Rare nonsynonymous variants in SORT1 are associated with increased risk for frontotemporal dementia

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30 Rare nonsynonymous variants in SORT1 are associated with increased risk for frontotemporal dementia
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INTRODUCTION

Frontotemporal lobar degeneration (FTLD) represents a heterogeneous group of neurodegenerative disorders characterized by neuronal loss in the frontal and temporal lobes of the brain. Clinically, 2 entities are defined: the behavioral variant of frontotemporal dementia (bvFTD) with main changes in personality and behavior (Neary et al., 1998; Rascovsky et al., 2011) and primary progressive aphasia (PPA) with language disturbances (Gorno-Tempini et al., 2011; Neary et al., 1998). PPA is further subdivided into progressive nonfluent aphasia (PNFA), characterized by apraxia of speech and/or agrammatism, semantic dementia (SD), characterized by impaired confrontation naming and single word comprehension, and logopenic variant PPA, characterized by impaired word retrieval and a deficit in repetition of sentences and, in contrast with the other 2 PPA variants, mostly associated with underlying atypical Alzheimer’s disease (AD) pathology (Gorno-Tempini et al., 2011; Neary et al., 1998). At neuropathology, FTLD brains show protein inclusions in degenating neurons, and based on the particular inclusion protein, FTLD can be further subdivided into FTLD-TDP (TAR DNA-binding protein 43 kDa), FTLD-tau (tau), FTLD-FUS (fused in sarcoma), FTLD—ubiquitin proteasome system or FTLD-ni (no inclusions) (Mackenzie et al., 2010).

About 30%–50% of frontotemporal dementia (FTD) patients have a positive family history, indicating a strong genetic contribution. In 10%–23% of FTD families, the segregation is compatible with autosomal dominant inheritance (Goldman et al., 2007). So far, 7 causal FTD genes have been identified: microtubule-associated protein tau (MAPT) (Hutton et al., 1998), valosin-containing protein (VCP) (Watts et al., 2004), charged multivesicular body protein 2B (CHMP2B) (Skibinski et al., 2005), progranulin (GRN) (Baker et al., 2006; Cruts et al., 2006), chromosome 9 open reading frame 72 (C9orf72) (Dejesus-Hernandez et al., 2011; Gijselinck et al., 2012; Renton et al., 2011), sequestosome 1 (SQSTM1) (Rubino et al., 2012; van der Zee et al., 2014), and TANK-binding kinase 1 (TBK1) (Gijselinck et al., 2015; Pottier et al., 2015).

GRN is the second major mutated gene after C9orf72, with loss-of-function mutations (Cruts et al., 2006, 2012; Sleegers et al., 2009) leading to a reduction of GRN levels in the CSF and serum or plasma, supporting haploinsufficiency as the underlying disease mechanism (Finch et al., 2009; Ghidoni et al., 2008; Schofield et al., 2010; Sleegers et al., 2009). GRN is widely expressed, but in the brain, intracellular expression is highest in the neurons and activated microglia (Petkau et al., 2010). Sortilin (SORT1) was identified as the main neuronal receptor for GRN and is expressed on the neuronal cell surface (Hu et al., 2010). Under stress conditions, GRN is secreted by activated microglia, binds to the neuronal receptor SORT1, and is rapidly endocytosed, leading to reduced levels of extracellular GRN (Hu et al., 2010). Furthermore, a genome-wide association study of plasma GRN levels in FTD patients and controls identified a significant association with 2 single-nucleotide polymorphisms, rs646776 and rs611917, located 34 kb and 37 kb downstream of SORT1 (Carrasquillo et al., 2010). In the present study, we investigated a role SORT1 in the genetic etiology of FTD.
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