# *RBFOX1*, encoding a splicing regulator, is a candidate gene for aggressive behavior

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## Abstract

The *RBFOX1* gene (or *A2BP1*) encodes a splicing factor important for neuronal development that has been related to autism spectrum disorder and other neurodevelopmental phenotypes. Evidence from complementary sources suggests that this gene contributes to aggressive behavior. Suggestive associations with *RBFOX1* have been identified in genome-wide association studies (GWAS) of anger, conduct disorder, and aggressive behavior. Nominal association signals in *RBFOX1* were also found in an epigenome-wide association study (EWAS) of aggressive behavior. Also, variants in this gene affect temporal lobe volume, a brain area that is altered in several aggression-related phenotypes. In animals, this gene has been shown to modulate aggressive behavior in *Drosophila*. *RBFOX1* has also been associated with canine aggression and is upregulated in mice that show increased aggression after frustration of an expected reward. Associated common genetic variants as well as rare duplications and deletions affecting *RBFOX1* have been identified in several psychiatric and neurodevelopmental disorders that are often

comorbid with aggressive behaviors. In this paper, we comprehensively review the cumulative evidence linking *RBFOX1* to aggression behavior and provide new results implicating *RBFOX1* in this phenotype. Most of these studies (genetic and epigenetic analyses in humans, neuroimaging genetics, gene expression and animal models) are hypothesis-free, which strengthens the validity of the findings, although all the evidence is nominal and should therefore be taken with caution. Further studies are required to clarify in detail the role of this gene in this complex phenotype.

## Introduction

Aggressive behavior and violence are major causes of mortality and morbidity in humans. These traits are observed in several psychiatric and neurodevelopmental disorders. Aggressive behavior is an evolutionary conserved trait of high importance for species survival. For this reason, it has been subject to selection throughout evolution and has a substantial genetic underpinning, while staying responsive to environmental cues. Accordingly, the heritability of aggressive behaviors has been estimated to be around 50% (reviewed by Veroude et al. (2016)). Several genes and pathways contributing to aggression have been identified, such as those involved in the serotonergic and dopaminergic neurotransmission and in hormone regulation, although most of the genetic contribution to aggression is still unexplained (Fernàndez-Castillo and Cormand, 2016).

In a recent review on the genetics of human aggressive behavior, we searched for genes and pathways involved in this phenotype using data from genome-wide association studies (GWAS), which so far have not produced genome-wide significant genes/loci (Fernàndez-Castillo and Cormand, 2016). Among others, we highlighted the *RBFOX1* gene (also known as *A2BP1*), which showed suggestive associations in three different GWAS (Anney et al., 2008; Mick et al., 2014; Sonuga-Barke et al., 2008). Interestingly, other complementary sources of evidence provide additional support for the contribution of this gene to the susceptibility to aggressive behavior and to several psychiatric disorders as well. *RBFOX1* encodes the RNA Binding Protein, Fox-1 Homolog 1, also known as Ataxin-2-binding protein. It is expressed mainly in the nervous system, heart, and muscle (Jin et al., 2003; Underwood et al., 2005). The gene encodes a splicing factor that plays an important role in the regulation of the alternative splicing of large neuronal gene networks important for brain development (Bill et al., 2013; Conboy, 2017; Li et al., 2015). Cytoplasmic and nuclear *RBFOX1* isoforms seem to play different roles, with the first one

contributing to mRNA stability and promoting translation and the second one acting as a splicing regulator (Hamada et al., 2016; Lee et al., 2016). The nuclear isoform is involved in neuron migration and synapse network formation during corticogenesis (Hamada et al., 2016) and is important for the control of neuronal excitation in the mammalian brain (Gehman et al., 2011). Alterations in the *RBFOX1* gene have been associated with several neurodevelopmental pathologies, especially autism spectrum disorder (reviewed by Bill et al. (2013)).

Here, we review the cumulative evidence supporting a contribution of *RBFOX1* to aggressive behaviors and to other psychiatric and neurodevelopmental disorders that often display aggressive behavior. We also present hitherto unpublished data derived from genetic association and neuroimaging genetics studies supporting our hypothesis.

