

Trem2 Variants and Risk of Alzheimer's Disease

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Abstract

Object: Alzheimer's disease (AD) is the most common form of dementia in the elderly. The genetic basis of late-onset AD (LOAD) is not well known. However, since 1993 the relationship with APOE gene is known, recently it has established a new relationship with the TREM2 gene. This review aims to show the implications of mutations in TREM2 gene in AD.

Background: Mutations in TREM2 have been involved in Nasu-Hakola disease that causes frontotemporal dementia like (FTD-like) phenotype. Recently it has been involved in AD with an odds ratio as strong as previously reported with APOE ϵ 4.

Methods and results: We review relevant papers concerning to TREM2 gene, not only its implication in neurodegenerative disease, but also those focused on Alzheimer's Disease.

Conclusion: There is an increased frequency of rare heterozygous TREM2 variations in AD and FTD, and TREM2 variants may play a role in neurodegenerative diseases in general. However, the relationship between TREM2 gene and neurodegenerative diseases is complex and ambiguous results. Surely the TREM2 variants have great interest in future research of neurodegenerative diseases.

Keywords: TREM2; Genetic risk; Alzheimer's disease; Frontotemporal dementia; Nasu-Hakola disease; Late-onset Alzheimer's disease.

Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder that is characterized by a slow and progressive loss of cognitive functions. In developed countries it is the most common form of late-onset dementia over 60 years old. The main pathological hallmarks of AD are extracellular amyloid plaques, intracellular neurofibrillary tangles, and loss of neurons and synapses. These changes result in a cerebral atrophy with cognitive and neuropsychiatric symptoms. The vast majority of cases of Alzheimer's disease are late-onset cases over 60 years. However, there are early forms of AD (EAD) in which the genetic load is high and associated with mutations in APP, PSEN1, and PSEN2 genes (encoding amyloid precursor protein, presenilin 1, and presenilin 2, respectively). These variants appear to be fully penetrant and result in Alzheimer's disease with an early onset, in most cases before the age of 60 years.

The genetic basis of late onset Alzheimer's Disease (LOAD) are less known and, until recently, only found regarding the gene encoding the ϵ 4 allele of apolipoprotein E (ApoE), originally discovered as a risk factor for AD in 1993. APO E is the only susceptibility gene involved in AD with an odds ratio (OR) 3-4 [1].

Current high-throughput sequencing technologies such as whole-exome and whole-genome sequencing enable the identification of rare genetic causes of disease. Using a whole-exome sequencing approach, homozygous mutations in the gene encoding triggering receptor

expressed on myeloid cells 2 (TREM2; 6p21.1) were identified as a cause of behavioral variant frontotemporal dementia (FTD) in 3 consanguineous Turkish families [2].

TREM2 is a receptor of the innate immune system, expressed on the cell membrane of myeloid cells, especially on immature dendritic cells, microglia, and osteoclasts. Homozygous loss-of-function mutations in TREM2 (e.g., p.Q33X) were previously found in patients with Nasu-Hakola disease (polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy: PLOSL). This is a rare recessively inherited disease that is characterized by early-onset progressive dementia and bone cysts [3].

TREM2 Gene and its Implication in Neurodegenerative Diseases

There are a number of pathways that are likely generalized across neurodegenerative diseases, including the mitochondrial dysfunction, ubiquitin-proteasome system and the inflammatory response. There is evidence that inflammation is an early event in the brains of patients with AD [4]. It has also been noted that the expression of genes associated with inflammation in the brain is increased in aging and that this effect is accentuated in AD. Genome wide association studies have also provided evidence of the importance of inflammation in AD.

TREM2 has an important role in the immune response and its loss-of-function mutations have been demonstrated to cause a spectrum of dementia-like phenotypes with or without bone cysts [2,3,5]. The identification of a rare TREM2 substitution (p.R47H) as a risk factor for AD suggests that the protein plays an important role in neurodegeneration. TREM2 is known to control two streams of

signaling, one of these streams regulates phagocytosis. Increased expression of TREM2 on microglia is coupled to enhanced phagocytic pathways and promotes the alternative activation state of microglia, which is thought to be protective [6-8]. The other signaling stream suppresses inflammatory reactivity and involves the repression of cytokine production and secretion. The inflammation response of TREM 2 inhibits macrophage response to ligation of toll-like receptor (TLR) [9], and it negatively regulates TLR-mediated maturation of dendritic cells, type I interferon responses, and the induction of antigen-specific T-cell proliferation [10]. Furthermore, TREM2 stimulation of dendritic cells induces partial activation without any production of pro-inflammatory cytokines [11].

