Mutations in *TYROBP* are not a common cause of dementia in a Turkish cohort

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Abstract

Mutations in *TYROBP* and *TREM2* have been shown to cause polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy. Recently, variants in *TREM2* were also associated with frontotemporal dementia and Alzheimer's disease. Given the functional proximity between these two genes we investigated the genetic variation of *TYROBP* in a Turkish cohort of 103 dementia patients. No mutations or copy number variants predicted to be pathogenic were identified. These results indicate that mutations in *TYROBP* are not a common cause of dementia in this Turkish cohort.

Keywords: *TYROBP*, dementia, genetic variant, Turkish cohort, whole-genome genotyping, whole-exome sequencing

1. Introduction

TYRO protein tyrosine kinase binding protein (TYROBP, also known as DAP12) is a transmembrane signaling protein. In microglia TYROBP binds to different receptors, including TREM2, SIRPβ1 and CR3 (Ma et al., 2015). The TYROBP-receptor complex activates microglia phagocytosis and inflammation response in the brain (Linnartz et al. 2010).

Biallelic mutations in *TYROBP* and *TREM2* have been described as causative of polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOSL, also known as Nasu-Hakola disease; OMIM: 221770). The same type of mutations in *TREM2* were also found to cause frontotemporal dementia (FTD) without the typical bone phenotypes found in PLOSL (Guerreiro et al., 2013a), and heterozygous rare variants have been shown to modulate the risk of Alzheimer's disease (Guerreiro et al., 2013b; Jonsson et al., 2013).

More recently an enrichment of *TYROBP* rare variants was reported in patients with early-onset Alzheimer's disease (EOAD) (Pottier et al., 2016), and increased mRNA

expression levels of *TYROBP* were found in the brain of LOAD patients (Zhang et al., 2013).

Given these recent results and the close functional interaction between TREM2 and TYROBP, we aimed to investigate the genetic variation of *TYROBP* in a cohort of Turkish dementia cases overlapping with the one where we previously identified three *TREM2* mutations as the cause of an atypical FTD phenotype (Guerreiro et al., 2013a).

2. Materials and Methods

We analysed a cohort of 103 Turkish dementia cases including patients with mild cognitive impairment (MCI) (20 patients), Alzheimer's disease (AD) (50 patients), FTD (24 patients) and other forms of dementia (9 patients) (**Table S1**). All cases were negative for pathogenic mutations in dementia genes (list of genes in Supplementary Material). Samples were genotyped by whole-genome genotyping (WGG) and data were analysed in order to identify large (>50 kb) copy number variants (CNVs) and large tracts of homozygosity (>1 Mb) within the *TYROBP* locus. Whole-exome sequencing (WES) was performed to retrieve variability in the coding and immediate intronic regions of *TYROBP* and Sanger sequencing was done in samples with no WES data and for exons with low coverage in WES. Details for the methods used are available in the **Supplementary data**.

3. Results

No CNVs or large tracts of homozygosity were identified at the *TYROBP* locus in the 103 samples studied. Similarly, the analysis of WES and Sanger sequencing data revealed no biallelic missense mutations or small insertions or deletions predicted to be pathogenic. The low frequency synonymous variant p.Gly41Gly (rs111477177) was identified in four patients. The missense variant p.Val55Leu (rs77782321) was found to always be associated with c.94+71T>C and c.*25A>C (Figure 1, Table S2)

and was identified in three patients with clinical diagnoses of AD, FTD or MCI. These variants (p.Gly41Gly and p.Val55Leu) were detected in the heterozygous state in all samples and predicted as benign according to *in silico* analysis.

4. Discussion

TYROBP is a transmembrane adaptor protein that couples with cell membrane receptors, including TREM2. Given the functional proximity of both genes we have studied the possible involvement of genetic variability in *TYROBP* in dementia, by assessing a cohort of Turkish dementia cases. This is a genetically well characterized cohort where we have previously identified *TREM2* biallelic mutations as the cause of an atypical FTD syndrome in three cases. This population has the ideal characteristics for such studies due to the high degree of consanguineous marriages and consequent high likelihood of autosomal recessive disorders.

No large structural variants or large regions of homozygosity were identified in the *TYROBP* locus. Three individuals were found to be carriers of the missense p.Val55Leu. This variant was previously found in a patient with EOAD also carrying the p.Gly2Glu and to be absent in control population (Pottier et al., 2016). The global allelic frequency of p.Val55Leu in the general population is 0.015, being more frequent in the Asian population. This variant is classified as benign by different *in silico* prediction software of pathogenicity. These results indicate that *TYROBP* mutations are not a common cause of dementia in the Turkish population. TYROBP was shown to be a key regulator of microglia functions (Zhang et al., 2013) and has a number of loss of function (LoF) variants lower than predicted by ExAC (probability of LoF intolerance of 0.49). These facts suggest that TYROBP may have a critical physiological role, and/or other biological functions that prevent a high rate of mutability. Given the low number of variants in the gene and the low frequency of minor alleles in the population, further studies including larger cohorts will be required to fully understand the involvement of this gene in dementia.

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Figures

Figure 1: Schematic representation of TYROBP (NP_003323) with the previously identified mutations in PLOSL (top) and EOAD (bottom). PLOSL mutations were found in the homozygous or compound heterozygous states. Variants identified in EOAD were found in the heterozygous state. The variant p.Val55Leu found in this study is represented in bold. PLOSL: polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy, EOAD: early-onset Alzheimer’s disease.