The Neurobiological Basis of Human Aggression: A Review on Genetic and Epigenetic Mechanisms

Regina Waltes, Andreas G. Chiocchetti, and Christine M. Freitag*
Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, Goethe University Hospital, Frankfurt am Main, Germany

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Aggression is an evolutionary conserved behavior present in most species including humans. Inadequate aggression can lead to long-term detrimental personal and societal effects. Here, we differentiate between proactive and reactive forms of aggression and review the genetic determinants of it. Heritability estimates of aggression in general vary between studies due to differing assessment instruments for aggressive behavior (AB) as well as age and gender of study participants. In addition, especially non-shared environmental factors shape AB. Current hypotheses suggest that environmental effects such as early life stress or chronic psychosocial risk factors (e.g., maltreatment) and variation in genes related to neuroendocrine, dopaminergic as well as serotonergic systems increase the risk to develop AB. In this review, we summarize the current knowledge of the genetics of human aggression based on twin studies, genetic association studies, animal models, and epigenetic analyses with the aim to differentiate between mechanisms associated with proactive or reactive aggression. We hypothesize that from a genetic perspective, the aminergic systems are likely to regulate both reactive and proactive aggression, whereas the endocrine pathways seem to be more involved in regulation of reactive aggression through modulation of impulsivity. Epigenetic studies on aggression have associated non-genetic risk factors with modifications of the stress response and the immune system. Finally, we point to the urgent need for further genome-wide analyses and the integration of genetic and epigenetic information to understand individual differences in reactive and proactive AB.

Key words: genetic association studies; animal models; aggression; epigenetics

INTRODUCTION

Aggressive behavior (AB) occurs in most species. In humans, who are considered as a highly aggressive species in comparison to other animals, aggression plays a role in survival, group cohesion, and sexual selection, with clear gender-specific effects and expression [Georgiev et al., 2013]. In addition to positive effects, for example, feeling of power, being in control or defending oneself or others, AB in children and adolescents can have long-term negative effects on the individual development, especially with regard to interaction with peers and other social relationships. Despite a general decrease into adulthood, high childhood AB is related to increased rates of antisocial personality disorder, oppositional behavior, and attention-deficit/hyperactivity disorder, but not anxiety or depression, in adulthood [Reef et al., 2011]. In addition, AB carries a strong risk for injuries, and also has a negative impact on society as a whole [Temcheff et al., 2011]. Therefore, studies have been performed to delineate if pathological aggression lies on a continuum with general AB, or if categorical models of pathological versus physiological aggression fit empirical data in a better way. Results of these studies clearly indicate that the continuum model fits better to the observed behavior in children and adolescents [Walton et al., 2011; Barry et al., 2013; Walters and Ruscio, 2013]. Thus, “pathological” AB needs to be conceptualized as the extreme of a normal distribution of AB in the general population.

AB is not a uniform behavioral construct. Factor analyses of different rating scales on AB in children and adolescents resulted in the distinction of different dimensions of AB. These dimensions are presumed to underlie a differential neurobiology. Common distinctions are the differentiation between reactive (impulsive) and proactive (pre-meditated) aggression [Mathias et al., 2007; Fung et al., 2009], that is, referring to the function of AB. Reactive aggression is more strongly associated with impulsive behavior and
is considered an aggressive response to a perceived threat or provocation, whereas proactive aggression is highly associated with callous-unemotional traits, and defined as planned antisocial behavior that anticipates a reward or dominance over others [Kempes et al., 2005; Thornton et al., 2013]. Several studies have replicated two groups of aggressive children and adolescents: one group with predominant reactive AB, and another group with a combination of reactive and proactive AB, who generally is more severely affected [Crapanzano et al., 2010; Marsee et al., 2014].

In parallel to proactive and reactive aggression, overt and covert forms have been described [Marsee et al., 2011; Olson et al., 2013] which also are found in male children and adolescents with conduct disorder [Kendler et al., 2013]. Covert forms of aggression strongly overlap with rule breaking behavior, which has been shown to originate from a different etiology to (overt) AB [Burt, 2009]. Overt forms of AB are often related to physical AB, as hitting, biting, pushing, and verbal AB toward others. In addition to physical aggression, social (relational) aggression can be observed [Burt and Donnellan, 2009] which includes harming others by harming their social relationships (e.g., gossiping or telling lies about them; excluding them from groups). Previous studies have observed reactive and proactive forms of both physical and relational aggression, the latter found predominantly in girls [Crapanzano et al., 2010; Marsee et al., 2014].