## 2. *RBFOX1* and aggressive behavior in humans

### 2.1. Association studies

In a previous review of the genetic basis of aggressive behavior in humans (Fernàndez-Castillo and Cormand, 2016), *RBFOX1* showed suggestive associations ($p < 5e-05$, Table 1) with aggressive traits or diagnostic categories in three GWAS (Anney et al., 2008; Merjonen et al., 2011; Sonuga-Barke et al., 2008). A common variant located within the first intron of the *RBFOX1* gene, rs6500744, was identified as one of the top association signals in a GWAS assessing gene by environment interactions (GxE) (Sonuga-Barke et al., 2008). The C allele of this single nucleotide polymorphism (SNP) was associated with conduct disorder (CD) symptoms in interaction with mothers' warmth (Table 1 , Figure 1 ). Another SNP, also located in intron 1 of *RBFOX1* , rs8062784, was associated with anger in a GWAS assessing hostility in adolescents and adults (Merjonen et al., 2011 ), and two variants located in intron 3 of the gene, rs10153149 and rs12921846, were associated with CD in a sample of ADHD trios (Anney et al., 2008) (see Table 1 and Figure 1).

**Table 1** Suggestive associations in the *RBFOX1* gene identified in GWAS of aggressive behaviors.

| SNP | Reference (GWAS) | Chr | bp (GRCh38) | Alleles[a] | MAF[b] | Phenotype associated | Sample | *P*-value | Risk allele |
|---|---|---|---|---|---|---|---|---|---|
| rs6500744 | Sonuga-Barke et al., 2008 | 16 | 6063660 | C>T | 0.46 | Conduct disorder symptoms interacting with mother's warmth | 938 trios | 3.65−05 | C |
| rs8062784 | Merjonen et al., 2011 | 16 | 6096633 | A>T | 0.085 | Anger (mean of 4 measurement phases) | 2,242 adults | 2.34\−05 | A |
| rs809682 | Pappa et al., 2016 | 16 | 6346372 | T>A | 0.26 | Children's aggressive behavior | 18,988 children | 2.62\−04 | T |
| rs12922093 | Pappa et al., 2016 | 16 | 6346947 | T>C | 0.26 | Children's aggressive behavior | 18,988 children | 3.21−04 | T |
| rs12373031 | Pappa et al., 2016 | 16 | 6347436 | T>C | 0.14 | Children's aggressive behavior | 18,988 children | 4.93−04 | T |
| rs10521042 | Pappa et al., 2016 | 16 | 6349836 | C>T | 0.14 | Children's aggressive behavior | 18,988 children | 4.35−04 | C |
| rs12921846 | Anney et al., 2008 | 16 | 6860384 | A>T | 0.16 | Conduct disorder | 938 trios | 1.39−05 | A |
| rs10153149 | Anney et al., 2008 | 16 | 6875239 | A>C | 0.16 | Conduct disorder | 938 trios | 3.64−05 | A |

[a] According to the forward strand.
[b] Minimum allele frequency in the European population from 1000 Genomes (http://www.internationalgenome.org/).

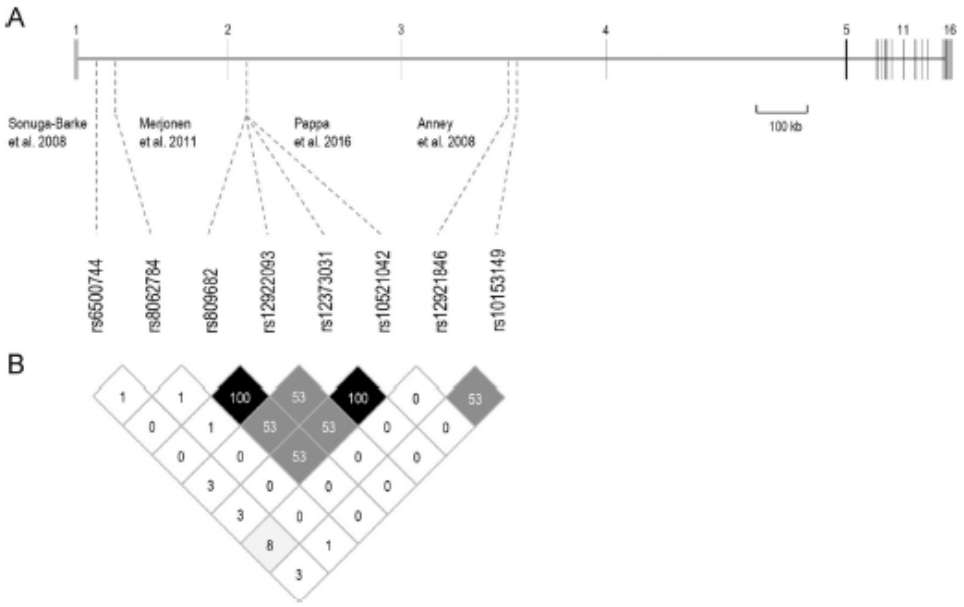


**Figure 1** (A) Diagram of the human *RBFOX1* gene (NM_018723, GRCh38 Chr16: 6,019,131-7,713,338). Solid boxes indicate exons, with the coding regions in black and the non-coding ones in grey. Exon numbering is shown on top of the figure. Eight SNPs found nominally associated with aggressive phenotypes in several genome-wide association studies (GWAS) are shown below, with their locations indicated by discontinuous lines. (B) Linkage disequilibrium (LD) plot of the SNPs considering $r^2$, according to Haploview 4.2. Black boxes indicate complete LD and grey is for moderate LD.

