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REVIEW

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 sclerosing leukoencephalopathy (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.

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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 *CLU*, 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 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 leukoencephalopathy (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 transmission 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 homozygous 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 leukoencephalopathy; 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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