There is growing evidence to support the role of activated microglia pathways in neuro-degeneration. A recent integrated systems approach identified that DAP12 (TYROBP) is one of the key genes. The authors have demonstrated that DAP12 is involved in amyloid-beta turnover and neuronal damage with TREM2, via β -catenin [12]. Recessive mutations in both TREM2 and DAP12 produce the clinical phenotype of Nasu-Hakola disease [13].

Discussion

Nasu-Hakola disease and Alzheimer's disease are distinct from each other, and the clinical symptoms of Nasu-Hakola disease (early onset, painful bone cysts, fractures of bones of the limbs, and sclerosing leukoencephalopathy) are incompatible with the diagnosis of AD. Taking into account that, it is possible that rare mutations accounting for a small proportion of cases of common diseases may define a clinical subgroup. It has been reported a homozygous mutation in the 5' consensus donor splice site in intron 1 of TREM2 in a Lebanese family, leading to early-onset dementia without bone cysts [14].

Furthermore, mutations in TREM2 have been reported in three Turkish probands with frontotemporal dementia-like disease in the absence of bone cysts [15]. In an Italian family, those heterozygous carriers with a loss-of-function mutation in TREM2, have been reported memory deficits [16]. These findings suggest that TREM2 may be crucial for the integrity of cognitive function. The R47H substitution encoded by rs75932628- T is located within the extracellular immunoglobulin-like domain of TREM2. The amino acid substitution may result in decreased affinity of TREM2 for its natural ligands and affect its signaling. It has been proposed that TREM2 may represent a proteolytic substrate for γ -secretase, although the exact cleavage site was not identified [17].

The rare variant p.R47H [18], (rs75932628), has demonstrated a strong association with late onset AD in two different studies [19]. This mutation codifies a protein with a substitution of arginine by histidine in 47 positions, with an allelic prevalence in Iceland 0.63%. This has been replicated in Spain [20] and French [21] population.

In a Belgian population study, the estimated PAF (population-attributable fraction) for TREM2 p.R47H was only 0.55%, very low if you compared with APOE ϵ 4 one (PAF> 30%). This study suggests that heterozygotes variants of TREM2 play a role as risk factors with a moderate penetrance, which is a lack of segregation [5].

The Cache County Study on Memory Health and Aging is a huge population study that began in 1994. It includes 5092 participants that represent 90% of the whole Cache County inhabitants, in Utah with 65 years old or older. Those with dementia had a blood sample, MRI and

cognitive examination, and Alzheimer diagnosis was according NINCDS-ADRDA criteria (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria) [22], included probable cases. In this study R47H variant was analyzed in late onset AD. The OR was 3.5 with a risk very similar to APOE4 one. However, this variant is very infrequent in general population (0.004 vs. 0.20 for APOE ϵ 4) [23].

Also we have information about the TREM2 variants in other neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS). Recently, Cady et al. [24] have published a paper of TREM2 Variant p.R47H as a risk factor for Sporadic ALS. Samples of DNA from 923 individuals with sporadic ALS and 1854 healthy control individuals self-reported as non-Hispanic white were collected from ALS clinics in the United States and genotyped for the p.R47H variant in TREM2. This variant was more common in patients with ALS than in the controls and is therefore a significant risk factor for ALS (odds ratio, 2.40; 95% CI, 1.29-4.15).

However, in contradiction with previous studies, there is a recently published study of TREM-like receptors with ambiguous results. TREM-Like2 is analogous to the original receptor TREM2 receptor, although this receptor is encoded in another genomic region. Unexpectedly, polymorphisms in this genomic region have been identified to be protective for AD in a recent paper [25].

In the same direction, a paper published by Miyashita A et al conducted a study using a well-characterized Japanese sample set, comprising 2,190 late-onset AD (LOAD) cases and 2,498 controls. They genotyped 10 non-synonymous TREM2 variants with no significant association with LOAD [26].

In conclusion, further insights into the pathophysiology of AD and, in general, neurodegenerative diseases are needed. Genetics play a main role in a deep knowledge of them and could lead us new therapeutic approaches. TREM2 variants have found a new risk for Alzheimer's disease. Although this variant occurs with less frequency than the ApoE ϵ 4 allele, it confers a risk of Alzheimer's disease with an effect size that is similar to that of ApoE ϵ 4. However, TREM2 variants appear to be associated with different phenotypes of neurodegenerative diseases, particularly ALS and FTD. Conversely, recent work with TREM-like 2 variants appears to provide protection against AD. In short, TREM2 variants provide an exciting way to investigate the neurobiological basis of neurodegenerative diseases [27].

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