A meta-analysis of nine population-based GWASs including around 19,000 children provided more evidence for the contribution of *RBFOX1* to aggressive behavior (Pappa et al., 2016). Four SNPs in this gene (rs809682, rs12922093, rs12373031, and rs10521042, all located in intron 2) showed suggestive associations with children's aggressive behavior in a meta-analysis ($p$ < 5e −04, Table 1 and Figure 1, data kindly provided by the authors).

Overall, eight *RBFOX1* variants from four GWASs showed a nominal association with aggression. The variants associated in each GWAS were not in linkage disequilibrium (LD) with those from the other studies. The LD between the four variants found associated in the meta-analysis (Pappa et al., 2016) was moderate to high. In an attempt to investigate the association of *RBFOX1* with aggressive behavior further, we genotyped four SNPs (the most significant one from each GWAS) in a sample of German male prisoners, not included in any of the GWASs ($n$ = 188, Supplementary material). A significant association was found for rs809682, when comparing aggressive prisoners to controls ($p$ = 0.03, additive model) as well as aggressive prisoners to non-aggressive prisoners ($p$ = 0.02), but not when comparing non-aggressive prisoners and controls ($p$ = 0.76) (Supplementary Table 1). However, the direction of the effect was opposite as that of the original study, with the A allele linked to aggression (Supplementary Table 1 and Table 1). The same

variant was also genotyped in a population-representative sample of 1176 individuals from the Estonian Children Personality Behaviour and Health Study, ECPBHS (Harro et al., 2001; Vaht et al., 2016) (see Supplementary material for details). Several traits related to aggressiveness were assessed in this population-based cohort, in particular those related to personality and anxiety. In the ECPBHS, five-factor personality data at young adulthood were available from the Estonian version of the NEO-PI-R questionnaire (Kallasmaa et al., 2000) and anxiety information from Spielberger's Trait Anxiety questionnaire (Spielberger, 1983). Aggressiveness is associated with certain facets in basic personality traits, in particular with low agreeableness and neuroticism (Caprara et al., 1996; Sharpe and Desai, 2001), and is also associated with anxiety (Clement and Chapouthier, 1998; Siddaway et al., 2017; Van Praag, 1998), higher negative emotionality (Caprara et al., 1996; Kodžopeljić et al., 2014; Tremblay and Ewart, 2005), and lower extraversion levels (Sharpe and Desai, 2001; Tremblay and Ewart, 2005). In the Estonian sample, rs809682 was nominally associated with extraversion ($p = 0.024$), the T/T homozygotes showing the lowest levels of extraversion (Supplementary Table 2). We recently showed that sex can influence the contribution of genes to aggression (van Donkelaar et al., under review). We therefore also investigated genotype by sex interactions. *RBFOX1* genotype and sex indeed had a significant interaction effect on agreeableness ($p = 6e-03$); male T/T homozygotes had the lowest scores of agreeableness. While NEO-PI neuroticism was not significantly associated with the genotype, data on Spielberger's Trait Anxiety showed a nominal association ($p = 0.043$), with the T-allele carriers having higher levels of anxiety. Findings in the Estonian sample are in the direction expected for a gene associated with aggression, and suggest that higher expression of aggressive behavior in the T-allele carriers of the *RBFOX1* rs809682 polymorphism may be related to basic personality traits and anxiety.

As indicated above, aggressive behavior is influenced by both genes and environment. For this reason, looking at epigenetic profiles linked to aggression also may provide insight into *RBFOX1* 's role. A recent epigenome-wide association study (EWAS) of aggressive behavior investigated DNA methylation levels associated with this phenotype in a sample of 2,029 individuals (van Dongen et al., 2015). This study did not produce any epigenome-wide significant findings, but two nominal associations between aggressive behavior and the methylation levels of sites located in *RBFOX1* were identified at cg12310850 (GRCh37/hg19 position; chr16: 6,533,700, $p = 8.7e-03$) and cg00499781 (chr16: 7,568,364, $p = 0.040$) (data kindly provided by the authors). The authors

also investigated the methylation levels of monozygotic twins highly discordant for aggression, identifying five nominal associations in sites located in *RBFOX1* at cg03934713 (chr16: 6,069,198, $p = 0.047$), cg16396980 (chr16: 6,633,344, $p = 0.041$), cg06705265 (chr16: 6,696,222, $p = 0.024$), cg00514665 (chr16: 7,703,812, $p = 0.049$), and cg03986562 (chr16: 7,703,893, $p = 0.037$).

