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Common and rare *TBK1* variants in early-onset Alzheimer disease in a European cohort

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ABSTRACT

TANK-binding kinase 1 (TBK1) loss-of-function (LoF) mutations are known to cause frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS), often combined with memory deficits early in the disease course. We performed targeted resequencing of *TBK1* in 1253 early onset Alzheimer's disease (EOAD) patients from 8 European countries to investigate whether pathogenic *TBK1* mutations are enriched among patients with clinical diagnosis of EOAD. Variant frequencies were compared against 2117 origin-matched controls. We identified only 1 LoF mutation (p.Thr79del) in a patient clinically diagnosed with Alzheimer's disease and a positive family history of ALS. We did not observe enrichment of rare variants in EOAD patients compared to controls, nor of rare variants affecting NFκB induction. Of 3 common coding variants, rs7486100 showed evidence of association (OR 1.46 [95% CI 1.13–1.9]; *p*-value 0.01). Homozygous carriers of the risk allele showed reduced expression of TBK1 (*p*-value 0.03). Our findings are not indicative of a significant role for *TBK1* mutations in EOAD. The association between common variants in *TBK1*, disease risk and reduced TBK1 expression warrants follow-up in FTD/ALS cohorts.

1. Introduction

TANK-binding kinase 1 (TBK1) is a serine/threonine-protein kinase involved in autophagy and inflammatory response (Weidberg and Elazar, 2011). TBK1 interacts with the optineurin (OPTN) protein and with multiple interferon regulatory factors, mediating NF-kappa-B (NFκB) activity (Cirulli et al., 2015; Clement et al., 2008; Larabi et al., 2013). Recently, TBK1 has been demonstrated to regulate mitosis and microtubule stability via the TBK1-CEP170 complex (Pillai et al., 2015).

Loss-of-function (LoF) mutations in the *TBK1* gene, including frameshift mutations and inframe amino acid deletions have been identified as a cause of disease in the frontotemporal dementia (FTD)–amyotrophic lateral sclerosis (ALS) spectrum of neurodegeneration (Cirulli et al., 2015; Freischmidt et al., 2015; Gijselinck et al., 2015). In addition, several missense variants have been reported to lead to loss of function, for example, by inhibiting TBK1 interaction with OPTN (Freischmidt et al., 2015; Pottier et al., 2015). Recently, missense mutations compromising NFκB activation in the IFN pathway were found to be enriched among FTD patients compared with neurologically healthy control individuals, suggestive of intermediate penetrant risk variants (van der Zee et al., 2017). However, given the range of functions and substrates of TBK1 and the current absence of insight in the pathomechanism linking *TBK1* LoF to FTD/ALS, causal inferences should be made with caution.

Episodic memory loss and disorientation in time and/or space appear to be frequent early symptoms in carriers of a pathogenic *TBK1* LoF mutation (Van Mossevelde et al., 2015), even resulting in a clinical diagnosis of Alzheimer's disease (AD) in some carriers (Pottier et al., 2015; Van Mossevelde et al., 2015). This has led to the recommendation to consider genetic diagnostic testing for *TBK1* LoF mutations in case of clinical ambiguity between FTD and AD (Van Mossevelde et al., 2015).

Here, we report a massive parallel resequencing of *TBK1* in a large European cohort consisting of 1253 early-onset AD (EOAD) patients, and comparison with 2117 origin-matched unaffected control individuals, to investigate to what extent genetic variability in *TBK1* contributes to the occurrence of AD.

2. Materials and methods

2.1. Study population

The cohort under study consisted of 1253 EOAD patients originating from Flanders-Belgium (n = 273), Spain ($n = 375$), Portugal ($n = 104$), Italy ($n = 182$), Sweden ($n = 155$), Greece (n = 62), Germany ($n = 91$), and Czech Republic ($n = 11$) and 2117 age-matched European control individuals originating from Flanders-Belgium (n = 1042), Spain ($n = 334$), Portugal ($n = 124$), Italy ($n = 340$), and Sweden ($n = 277$) (Table 1). A detailed description of cohort procedures and characteristics is provided in (Verheijen et al., 2016). In the patient cohort, average onset age was 58.9 ± 6.2 years. Information on familial history of AD was present for 756/1253 (60%) patients. Of these, 338/756 (45%) individuals had a positive familial history (defined as presence of at least 1 first-degree relative with AD). Patients with known pathogenic mutations in genes *APP*, *PSEN1*, *PSEN2*, *ABCA7*, *C9orf72*, *MAPT*, *PRNP*, and *GRN* were excluded from the cohort (Cruts et al., 2012; Cuyvers et al., 2015a) (Cuyvers et al., 2015). Average age at inclusion for the control cohort was 67.5 ± 10.0 years. The percentage of women was 59% for both the patient and the control cohort.