Given the genetic influence on AB etiology, the current qualitative literature review aims at (1) summarizing results of recent twin studies on different subtypes of AB to inform geneticists about the underlying genetic and/or environmental background of different forms and functions of AB, (2) detailing results of molecular genetic studies on AB, (3) summarizing results on animal studies, and (4) summarizing epigenetic findings related to AB. We aim at specifically elucidating the genetic etiology of proactive and reactive aggression.

**METHODS**

In this review on genetic and epigenetic mechanisms of human aggression, we performed a systematic search on aggression studies using the database PubMed and adding information from references of published articles. The following key words were used: “aggression,” “aggressive behavior,” “combination with proactive,” “reactive,” “genetics,” “epigenetics,” “environment,” “GWAS,” “quantitative trait,” “linkage,” “animals,” “neuroendocrine,” “steroid,” “serotonin,” “dopamine,” “sex-hormones,” “testosterone,” “estrogen,” “cortisol,” “corticoid.” We excluded studies involving patients diagnosed with schizophrenia, bipolar disorder, depression and autism, as well as externalizing, conduct, and antisocial behavior including impulsivity when investigated as single characteristic without any additional aggression scales. We found and included studies that used the following aggression scales: Composite measure of conduct problems and crime and analogous behavior scale (CAB), Barratt impulsiveness scale (BIS), behavioral pathology in Alzheimer’s disease (BEHAVE-AD), Brown–Goodwin lifetime history of aggression (BGHA), Buss–Durkee hostility inventory (BDHI), Buss–Perry aggression questionnaire (BPAQ), child behavior checklist—aggressive behavior subscale (CBCL), Conners comprehensive behavior rating scales—defiant/aggressive behavior subscale (Conners CBRS), Eysenck personality questionnaire—anger subscales (EPQ), life history of aggression (LHA), measuring factors of aggression (FAF), neuro-psychiatric inventory agitation/aggression subscale (NPI), overt aggression scale (OAS), past feelings and acts of violence scale (PFAVS), revised behavior problem checklist (RBPC), revised teacher rating scale for reactive & proactive aggression (RSRPA), state trait anger expression inventory (STAXI), UPPS-P impulsivity scale, Aggressive behavior scale (ABS), vragenlijst instrumentele en reactieve agressie (VIRA-R), reactive–proactive aggression questionnaire (RPQ), aggressive risk-taking scale (ART), non-aggressive risk-taking scale (NART). Reported gene names refer to the official symbols suggested by the HUGO Gene Nomenclature Committee (HGNC).

**Twin Studies**

A meta-analysis on twin and adoption studies including studies published before July 2007 reported a heritability of 65% on AB measured by different rating scales [Burt, 2009]. Shared environment accounted for 5% in phenotypic variability, and non-shared environment for 30%. In preschool aged children, heritability was slightly lower (55%), whereas in adolescence, heritability increased (63%). Similar estimates of heritability and environment effects for boys and girls were found, despite higher mean aggression scores in boys. Considerable differences between raters were observed, with teacher ratings showing highest heritability (71%), followed by mothers (59%), fathers (54%), and child self-report (44%). This shows the importance of choice of phenotypic measures in genetic studies. Other meta-analyses had reported slightly lower heritability estimates of approx. 50% [Tuvblad and Baker, 2011].