### 2.2. Neuroimaging genetics studies and gene expression

Human neuroimaging genetics studies suggest that the *RBFOX1* gene contributes to brain function and structure. Thus, *RBFOX1* has been shown to influence temporal lobe volume with genome-wide significance in the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort including patients with Alzheimer's disease, patients with mild cognitive impairment, and cognitively healthy elderly controls (Kohannim et al., 2012b). In a related genome-wide study on the ADNI cohort, Kohannim et al. (2012a) observed that a variant in the *RBFOX1* gene was highly predictive of temporal brain volume. The association between a specific variant in *RBFOX1* and temporal lobe structure has been confirmed in voxel-wise whole-brain analyses in the ADNI cohort (Kohannim et al., 2012a, 2012b). In line with these findings, the *RBFOX1* gene has been identified as specifically contributing to grey matter loss in the temporal lobe in patients with mild cognitive impairment, in a sample of Alzheimer's Disease (Vounou et al., 2012). While the aforementioned studies consistently show a link between *RBFOX1* and temporal lobe volume at genome-wide significance, caution in drawing conclusions for healthy younger adults is required as all findings are based on the ADNI cohort studying associations between temporal lobe volume in older adults with and without cognitive impairment and manifesting Alzheimer's disease. Thus, these associations between *RBFOX1* and brain structure might be explained by the decline in temporal lobe volume observed in Alzheimer's disease and mild cognitive impairment (e.g., Vounou et al., 2012). Still, the link between *RBFOX1* and temporal lobe volume is intriguing because Alzheimer's disease often presents with aggressive behavior (Zhao et al., 2016). Moreover, animal and human studies have underlined the role of the temporal lobe for aggression, especially with the amygdala and hippocampus being located in its medial part (Gregg and Siegel, 2001; Potegal, 2012; Siever, 2008). Abnormalities in temporal lobe function and structure have been observed in aggressive populations including individuals with conduct disorder (CD) (Cappadocia et al., 2009; Kruesi et al., 2004), psychopathy (Raine et al., 2004), and aggressive schizophrenia (Hoptman et

al., 2011; Soyka, 2011). Structural and functional changes in the temporal lobe in aggressive populations may be related to impaired emotion regulation (Bufkin, 2005) and/or to the lack of empathy in CD and antisocial behavior (Cappadocia et al., 2009). Still, although *RBFOX1* seems to contribute to temporal lobe functioning, that does not directly support its contribution to aggressive behavior and further studies should investigate the effect of these variants.

In a recent study, we found the first evidence that the risk variant rs6500744 in the *RBFOX1* gene, which had been associated with aggression in the GWAS of Sonuga-Barke et al. (2008) , might be relevant to brain activity during neurocognitive processes such as inhibitory control and emotional reactivity (Gan et al., in preparation). In a sample of 331 healthy human participants, carriers of the risk allele C (C/C and C/T) showed an increased brain response in the dorsal anterior cingulate cortex (ACC) during emotion processing, and reduced brain responses in the left inferior/middle frontal gyrus during inhibitory control measured with a combined Flanker/Go-Nogo task. Moreover, we observed a sex by SNP interaction, in which female C/Ccarriers showed increased and male C/C-carriers showed decreased responding in the fusiform face area and the hypothalamus/ventral striatum compared to T-allele carriers during a Hariri emotional face recognition task (for fMRI tasks, compare (Meyer-Lindenberg et al., 2006)). Importantly, these findings converge with neuroimaging phenotypes including impaired brain functioning in prefrontallimbic networks during inhibitory control and emotional reactivity in carriers of the MAOA-L genotype, the most widely studied risk genotype for aggression (Alia-Klein et al., 2011; Buckholtz and Meyer-Lindenberg, 2008; Fan et al., 2003; Meyer-Lindenberg et al., 2006; Passamonti et al., 2006).

