Neurobiology of Aging xxx (2013) 1–8

Contents lists available at SciVerse ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Variants in triggering receptor expressed on myeloid cells 2 are associated with both behavioral variant frontotemporal lobar degeneration and Alzheimer's disease

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ARTICLE INFO

Article history:
Received 20 February 2013
Accepted 22 February 2013

Keywords:
TREM2
Alzheimer's disease
FTLD
neurodegeneration

ABSTRACT

Recent evidence suggests that rare genetic variants within the *TREM2* gene are associated with increased risk of Alzheimer's disease. *TREM2* mutations are the genetic basis for a condition characterized by polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOSL) and an early-onset dementia syndrome. TREM2 is important in the phagocytosis of apoptotic neuronal cells by microglia in the brain. Loss of function might lead to an impaired clearance and to accumulation of necrotic debris and subsequent neurodegeneration. In this study, we investigated a consanguineous family segregating autosomal recessive behavioral variant FTLD from Antioquia, Colombia. Exome sequencing identified a nonsense mutation in *TREM2* (p.Trp198X) segregating with disease. Next, using a cohort of clinically characterized and neuropathologically verified sporadic AD cases and controls, we report replication of the AD risk association at rs75932628 within *TREM2* and demonstrate that TREM2 is significantly overexpressed in the brain tissue from AD cases. These data suggest that a mutational burden in *TREM2* may serve as a risk factor for neurodegenerative disease in general, and that potentially this class of *TREM2* variant carriers with dementia should be considered as having a molecularly distinct form of neurodegenerative disease.

1. Introduction

Triggering receptor expressed on myeloid cells 2 (*TREM2*) is an immunoreceptor expressed on activated macrophages, osteoclast, immature dendritic cells, and microglia (Colonna, 2003). It is a 26-kDa transmembrane glycoprotein that consists of a single extracellular immunoglobulin-like domain, a transmembrane region with a charged lysine residue, and a short cytoplasmic tail lacking any signaling motifs (Colonna, 2003). TREM2 forms a receptor signaling complex with TYROBP (Paloneva et al., 2002). The charged lysine in the transmembrane domain of TREM2 is needed for its association with TYROBP (Bouchon et al., 2000; Bouchon et al., 2001) and as TREM2 lacks an intracellular signaling tail, it is completely dependent on the presence of the adaptor protein TYROBP (Colonna, 2003). The TREM2/TYROBP complex

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http://dx.doi.org/10.1016/j.neurobiolaging.2013.02.016

regulates key signaling events involved in immune responses, differentiation of dendritic cells and osteoclasts, and phagocytic activity in microglia (Bouchon et al., 2001; Hsieh et al., 2009; Otero et al., 2012).

After neuronal injury, microglia initiate repair by phagocytizing dead neurons without eliciting inflammation. TREM2 has been shown to play a role in the phagocytosis of apoptotic neuronal cells by microglia and resolution of inflammation (Hsieh et al., 2009). TREM2 can directly bind to neuronal cells, with increased binding to apoptotic neuronal cells. When neuronal cells undergo apoptosis, they increase the expression of TREM2-ligands, which mediate signal transduction by TREM2 on microglia and promote phagocytosis (Hsieh et al., 2009). In osteoclasts, TREM2 has been shown to regulate bone mass by regulating the rate of osteoclast generation (Otero et al., 2012).

Genetic mutations in either *TREM2* or *TYROBP* cause a similar clinical phenotype, the Nasu-Hakola syndrome (or polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy [PLOSL]) (Fig. 1), which is characterized by cystic-like lesions of the bone and brain demyelination that lead to fractures and presenile dementia (Paloneva et al., 2002). The disease is characterized by different stages. The first symptoms present with an osseous stage at the third decade of life with pathological bone fractures. This is followed by the early neuropsychiatric stage in the fourth decade, presenting a frontal lobe syndrome, and the late neuropsychiatric stage, with profound dementia and usually death by the age of 50 years (Bianchin et al., 2004; Numasawa et al., 2011). Neuropathological findings include loss of myelin and axons in the brain, with reactive astrocytosis and microglial activation (Klunemann et al., 2005). Mutations in *TREM2* have also been described in pure early-onset dementia without bone cysts, and frontotemporal dementia (FTD)–like syndrome (Chouery et al., 2008). Recently, a variant in *TREM2* (rs75932628) has also been implicated as a risk factor for both early-onset and late-onset Alzheimer's disease (Jonsson et al., 2012; Pottier et al., 2013; R. Guerreiro et al., 2012).