Twin studies published after July 2007 aimed at eliciting also dominant genetic effects, and reported heritability estimates for different AB subtypes (Table 1). In addition, longitudinal genetic and environmental influences were studied. In these more recent studies, sex differences were observed when different self-report measures were implemented, with boys showing considerably higher heritability estimates than girls, especially around and after adolescence [Baker et al., 2008; Wang et al., 2013]. Mother and teacher ratings did not result in sex differences of heritability measures. Of the different forms and functions of AB, physical, proactive, and reactive aggression were studied. Proactive aggression showed slightly higher heritability estimates (32–48%) than reactive aggression (20–43%) [Baker et al., 2008; Tuvblad et al., 2009]. Highest, but strongly culturally variable, heritability estimates (29–68%) were obtained for the aggression subscale of the CBCL [Burt and Klump, 2012; Chen et al., 2015], which does not differentiate between reactive and proactive forms of aggression, and contains several items on physical aggression. The latter also shows relatively high heritability when assessed by other scales (38–60%) [Yeh et al., 2010; Lacourse et al., 2014]. For the CBCL aggression subscale, genetic dominance in addition to additive effects was reported by implementing a nuclear twin family model [Burt and Klump, 2012]. In an adult cohort, two factors extracted from the LHA scale, that is, general aggression and physical aggression showed moderate genetic additive effects (54% and 38%, respectively) [Yeh et al., 2010].
| Reference | Country of origin | Study type | Quantitative phenotype | Sample size | Age (years) | Gender effects [GE] | Additive genetics | Dominant genetics | Common Env. | Non-shared Env. | Remarks |
|-----------|-------------------|------------|------------------------|-------------|-------------|---------------------|------------------|------------------|--------------|----------------|---------|
| Baker et al. [2008] | USA California | Twin registry | Reactive aggression RPQ (C, M, T) | 605 families | 9–10 | 51% female GE pres. | C-B 38% | C-B NO | C-B NO | C-B 62% | CTD |
| Baker et al. [2008] | USA California | Twin registry | Proactive aggression RPQ (C, M, T) | 605 families | 9–10 | 51% female GE pres. | C-B 50% | C-B NO | C-B NO | C-B 50% | CTD |
| Burt and Klump [2012] | USA Michigan | Twin registry | Aggression scale CBCL (M) | 312 families | 6–10 | 47% female GE pres. | C 56% | C 68% | C 68% | C 64% | CTD |
| Chen et al. [2015] | China Beijing | Twin registry | Aggression scales CBCL, TRF, YSR | MZ 661 DZ 247 | 10–18 | 53% female GE pres. | C 6% | M 11% | M 11% | M 26% | CTD |
| Yeh et al. [2010] | USA Pennsylvania | Population based | General and physical aggression LHA (M) | MZ 681 DZ 246 | 24–55 | 58% female GE pres. | Gen. A. 54% | NA | NA | Gen. A. 46% | CTD |
| Lacourse et al. [2014] | Canada Quebec | Population based | Physical aggression 3-item questionnaire twins | 588 twins | I 0.5–2 | NA | I 60% | NA | I 9% | I 31% | LTD |
| Niv et al. [2013] | USA California | Twin registry | Aggression Scale CBCL (M) | I 602 twins | I 9–10 | 52% female GE pres. | I 29% | NA | I 29% | I 44% | LTD |
| Tuvblad et al. [2009] | USA California | Twin registry | Reactive aggression RPQ (M) | 607 twins | I 9–10 | 51% female GE pres. | I 26% | NA | I 27% | I 46% | LTD |
| Tuvblad et al. [2009] | USA California | Twin registry | Proactive aggression RPQ (M) | 607 twins | I 9–10 | 51% female GE pres. | I 32% | NA | I 21% | I 47% | LTD |
| Wang et al. [2013] | USA California | Twin registry | Aggressive Behavior of Self-Report Delinquency interview (C) | 780 twins | I 9–10 | 52% female GE pres. | I-B 3% | NA | I-B 28% | I-B 69% | LTD |

B, boy; C, child self-report; CBCL, child behavior checklist; CTD, classical twin design; Env., environment; G, girls; GE pres., gender effects present; LHA, life history of aggression questionnaire; LTD, longitudinal twin design; M, mother report; NA, not available; NTFD, nuclear twin family design; RA, reactive aggression; RPQ, Reactive–Proactive Aggression Questionnaire; PA, proactive aggression; T, teacher report; TRF, teacher report form; YSR, youth self report form; I: first assessment; II: second assessment; III: third assessment.
Based on longitudinal studies, a slight increase in heritability from childhood to adolescence was observed for all mother rated functions of AB [Tuvblad et al., 2009; Niv et al., 2013; Wang et al., 2013; Lacourse et al., 2014]. In preschool age, stability of physically AB was mainly due to genetic factors, with additional genetic and predominantly non-shared environmental factors adding at later assessments [Lacourse et al., 2014]. Similar findings were observed in school aged children for the mother rated CBCL aggression scale [Niv et al., 2013]. Strongest genetic findings on stability of aggressive symptoms were observed for proactive (85%) compared to reactive (48%) aggression from school age to puberty, with non-shared environmental effects accounting for the remaining phenotype stability. Non-shared environmental effects also showed a strong influence on all forms of AB in this US-American twin sample [Tuvblad et al., 2009]. A recent review has delineated some potential environmental moderators of genetic influence, as family adversity, maltreatment, social disadvantage, especially regarding neighborhoods, and socio-economic status [Tuvblad and Baker, 2011]. This shows the additional relevance of gene x environment interaction, which needs to be considered in molecular genetic studies on AB. We will partly address this topic in the epigenetic section below.