As expected, given its role in neurodevelopment, the expression of *RBFOX1* in humans is mainly restricted to the brain, although it is also expressed in skeletal muscle and heart (Figure 2). Interestingly, the prefrontal cortex (PFC) including the anterior cingulate cortex (ACC) shows the highest *RBFOX1* expression levels in humans (Figure 2). The PFC has been shown to play a role in impulsive aggression (Blair, 2016; Fan et al., 2003; Passamonti et al., 2006), most likely through its involvement in inhibitory control and behavioral self-regulation (Buckholtz and Meyer-Lindenberg, 2008; Davidson et al., 2000; Heatherton and Wagner, 2011). Also, ACC impaired functioning and structural abnormalities of this area has been repeatedly linked to a propensity for impulsive/reactive aggression (Buckholtz and Meyer-Lindenberg, 2008; Meyer-Lindenberg et al., 2006; Sterzer et al., 2005). Moreover, high expression levels of *RBFOX1* are also found in the

basal ganglia including the nucleus accumbens, putamen and caudate, brain areas previously linked to impulsive aggression across species (Buckholtz et al., 2010; Couppis and Kennedy, 2008; Ferrari et al., 2003; Gan et al., 2015; Krämer et al., 2007). A similar but less pronounced *RBFOX1* expression level emerges for the amygdala, a crucial brain area for impulsive reactive aggression due to its involvement in emotional reactivity to threatening cues (Buckholtz et al., 2008; Coccaro et al., 2007; Meyer-Lindenberg et al., 2006). To conclude, although the observation of high *RBFOX1* expression in brain areas relevant to aggression is interesting, this fact does not necessarily link this gene with aggression, as many other genes may show similar expression patterns and also many brain regions are involved in aggressive behavior. Future imaging genetic studies may shed light on the impact of *RBFOX1* genotypes and pathways on brain function and structure within these areas.

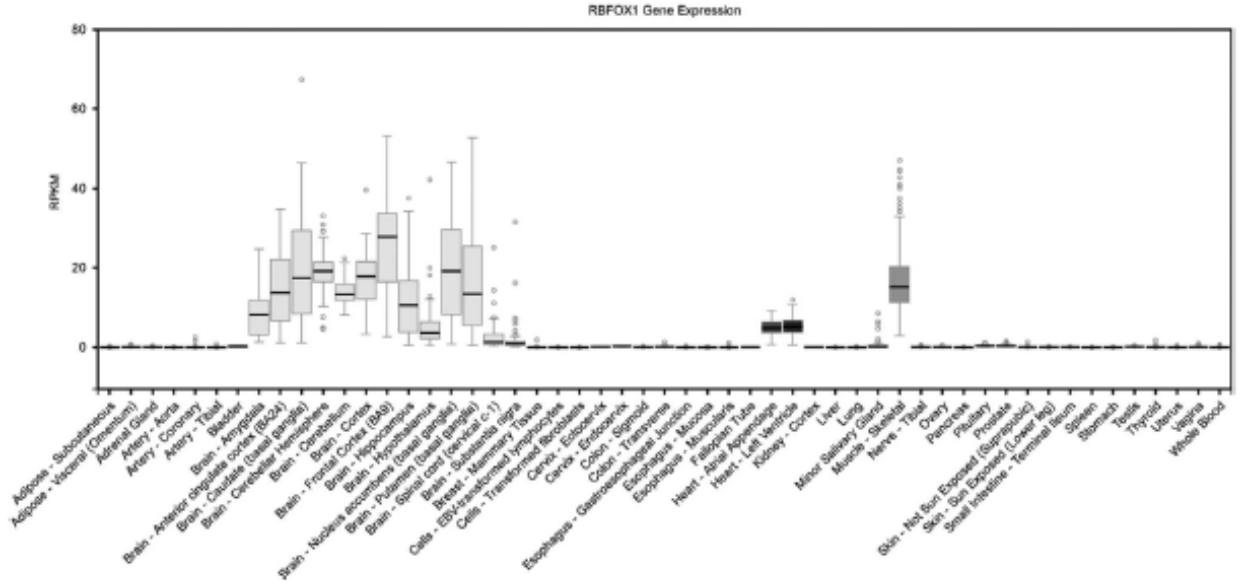


**Figure 2** Expression of the *RBFOX1* gene in different human tissues according to GTEx (www.gtexportal.org). RPKM: reads per kilobase per million mapped reads.

### 3. *RBFOX1* and aggressive behavior in animals

*RBFOX1, also known as A2BP1,* has been related to aggressive behavior in animal models of aggression. In *Drosophila , A2bp1* was one of the genes identified through a genomewide analysis aimed at mapping loci involved in aggressive behavior (Shorter et al., 2015). The study used the sequenced inbred lines of the *Drosophila melanogaster* Genetic Reference Panel (DGRP) to

investigate natural genetic variation related to aggression. Male-to-male aggression was quantified in 200 DGRP lines to identify the underlying genetic variation. Extreme quantitative trait locus (QTL) genome-wide association analysis was also performed in a population derived from DGRP lines with extremely high and extremely low aggression scores. From both analyses, the authors obtained a genetic interaction network with 741 genes, in which *A2bp1* was present as an important node. The functional validation of the finding for the *A2bp1* gene, using a mutant line with a *Mi{ET1}* element insertional mutation, yielded significant evidence that homozygous mutant flies for this gene show decreased aggression ($p < 0.001$).

