clinical phenotypes in R47H carriers.

Putting TREM2 in context

Innate immune signaling in the brain is highly complex and may reflect varying states of immune activation and suppression in both health and disease. A potentially useful framework to classify innate immune activation states that was adopted from studies of peripheral macrophages has been to describe microglial phenotype as a classic activation (M1) or alternative activation (M2) state [38-40]. However, though this classification system is a useful framework, there is growing recognition that a rigid application of these dichotomous microglial phenotypes may be too simplistic [6]. In general, M1 microglial phenotypes have been associated with neurotoxicity and M2 with a neuroprotective/neuro-remodeling role. Based on what we know about TREM2 functions in myeloid cells and the presumed loss of function effects of TREM2 variants associated with AD, one could suggest that the genetic association of TREM2 with AD indicates that suppression of an M2-like neuroprotective microglial response with decreased phagocytosis and increased cytokine production might promote AD pathologies. However, a survey of published studies in the field suggests that a unified view of the role of innate immunity, microglial activation states and AD pathology is not feasible at this time [5,6]. For example, our data and that from other groups show that an M1-like pro-inflammatory microglial activation state protects from Aβ pathology, whereas an M2-like alternative activation state can promote Aβ pathology [41-49]. In contrast, others have reported that an M2-like microglial activation state protects from both Aβ pathology and cognitive and synaptic dysfunction [50-56]. There is also evidence, albeit much more limited, that factors that might protect from Aβ pathology might promote tau pathology and vice versa [57-60]. Like the preclinical data generated to date, epidemiologic and clinical data reveal a fairly conflicted literature on observational and clinical trial findings on non-steroidal anti-inflammatory drug (NSAID) use and AD [61-72]. Long-term NSAID use has been repeatedly shown to confer protection in epidemiologic studies, but clinical trials in AD patients with celecoxib and naproxen have not shown any benefit [73]. The Alzheimer’s Disease Anti-inflammatory Prevention Trial (ADAPT) testing AD ‘prevention’ with naproxen and celecoxib was halted due to cardiovascular side-effects induced by naproxen; however, follow-up studies along with some post hoc analysis of this trial suggests that treatment effects could vary depending on underlying, clinically silent AD pathology at the time of trial enrollment [68-72]. Another intriguing observation relating to human NSAID use and AD was a report showing that naproxen use was associated with increased post-mortem brain Aβ pathology [74].

A final factor that must be taken into account when trying to understand the role of the innate immune system in the AD brain is the recent data that indicate widespread upregulation of innate immune gene expression in the aging human brain [4]. At this point, it is unclear how this underlying age-related ‘skewing’ of the innate immune response towards an activated state affects development and progression of AD. By inference from other chronic inflammatory conditions, one could argue that a chronic pro-inflammatory environment would be harmful, and could either directly promote age-associated decline in function, sensitize the brain to a second insult or even trigger a proteinopathy. Alternatively, one could argue that a proinflammatory environment might actually help to remodel the brain and protect it from proteinopathies by promoting the removal of misfolded proteins and danger signals released by degenerating cells. In actuality, the effects may be quite complex, with the balance between positive and negative effects of innate immune activation on proteostasis and neurodegeneration in AD contextually dependent on the nature, timing, duration, and strength of the specific signals. Furthermore, immune ‘manipulations’ probably have more complex effects on innate immune activation and other factors that could influence AD pathologies than what are currently being surveyed, and thus a broader approach may be needed to understand how manipulations of a given innate immune pathway impacts AD.

While there has been previous interest in therapeutic strategies targeting inflammation and innate immunity in AD, probably because of the conflicted preclinical and clinical data, there has been limited activity relating to
development of novel innate immune targeting therapies in AD. If future studies can tie the action of AD-associated TREM2 variants to changes in microglial function that influence AD-relevant phenotypes, there will be direct genetic evidence that alterations in innate immune responses confer risk for AD. Such data will likely spur renewed interest in development of innate immune modulatory strategies for AD. Indeed, as opposed to therapies targeting the protein aggregates that are most likely to be effective as prophylactics, therapies modulating innate immune targets could be predicted to have efficacy during later disease stages. Given our current understanding of TREM2 function, as well as the large body of data showing that innate immunity can alter proteostasis and neurodegeneration, it is likely that many different novel therapeutic approaches may arise from these studies. Some of these approaches may directly target TREM2 whereas others might target parallel pathways that also regulate microglial activation.

