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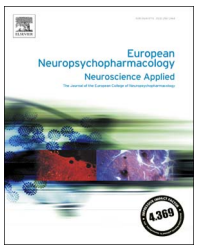

Replicated association of Synaptotagmin (*SYT1*) with ADHD and its broader influence in externalizing behaviors

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Abstract
Attention-Deficit/Hyperactivity Disorder (ADHD) is a common psychiatric disorder, affecting both children and adults. The Soluble N-ethylmaleimide sensitive factor Attachment REceptors (SNARE) complex has been implicated in ADHD pathophysiology since it is a key component of neurotransmitter release events and neurodevelopment processes, and SNPs in this complex have been associated with ADHD. Here we aim to analyze the effects of SNARE complex variants on ADHD susceptibility and its clinical heterogeneity in affected adults. We tested the association between ADHD and polymorphisms on the SNARE genes *STX1A* (rs2228607), *SYT1* (rs1880867 and rs2251214), *VAMP2* (26bp Ins/Del) and *SNAP25* (rs6108461 and rs8636) on a sample comprised of 548 adults with ADHD and 644 non-affected controls. Regarding clinical heterogeneity, we further investigated the effects of associated SNPs on age at onset of

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impairment due to ADHD and on relevant externalizing behaviors (i.e. school suspensions/expulsions and problems with law/authority) and comorbidities (i.e. Substance Use Disorder, Oppositional Defiant Disorder, Conduct Disorder and Antisocial Personality Disorder). We replicated a previously reported association between *SYT1*-rs2251214 and ADHD in adulthood. This SNP was also associated with age at onset of impairment due to ADHD symptoms and with a range of externalizing phenotypes. These findings involving *SYT1* suggest that variation in neurotransmitter exocytosis mechanisms may represent an underlying genetic factor shared by a spectrum of externalizing behaviors and disorders, including - but not restricted to - ADHD.
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1. Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a highly prevalent disorder, occurring in about 5% of children (Polanczyk et al., 2014) and 2.5–4.4% of adults (Kessler et al., 2006; Simon et al., 2009). It has a high heritability estimate (70–80%) both in children and adults (Faraone et al., 2005; Chang et al., 2013; Brikell et al., 2015); however, the knowledge on specific variants underpinning the genetic component of ADHD, especially in adulthood (Franke et al., 2011; Hawi et al., 2015), is still very limited. Inconclusive findings and the variability in odds ratios observed among ADHD genetic association studies (Gizer et al., 2009) may be assigned to the high clinical heterogeneity, such as the presence of comorbid psychiatric disorders.

ADHD has high comorbidity rates. Additional psychiatric disorders are observed in 60% of children (Gillberg et al., 2004) and 65–89% of adults (Sobanski, 2006) with ADHD, leading to worse prognosis, greater neurophysiological deficits and poorer treatment response (Sobanski, 2006). The most frequent comorbidities are Oppositional Defiant Disorder (ODD), Conduct Disorder (CD), Antisocial Personality Disorder (ASPD), Major Depressive Disorder (MDD), Bipolar Disorder (BD), Generalized Anxiety Disorder (GAD) and Substance Use Disorders (SUD) (Gillberg et al., 2004; Biederman et al., 2006; Sobanski 2006). Among adults, earlier impairment of ADHD symptoms has been associated with a more externalizing profile (e.g hyperactivity symptoms, problems with authority and discipline and novelty seeking scores) (Karam et al., 2009; Guimarães-da-Silva et al., 2012; Lin et al., 2015).

Genome-wide association studies (GWAS) have become a main source of potentially implicated genes or systems for further investigations; yet, ADHD GWAS have still not been able to obtain significantly associated hits (Neale et al., 2010; Hinney et al., 2011; Stergiakouli et al., 2012). Alternatively, animal models and cell function assays can also provide insights for plausible hypotheses in specific phenotypes. Evidence shows that dysregulation in neurotransmitter systems has a central role in the pathophysiology of all psychiatric disorders, including ADHD (Genro et al., 2010). Since the Soluble N-ethylmaleimide sensitive factor Attachment REceptors (SNARE) complex is essential to neurotransmitter release by approximating plasma and synaptic vesicle membranes, and allowing their fusion (Südhof, 2013), its genetic variants may be related to various neurotransmitter dysfunctions determining phenotypic modifications (Katrancha and Koleske, 2015). The core proteins forming neuronal SNARE complex are Synaptosomal-Associated Protein 25 (SNAP-25), Syntaxin 1A (*STX1A*) and Synaptobrevin/Vesicle-Associated Membrane Protein (VAMP). They bind to each other, as well as to regulatory proteins, such as Synaptotagmin 1 (*SYT1*). This regulatory protein binds to SNARE complex in response to calcium influx, changing the SNARE-binding affinity and allowing vesicles to fuse with the plasma membrane (Davletov and Südhof, 1994; Tang et al., 2006). In addition to its clear functions in neurotransmitter release, SNARE complex may affect ADHD susceptibility through its extensive role in the development of the brain and other systems (Cupertino et al., 2016).

Concerning SNARE complex components, *SNAP25* gene has been widely studied in ADHD, including positive association findings regarding severity scores (Salatino-Oliveira et al., 2016) and ADHD susceptibility meta-analyses (Forero et al., 2009; Gizer et al., 2009; Liu et al., 2016). Initial evidence suggesting the involvement of *SNAP25* in the etiology of ADHD came from animal model studies, which reported that mice lacking the *SNAP25* (*Coloboma* mice) show locomotor hyperactivity, delayed achievement of behavioral milestones and abnormal catecholamine regulation (Hess et al., 1992, 1996; Heyser et al., 1995; Jones et al., 2001). The effects of other genes encoding SNARE complex core components (*STX1A* and *VAMP2*) and its regulatory proteins (such as *SYT1*) have also been studied regarding ADHD susceptibility (Brookes et al., 2005, 2006; Guan et al., 2009; Sánchez-Mora et al., 2013; Kenar et al., 2014; Gao et al., 2015). It is noteworthy that previous studies have reported association of *SYT1* not only to ADHD susceptibility (Guan et al., 2009; Sánchez-Mora et al., 2013) but also to age at onset of ADHD (Lasky-Su et al., 2008).

Since psychiatric disorders seem to be associated with a neurotransmitter system dysregulation and most studies of SNARE complex genes on ADHD were restricted to children samples, this study aims to analyze the effects of polymorphisms on SNARE complex genes - *STX1A* (rs2228607), *SYT1* (rs1880867 and rs2251214), *VAMP2* (26 bp Ins/Del) and *SNAP25* (rs6108461 and rs8636) - on ADHD susceptibility in adults. Additionally, clinical heterogeneity among subjects with ADHD was explored regarding age at onset of impairment due to ADHD symptoms and externalizing behaviors and comorbidities related to earlier ADHD manifestation.

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