In a genome-wide mapping study of aggression in dogs, several nominal associations with *A2bp1* were identified in two different cohorts (Zapata et al., 2016). Some of these signals in *A2bp1* were associated with the four measures of aggression that were assessed: stranger-directed aggression (towards unfamiliar humans), dog-directed aggression (towards unfamiliar dogs), owner-directed aggression (towards familiar humans) and dog rivalry (towards familiar dogs). Four *loci* in *A2bp1* were nominally associated with all four measures in one cohort (chr6: 35,449,934, chr6: 35,459,495, chr6: 35,557,330 and chr6: 35,557,812) and two in another cohort (chr6: 35,641,555 and chr6: 35,672,733).

Finally, in a murine model of frustration that showed increased aggressive behavior when the access to an expected reward was denied (Burokas et al., 2012), *A2bp1* expression was upregulated (fold change = 1.32, $p = 1.29e-03$, FDR < 5%) in ventral striatum of frustrated mice (Martín-García et al., 2015).

Mutant animal models of *Rbfox1* exist, but they have not been evaluated for aggressive behavior: a knockdown of *rbfox1* in zebrafish was investigated for heart phenotypes and was shown to produce cardiac dysfunction and heart failure (Frese et al., 2015); knockout mice for *Rbfox1* (−/−), central nervous system-specific, have been reported to present seizures and increased neuronal excitability (Gehman et al., 2011). Electrophysiological recordings of rat cortical neurons with increased expression of this gene also showed increased neuronal activity (Wen et al., 2015). A very recent study shows that RBFOX1 plays an important role in coordinating the synaptic downscaling of excitatory synapses (Rajman et al., 2017). Previous studies have reported that both excitatory and inhibitory neurotransmission are altered in aggression and that changes in neuronal excitation or inhibition modify aggressive behavior (Ende et al., 2015; Lin et al., 2011; Luque et

al., 2009; Takahashi et al., 2015; Vekovischeva et al., 2004). Also, *RBFOX1* is highly expressed in GABAergic neurons of the developing forebrain in mice (Hammock and Levitt, 2011). Thus, since changes in *RBFOX1* seem to affect neuronal excitability, we could hypothesize that it may contribute to aggressive behavior by triggering alterations in inhibition/excitability balance, although no direct evidence of this has been observed so far. Further studies assessing aggressive behavior in knockout and knockin animals for *Rbfox1* are required to confirm this hypothesis and the role of this gene in this complex phenotype.

## 4. *RBFOX1* and psychiatric neurodevelopmental and neurodegenerative disorders

Genetic variation in *RBFOX1* – both common and rare - has been associated with anxiety disorder, substance use disorders, schizophrenia, bipolar disorder, attentiondeficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD) as well as Alzheimer disease. All these disorders present with aggressive behaviors (Brady et al., 1998; Bubier and Drabick, 2009; Fitzpatrick et al., 2016; Granic, 2014; Hoaken and Stewart, 2003; King and Waschbusch, 2010; Látalová, 2009; Volavka, 2013; Zhao et al., 2016).

Findings for associations with common variants in the gene originate mainly from GWAS. In anxiety disorder, a variant in intron 1 of the *RBFOX1* gene (rs13334105) showed a genome-wide significant association with sensitivity to anxiety. Several other SNPs within the same intron also showed suggestive associations ($p < 1e-07$) (Davies et al., 2015). The authors also inspected this region in a GWAS metaanalysis of anxiety disorder and observed several nominal associations. *RBFOX1* variants have been found associated with substance dependence and the ability to quit smoking in 13 different datasets (reviewed by Zhong et al. (2015)). Also, several genetic markers in a genomic region containing *RBFOX1* displayed suggestive linkage to substance dependence-related phenotypes (Zhong et al., 2015). For schizophrenia, suggestive associations were found with *RBFOX1* in Ashkenazi Jews (Goes et al., 2015). Also, suggestive signals in this gene were found associated with both Schizophrenia and bipolar disorder (Wang et al., 2010). In Alzheimer disease, genome-wide significant signals have been identified in the gene (Herold et al., 201 ). Alzheimer Disease presents a high occurrence of aggression, estimated to occur in around 40% of individuals with this disorder (Zhao et al., 2016).