Another intriguing aspect of these new data is that they represent another example of how variants within a genetic locus can confer risk for or cause one type of neurodegenerative disorder when present in a heterozygous state and cause a distinct disorder in the compound heterozygous or homozygous state. Other known examples are i) heterozygous progranulin (PRGN) mutations resulting in frontal temporal lobar degeneration and homogygous or compound heterozygous PRGN mutants causing neuronal ceroid lipofuscinosis [75,76], and ii) heterozygous glucocerebrosidase (GBA) mutations associated with risk for Parkinson’s disease and homozygous or compound heterozygous GBA mutations causing Gaucher’s disease [77,78]. Why variants or mutations produce these different neurological phenotypes in the heterozygous versus the compound heterozygous or homozygous states is quite enigmatic, but certainly an area worthy of further study.

Conclusions

With the spotlight firmly placed on TREM2’s role in AD, research advances will likely be quite rapid, and the emerging data will likely enable a more unified understanding of the function of innate immune signaling in AD. Although the possibility of harnessing TREM2 for therapeutic benefit is tempting, until we learn more about the functionality and regulation of this protein in the brain, it is challenging to envision how one would target TREM2 in AD. More generally, future genomic studies aimed at identifying rare functional variants in i) innate immune loci already associated with AD through genome-wide association studies or ii) innate immune genes shown to modulate relevant disease-associated pathology could provide a steady stream of new rare functional variants in innate immune genes that might impact AD risk. Indeed, it is important to note that TREM2 never reached genome-wide significance in the published genome-wide association studies. Thus, combining biological inference with whole exome or whole genome sequencing strategies is likely to yield a treasure chest of novel genetic variants in innate immune signaling factors that influence risk for AD. Hopefully, these will not only tell us more about AD pathogenesis, but will also reveal tractable therapeutic targets.

Abbreviations

Aβ, amyloid β; AD, Alzheimer’s disease; IL, interleukin; ITAM, immunoreceptor tyrosine-based activation motif; NSAID, non-steroidal anti-inflammatory drug; PLOSL, polycystic lipomembranous osteodysplasia with sclerosing leuкоencephalopathy; SNP, single-nucleotide polymorphism; TREM2, triggering receptor expressed on myeloid cells 2.

Competing interests

The authors declare that they have no competing interests.

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References

1. Ransohoff RM, Brown MA: Innate immunity in the central nervous system. J Clin Invest 2012, 122:1164-1171.
2. Aguzzi A, Barnes BA, Bennett ML: Microglia: scapegoat, saboteur, or something else? Science 2013, 339:156-161.
3. Akiyama H, Barger S, Barnum S, Bradt B, Bauer J, Cole GM, Cooper NR, Eikelenboom P, Emmerling M, Fiebich BL, Finch CE, Frautschy S, Griffin WS, Hampel H, Hull M, Landreth G, Lue L, Mirak R, Mackenzie IR, McGeer PL, O’Banion MK, Pachter J, Pasinetti G, Plata-Salaman C, Rogers J, Rydel R, Shen Y, Streit W, Strohmyrer R, Tooyoma I, et al: Inflammation and Alzheimer’s disease. Neurobiol Aging 2000, 21:383-421.
4. Cribbs DH, Berchtold NC, Pereau V, Coleman PD, Rogers J, Tenner AJ, Cotman CW: Extensive innate immune gene activation accompanies brain aging, increasing vulnerability to cognitive decline and neurodegeneration: a microarray study. J Neuroinflammation 2012, 9:179.
5. Czirr E, Wyss-Coray T: The immunology of neurodegeneration. J Clin Invest 2012, 122:1156-1163.
6. Town T, Nikolic V, Tan J: The microglial “activation” continuum: from innate to adaptive responses. J Neuroinflammation 2005, 2:24.
7. Wyss-Coray T: Inflammation in Alzheimer disease: driving force, bystander or beneficial response? Nat Med 2006, 12:1005-1015.
8. Taylor PC, Feldmann M: Anti-TNF biologic agents: still the therapy of choice for rheumatoid arthritis. Nat Rev Rheumatol 2009, 5:578-582.
9. Allen M, Zou F, Chai HS, Younkin CS, Crook J, Pankratz VS, Carrasquillo MM, Rowley CN, Nair AA, Middha S, Maharan S, Nguyen T, Ma L, Malphrus KG, Palusak R, Lincoln S, Bisciglio G, Georgescu C, Schultz D, Rackiathan F, Kolbert CP, Jen J, Haines JL, Mayeux R, Pericak-Vance MA, Farrer LA, Schellenberg GD, Alzheimer’s Disease Genetics Consortium, Petersen RC, Graft-Raford NR, et al: Novel late-onset Alzheimer disease loci variants associate with brain gene expression. Neurology 2012, 79:221-228.
10. Bellin O, Carrasquillo MM, Crump M, Culley OJ, Hunter TA, Ma L, Bisciglio G, Zou F, Allen M, Dickson DW, Graft-Raford NR, Petersen RC, Morgan K, Younkin SG: Investigation of 15 of the top candidate genes for late-onset Alzheimer’s disease. Hum Genet 2011, 129:273-282.
neuropathologically verified individuals. Hum Mol Genet 2010, 19:3295-3301.