In this study, we identified a nonsense mutation in *TREM2* in a consanguineous Colombian family segregating autosomal recessive FTLD. Frontotemporal lobar degeneration (*FTLD*) is the second most common cause of early-onset dementia and the fourth most common cause of late-onset dementia, and is characterized by atrophy of the prefrontal and anterior temporal lobes. FTLD is a clinically and genetically heterogeneous degenerative disorder. Patients usually show prominent behavioral and/or language deficits, which evolve gradually into cognitive impairment and dementia (McKhann et al., 2001; Neary et al., 1998). The most common clinical manifestation of FTLD consists of behavioral or personality changes (behavioral variant frontotemporal dementia or bvFTD) (Neary et al., 1998). Two other prototypic clinical phenotypes that occur in FTLD are language impairment disorders: semantic dementia (SD) and progressive nonfluent aphasia (PNFA) (Neary et al., 1998).

In this article, we report that a nonsense mutation in *TREM2* is the cause of FTLD in a Colombian family from the province Antioquia. In addition, we provide replicative evidence demonstrating a role for the rs75932628 *TREM2* variant in Alzheimer's disease, thereby suggesting *TREM2* mutations as a risk factor for neurodegenerative disease in general.

2. Methods

2.1. Clinical diagnosis

A large consanguineous Colombian family segregating autosomal recessive FTLD was collected through the Grupo Neurosciencias, University of Antioquia, Colombia (Fig. 2). Three patients and 5 unaffected relatives from the family were included. Our patients met published criteria for behavioral variant FTD (Rascovsky et al., 2011). The index case was a female offspring of first cousins who first showed symptoms of sexual disinhibition at age 47. She was excessively familiar with strangers and had abandoned all her responsibilities in the home. A paternal uncle and a brother had similar symptoms before age 60.

2.1.1. Clinical tests

All patients and controls underwent a standard medical and neurological history, physical examination, and office-based clinical cognitive assessment. Patient III:16 (index patient) and her brother (patient III:10) additionally underwent more detailed neuropsychological assessment that included the following: general: mental status examinations (maximum score 30 points); memory: 10-item, 3 learning trials word-list learning with delayed free recall and recognition, and the Rey-Osterrieth Complex Figure Test (copy and recall, 36 points maximum for each); Attention/Psychomotor Speed: Trail Making Test (seconds to complete), Wechsler Adult Intelligence Scale-Revised Digit Symbol Substitution Test (raw total score); Language: FAS letter fluency (numbers of words generated in one minute for each letter), Category Fluency (animals named in 1 minute), and sentence writing; executive functions: Wisconsin Card Sorting Test (categories and perseverative responses).

This study was conducted according to the guidelines of the ethical committee at the University of Antioquia. Informed consent

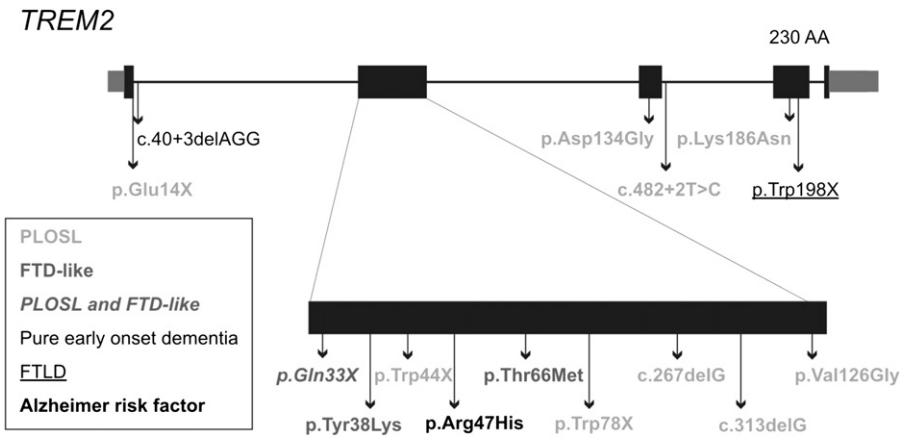

Fig. 1. Overview of the mutations found in *TREM2*. ENST00000373113.3; ENSP00000362205.3.