Using the Ricopili web tool (https://data.broadinstitute. org/mpg/ricopili/) we identified additional common genetic variants in *RBFOX1* that show suggestive association with several psychiatric phenotypes: bipolar disorder and schizophrenia (cross-disorder meta-analysis; rs12444931, $p$ = 5e −06), schizophrenia (rs12447542, $p$ = 1.1e −06), smoking behavior (rs3112740, $p$ = 6e −06) and number of cigarettes per day (rs8055842, $p$ = 3.4e −05). Evidence for rare *RBFOX1* variants being linked to brain disease come from several study designs. Copy number variants (CNVs) spanning the *RBFOX1* gene have been reported in individuals with several psychiatric disorders. A partial duplication of *RBFOX1* was associated with risk for schizophrenia, with an estimated eight-fold increased risk for males, but not for females (Melhem et al., 2011). Another partial duplication was identified in another patient with schizophrenia (Xu et al., 2008). A gain CNV spanning the first two exons of *RBFOX1* and a loss in an intronic region have been reported for bipolar disorder (Noor et al., 2014). Also, hemizygous intronic *RBFOX1* deletions and a duplication were identified in ADHD patients (Elia et al., 2010).

Another study identified CNVs in *RBFOX1* in patients with neuropsychiatric and neurodevelopmental disorders such as ASD and global developmental delay, many of them presenting also with epilepsy (Zhao, 2013). Interestingly, in this study, one patient with intellectual disability, marked aggressive behavior, and epilepsy was found to bear a deletion in the *RBFOX1* gene. Other studies identified deletions in *RBFOX1* in autistic patients (Davis et al., 2012; Griswold et al., 2012; Martin et al., 2007; Sebat et al., 2007). One of these studies characterized a deletion in a proband with autism, global developmental delay, and epilepsy. The deletion was located at the boundary between the first exon and intron and reduced *RBFOX1* mRNA expression in lymphocytes from the subject (Martin et al., 2007). More evidence connects *RBFOX1* with ASD. A *de novo* truncating mutation in this gene and a duplication were identified in autistic patients (Griswold et al., 2015; Kanduri et al., 2016). A transcriptomic analysis of post-mortem autistic brains identified a module of co-expressed genes in which *RBFOX1* was an important node (Voineagu et al., 2011). This gene module was enriched for associated genetic variants in an autism GWAS dataset. Furthermore, the authors performed RNAseq to compare brain samples of autistic patients with decreased expression of *RBFOX1* (FC = −5.9) and controls with average expression of this gene, and observed a broad dysregulation of alternative splicing in the brain of autistic patients that is dependent on *RBFOX1* .

Several genetic alterations in *RBFOX1* have been identified in individuals with epilepsy, a neurological disorder that has also been related to aggressive behavior (Brodie et al., 2016). In line with this, as mentioned above, the knockout mice for *Rbfox1* show susceptibility to seizures and increased neuronal excitability (Gehman et al., 2011). Another study observed upregulation of *RBFOX1* in patients with malformed cortex and epilepsy, and showed that this upregulation produces an increase in the neuronal activity of rat cortical neurons (Wen et al., 2015).

The fact that *RBFOX1* has been related to many psychiatric disorders make it an appealing candidate gene for aggression, although the increased incidence of aggression in many of these disorders does not connect *RBFOX1* with aggressive behavior. In this regard, exploration of large cohorts of aggression is needed to investigate the effect of genetic variants in *RBFOX1* that have been reported as risk factors for other psychiatric disorders. Also, we need to get more insight into the contribution to aggression of CNVs spanning *RBFOX1* .

## 5. Discussion and future perspectives

In this review, we bring together different lines of evidence that implicate *RBFOX1* in the etiology of aggressive behavior, including genetic association and mutation studies, neuroimaging genetics data, transcriptomic analyses, and animal models. Although the convergence of evidence is impressive, most of this supportive data is of nominal significance in the individual studies and should therefore be interpreted with caution.

Four independent GWASs (one of them including nine datasets) associated *RBFOX1* with aggression. However, it should be noted that this gene spans a wide region in the genome (1.7 Mbp, more than 30 times the average length of a human gene) and carries many common variants, increasing the probability for identifying spurious associations. Speaking against such false positive effects, according to the GWAS catalog ( https://www.ebi.ac.uk/gwas/ ), so far only very few disease or trait associations have been identified for *RBFOX1* with $p$ -values $< 1e-05$, (including obesity and body mass index, heart rate, periodontitis, and eye related diseases). In any case, we cannot discard that gene length may influence the appearance of false positive associations. Finally, given the high degree of phenotypic heterogeneity of aggressive behaviors, association studies in larger and more homogeneous samples are required to confirm the involvement of *RBFOX1* .