12. Lambert JC, Heath S, Even G, Campion D, Sleighers K, Hiltunen M, Combarros O, Zelenika D, Bulldo MJ, Tavneren B, Lethem L, Betens K, Bers K, Pasquier F, Shovet N, Barber-Reed Getae F, Engelborghs S, De Deyn P, Mateos F, Franck A, Heslemann S, Porcelloti E, Hanon O. European Alzheimer’s Disease Initiative. Investigators, de Pancorbo MM, Lendon C, Dufoil 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.

13. Harold D, Abraham R, Hollingsworth P, Sims R, Gerrish A, Hamshere ML, Paiva JS, Moskvina V, Dowzell K, Williams A, Jones N, Thomas C, Stretton A, Morgan AR, Lovestone S, Powell J, Protiu 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.

14. Bentham L, McQueen MB, Mullin K, Blacker D, Tanzi RE. Systematic meta-analyses of Alzheimer disease genetic association studies: the Alzbase database. Nat Genet. 2007, 39:17-23.

15. Hollingsworth P, Harold D, Sims R, Gerrish A, Lambert JC, Carrausillo MM, Abraham R, Hamshere ML, Paiva JS, Moskvina V, Dowzell K, Jones N, Stretton A, Thomas C, Richards A, Ivanov D, Diddowson C, Chapman J, Lovestone S, Powell J, Protiu P, Lupton MK, Brayne C, Rubinsztein DC, Gill M, Lawlor B, Lynch A, Bryson KS, Passmore PA, Craig D, et al. - Common variants at ABC7, MS4A6A/MS4A4E, EPHA1, CD33 and CD2AP are associated with Alzheimer’s disease. Nat Genet. 2011, 43:429-435.

16. Lambert JC, Genere-Boley B, Chouraki V, Heath S, Zelenika D, Fievet N, Haltia M, Konttinen YT, Peltonen L; Alzheimer Genetic Analysis Group; A, Thomas C, Richards A, Ivanov D, Widdowson C, Chapman J, Lovestone S, Powell J, Protiu P, Lupton MK, Brayne C, Rubinsztein DC, Gill M, Lawlor B, Lynch A, Morgan K, Brown KS, Passmore PA, Craig D, et al. - Genetic evidence implicates the immune system and cholesterol metabolism in the aetiology of Alzheimer’s disease. PLoS One. 2010, 5:e13950.

17. Jones L, Holmans PA, Hamshere ML, Harold D, Moskvina V, Ivanov D, Pocklington A, Abraham R, Hollingsworth P, Sims R, Gerrish A, Paiva JS, Jones N, Stretton A, Morgan AR, Lovestone S, Powell J, Protiu 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, et al. - Essential role of the microglial triggering receptor expressed on myeloid cell-like transcript-1 (TREM-1) in the regulation of microglial activity. Neurobiol Aging. 2010, 31:1711-118.

18. Johannes T, Stefanhoff H, Steinberg S, Jonisdottir J, Jonsson PV, Snaedal J, Bjornsson S, Huttenlocher J, Rejey AE, Lah JJ, Berr C, Dartigues JF, Tzourio C, Campion D, Larheip M, Amouley P. - Implication of the immune system in Alzheimer’s disease: evidence from genome-wide pathway analysis. Alzheimers Res. 2010, 12:107-118.