All the *RBFOX1* variants identified by the different GWASs of aggression lie in the first three introns of the gene. This localization also applies to the SNPs and CNVs associated with other psychiatric disorders. This clustering of risk variants may be due to the presence of regulatory elements of *RBFOX1* in this region , as suggested by others ( Martin et al., 2007 ). To our knowledge, CNVs in *RBFOX1* have not been investigated in relation to aggressive behavior directly. Such studies may be informative as they have been for schizophrenia, bipolar disorder, ADHD or autism.

The neuroimaging genetics studies reported here highlight structural and functional brain alterations correlating with *RBFOX1* variation, both in population-based cohorts and in clinical samples. These results point to the temporal lobe and to alterations in neurocognitive performance. However, to our knowledge, no investigations have been performed in clinical samples with pathological levels of aggression (e.g., conduct disorder, antisocial personality disorder, intermittent explosive disorder). Such studies may shed light on the functional significance of *RBFOX1* with regard to brain regions previously linked to aggressive behavior, such as the temporal and frontal lobes, the basal ganglia and the amygdala, where the gene is highly expressed.

Animal models can provide more insights into the role of this gene in aggression. The data from *Drosophila* reviewed above are convincing. In this regard (and given the *Drosophila* phenotype as well as the findings of duplications in the gene in human brain disorders), it might be interesting to assess aggressive behavior not only in knockout animals for *RBFOX1* , but also in knockin animals, where the gene is upregulated.

Taken together, evidence from complementary study designs point to *RBFOX1* as a strong candidate for susceptibility to aggressive behavior and to several psychiatric disorders. Still, further association and neuroimaging genetics studies in larger samples, as well as studies in transgenic animals for *RBFOX1* , are needed to confirm the contribution of this gene to aggression. If confirmation is obtained, *RBFOX1* could be a promising pharmacological target for the treatment of aggression, given its broad role in the development and functioning of brain processes.

**Role of the funding source**

The research leading to these results has received funding from the European Union Seventh Framework Programme [FP7/2007-2013] under grant agreements n ° 602805 , 602450 and 278948 and from the European Union H2020 Programme [H2020/2014-2020] under grant agreements n ° 643051 and 667302. Additionally, N. Fernàndez-Castillo is supported by a contract of the 'Centro de Investigación Biomédica en Red de Enfermedades Raras' (CIBERER) and B. Cormand by the Spanish 'Ministerio de Economía y Competitividad' (SAF2015-68341-R) and AGAUR, ' Generalitat de Catalunya ' ( 2014SGR932 ). Further funding was received from the European College of Neuropsychopharmacology (ECNP) by a grant for the ECNP Network 'ADHD across the lifespan'. G. Gan was supported by the German academic exchange service (DAAD), and the Olympia-Morata Program of the University of Heidelberg, Germany. J. Harro received funding from EMES Grant IUT-20-40. Prof. Faraone is supported by the K.G. Jebsen Centre for Research on Neuropsychiatric Disorders, University of Bergen, Norway, and NIMH grants 5R01MH101519 and U01 MH109536-01. Prof. B. Franke and M. van Donkelaar are supported by funding from a personal Vici grant of the Netherlands Organisation for Scientific Research (NWO; grant 016-130-669 , to BF). None of the funding institutions had any role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

**Contributors**

N. Fernàndez-Castillo and B. Cormand identified the gene as a possible candidate and led the work and together with S.V. Faraone coordinated the study. N. Fernàndez-Castillo performed the literature review and wrote the first draft of the manuscript. B. Cormand and S.V. Faraone gathered new data. G. Gan, M.J. van Donkelaar, B. Franke and A. Meyer-Lindenberg performed neuroimaging genetic analyses. G. Gan contributed to the writing of the neuroimaging section. H. Weber, A. Reif and W. Retz performed the association study in the German sample of prisoners, and M. Vaht and J. Harro in the Estonian sample. All authors contributed to the final version of the manuscript.

## Conflict of interest

None of the authors declare any conflict of interest.


## Acknowledgement

We would like to thank the EAGLE consortium, Dorret Boomsma and Jenny van Dongen for kindly providing us with the results from their human GWAS and EWAS studies, and to Carlos Álvarez and Isain Zapata for the results of their study on canine aggression. We would like to thank Jeffrey Glennon, Heike Tost and Anais Harneit for providing useful comments and literature.


## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.euroneuro.2017.11.012 .

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