19. Jones L, Holmans PA, Hamshere ML, Harold D, Moskvina V, Ivanov D, Pocklington A, Abraham R, Hollingsworth P, Sims R, Gerrish A, Paiva JS, Jones N, Stretton A, Morgan AR, Lovestone S, Powell J, Protiu 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, et al. - Essential role of the microglial triggering receptor expressed on myeloid cell-like transcript-1 (TREM-1) in the regulation of microglial activity. Neurobiol Aging. 2010, 31:1711-118.
increases Abeta deposits and exacerbates cognitive deficits in a mouse model of Alzheimer's disease. J Neuroinflammation 2011, 8:92.
56. Herber DL, Mercer M, Roth LM, Symmonds K, Maloney J, Wilson N, Freeman MJ, Morgan D, Gordon MH: Microglial activation is required for Abeta clearance after intracranial injection of lipopolysaccharide in APP transgenic mice. J Neuroimmune Pharmacol 2007, 2:222-231.
57. Michaud JP, Hallé M, Lampron A, Théault P, Prétor fusante P, Filali M, Tribout-Jover P, Lanteigne AM, Jodoin R, Cluff B, Brichard V, Palmantier R, Pioroguet A, Laroccoque D, Rivest S: Toll-like receptor 4 stimulation with the detoxified ligand monophosphoryl lipid A improves Alzheimer's disease-related pathology. Proc Natl Acad Sci U S A 2013, 110:1941-1946.
58. Boissoneault V, Filali M, Lessard M, Relton J, Wong G, Rivest S: Powerful beneficial effects of macrophage colony-stimulating factor on beta-amyloid deposition and cognitive impairment in Alzheimer's disease. Brain 2009, 132:1078-1092.
59. Chakrabarty P, Tianbai L, Herring A, Ceballos-Diaz C, Das P, Golde TE: The beneficial effects of macrophage colony-stimulating factor on beta-amyloid deposition and cognitive impairment in Alzheimer's disease. Blood 2009, 113:817-822.
60. Heneka MT, Kummer MP, Stutz A, Delekate A, Schwartz S, Vieira-Saecker A, Breitner JC: Nuclear receptors as therapeutic targets for Alzheimer's disease. Alzheimers Dement 2013, 9:243-255.
61. Reed-Geaghan EG, Reed QW, Cramer PE, Landreth GE: Microglia are required for fibrillar A beta-stimulated microglial activation. J Neurosci 2012, 32:17823-17829.
62. Chen XM, Wang W: Microglia are required for fibrillar A beta-stimulated microglial activation. J Neurosci 2012, 32:17823-17829.
63. Breitner JC, Baker LD, Montine TJ, Meinert CL, Lyketsos CG, Aspe, KH, Brandt J, Craft S, Evans DE, Green RC, Ismail MS, Martin BK, Mullany ML, Sabaghi M, Tanot PN, ADAPT Research Group: Extended results of the Alzheimer's Disease Anti-inflammatory Prevention Trial. Alzheimers Dement 2011, 7:402-411.
64. Sonnen JA, Larson EB, Walker RL, Haneuse S, Crane PK, Gray SL, Breitner JC, Thomas RG, Thal LJ: Effects of rofecoxib or naproxen vs placebo on Alzheimer disease progression: a randomized controlled trial. JAMA 2003, 289:2819-2826.
65. Breitner JC, Baker LD, Montine TJ, Meinert CL, Lyketsos CG, Efentakis J, Antin MR, Breitner JC, Montine TJ: Nonsteroidal anti-inflammatory drugs and the risk of Alzheimer's disease. N Engl J Med 2001, 345:1515-1521.
66. Zandi PP, Breitner JC: Do NSAIDs prevent Alzheimer's disease? And, if so, why? The epidemiological evidence. Neurobiol Aging 2001, 22:811-817.
67. Sonnen JA, Larson EB, Walker RL, Haneuse S, Crane PK, Gray SL, Breitner JC, Montine TJ: Nonsteroidal anti-inflammatory drugs are associated with increased neurtic plaques. Neurology 2010, 75:1303-1312.
68. Baker M, Mackenzie IR, Pickering-Brown SM, Gass J, Rademakers R, Lindholm C, Snowden J, Adamson J, Sadovnick AD, Rollinson S, Cannon A, Dwosh E, Neady D, Melquist S, Richardson A, Dickson D, Berger Z, Eriksen J, Robinson T, Zehr C, Dickey CA, Crock R, McGowan E, Mann D, Roeve B, Feldman H, Hutton M: Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. Nature 2006, 442:616-919.
69. Smith KR, Damiano J, Franceschetti S, Carpenter P, Canafoglia L, Morbin M, Rossi G, Pareyson D, Mole SE, Staropoli JF, Sims KB, Lewis J, Lin WL, Dickson DW, Dahl HH, Bahlo M, Berkovic SF: Strikingly different clinicopathological phenotypes determined by progranulin-mutation dosage. Am J Hum Genet 2012, 90:1102-1107.
70. Tayebi N, Callahan M, Madixe V, Stubbfield BK, Orvisky E, Kravchienew D, Filiano JJ, Sidransky E: Gaucher disease and parkinsonism: a phenotypic and genotypic characterization. Mol Genet Metab 2001, 73:313-321.
71. Sidransky E, Lopez G: The link between the GBA gene and parkinsonism. Lancet Neurol 2012, 11:986-998.

In 't Veld BA, Launer LJ, Hoes AW, Ott A, Hofman A, Breteler MM, Stricker BH: NSAIDs and incident Alzheimer's disease. The Rotterdam Study [see comments]. Neurobiol Aging 1998, 19:607-611.
72. Anthony JC, Breitner JC, Zandi PP, Meyer MR, Jurassova J, Norton MC, Stone SV: Reduced prevalence of AD in users of NSAIDs and H2 receptor antagonists: the Cache County study. Neurology 2001, 56:2066-2071.
73. Combs CK, Johnson DE, Kario JC, Cannady SB, Landreth GE: Inflammatory mechanisms in Alzheimer's disease: inhibition of beta-amyloid-stimulated proinflammatory responses and neurotoxicity by PPARgamma agonists. J Neurosci 2000, 20:538-567.
74. Breitner JC, Baker LD, Montine TJ, Meinert CL, Lyketsos CG, Efentakis J: Effects of non-steroidal anti-inflammatory drug treatments on cognitive decline vary phase by phase in pre-clinical Alzheimer disease: findings from the randomized controlled Alzheimer's Disease Anti-inflammatory Prevention Trial. Int J Gen Intern Psychiatry 2012, 27:364-374.
75. Meinert CL, McCaffrey LD, Breitner JC: Alzheimer's Disease Anti-inflammatory Prevention Trial: design, methods, and baseline results. Alzheimers Dement 2009, 5:93-104.
76. Breitner JC, Evans D, Lyketsos C, Martin B, Meinert C: ADAPT trial data. Am J Med 2007, 120:A63, author reply e4; discussion e7.
77. Breitner JC, Martin BK, Meinert CL: The suspension of treatments in ADAPT: concerns beyond the cardiovascular safety of celecoxib or naproxen. PLoS Clin Trials 2006, 1:e41.
78. Zandi PP, Breitner JC: Do NSAIDs prevent Alzheimer's disease? And, if so, why? The epidemiological evidence. Neurobiol Aging 2001, 22:811-817.
79. Sonnen JA, Larson EB, Walker RL, Haneuse S, Crane PK, Gray SL, Breitner JC, Montine TJ: Nonsteroidal anti-inflammatory drugs are associated with increased neurtic plaques. Neurology 2010, 75:1303-1312.
80. Baker M, Mackenzie IR, Pickering-Brown SM, Gass J, Rademakers R, Lindholm C, Snowden J, Adamson J, Sadovnick AD, Rollinson S, Cannon A, Dwosh E, Neady D, Melquist S, Richardson A, Dickson D, Berger Z, Eriksen J, Robinson T, Zehr C, Dickey CA, Crock R, McGowan E, Mann D, Roeve B, Feldman H, Hutton M: Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. Nature 2006, 442:616-919.
81. Smith KR, Damiano J, Franceschetti S, Carpenter P, Canafoglia L, Morbin M, Rossi G, Pareyson D, Mole SE, Staropoli JF, Sims KB, Lewis J, Lin WL, Dickson DW, Dahl HH, Bahlo M, Berkovic SF: Strikingly different clinicopathological phenotypes determined by progranulin-mutation dosage. Am J Hum Genet 2012, 90:1102-1107.
82. Tayebi N, Callahan M, Madixe V, Stubbfield BK, Orvisky E, Kravchienew D, Filiano JJ, Sidransky E: Gaucher disease and parkinsonism: a phenotypic and genotypic characterization. Mol Genet Metab 2001, 73:313-321.
83. Sidransky E, Lopez G: The link between the GBA gene and parkinsonism. Lancet Neurol 2012, 11:986-998.

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