Taken together, heritability estimates from twin studies are highly variable and likely are influenced by environmental effects and the population in which they are obtained. The results summarized above and elsewhere confirm some important observations: (1) Additive and dominant genetic, and some shared and mainly non-shared environmental effects seem to be responsible for individual differences in AB; (2) estimates of these measures are influenced by rating scales, raters, and age of the studied individual; (3) physical as well as proactive aggression showed highest heritability; (4) stability of especially proactive aggression is strongly influenced by genetic factors. In conclusion, proactive aggression is the most promising phenotype for genetic studies on AB.

Molecular Genetics of Aggression in the Human Population—Implication of Pathways

So far, there has been little focus on genome-wide approaches of AB in humans. Only recently, Pappa et al. performed a genome-wide association study (GWAS) in a large cohort of children (N = 18,988) comprising measurement of AB by CBCL at two developmental stages (early childhood and middle childhood/early adolescence) within the framework of the early genetics and lifecourse epidemiology (EAGLE) consortium. Meta-analysis of the total cohort identified a near genome-wide significant region on chromosome 2p12 whereby the top SNP rs11126630 (P ≤ 5.3 × 10^{-8}) is located near LRRTM4, a gene which is involved in the regulation of excitatory synapse development. The gene-based analysis revealed an enrichment of AVPR1A indicating its association with AB [Pappa et al., 2015].

Few GWAS have been performed comprising related phenotypes. One GWAS investigated proneness to anger, a phenotype related to reactive aggression, in 45–64-year-old individuals [Ramírez and Andreu, 2006]. This study identified a significant increase in the Spielberger state-trait anger scale (STAXI) in carriers of rs2148710T of the gene coding for the non-receptor protein-tyrosine kinase, FYN [Mick et al., 2014].

A second GWAS was performed in Finnish violent offenders (phenotypic measures defined by counting any violence offence) compared with the general population. Strongest association signals (P ≤ 1 × 10^{-5}) were observed for two markers located on 16q23.3 at the intronic region of the CDH13, a gene which was associated with ADHD [Tiihonen et al., 2015].

A third genome wide study focused on children with ADHD and comorbid conduct disorder (CD). Here, an ADHD-related polygenic risk score including 46,156 alleles correlated positively with the number of aggressive conduct disorder symptoms, but not covert conduct disorder symptoms [Hamshere et al., 2013]. In addition, quantitative trait loci (QTL) for phenotypic measures of conduct problems based on DSM-IV criteria, the parent account of childhood symptoms (PACS) and the Conners parent rating scale (CPRS-RL) were defined. Although no marker reached genome-wide significance P ≤ 5 × 10^{-8}, potentially interesting targets already previously mentioned in the psychiatric literature, that is, PAWR, GPR85, A2BP1, and YHWAZ [Anney et al., 2008] were identified with strong association signals (P ≤ 1 × 10^{-5}). Further studies are needed to understand the functional implication of these genes in aggression.

In contrast to the few GWAS studies, several association studies have been performed on targeted genes (Table II). Candidate genes were mainly selected based on their relation to the monoaminergic neurotransmitter systems (e.g., serotonin, dopamine pathways) which are postulated to play a major role in proactive and reactive aggression and other aggression-related behavior. Similarly, the genes regulating the hypothalamic–pituitary–adrenal (HPA) axis or sexual hormone pathways, that is, the endocrine system, are hypothesized to be involved in reactive aggression regulation [Craig and Halton, 2009; Pavlov et al., 2012]. Here, we will summarize the recent molecular genetic findings on genes targeting the serotonergic, the dopaminergic as well as the hormonal signaling pathways (see Methods).

Serotonin pathway. Brain serotonin, or 5-hydroxytryptamine (5HT), is a product of the tryptophan metabolic pathway, mainly produced by neurons in the Raphe nuclei, which are connected to the entire cortex, the limbic system, the cerebellum as well as the spinal cord. The serotonin system plays an important role in learning, memory, sleep, and mood. 5HT transmits its action through activation of several cognate receptors (e.g., HTR1A/B, HTR1F, HTR2, HTR3, HTR5A, HTR4/6/7) on the postsynaptic neuron [Nebigil et al., 2001]. These receptors mediate their biological effects through kinase and phospholipase signaling cascades that ultimately alter the postsynaptic potentials, plasticity, and gene-expression. In addition, the 5HT auto-receptors 1A and 1B (HTR1A, HTR1B) on the presynaptic neuron provide negative feedback loops potentially regulating AB [reviewed in Nelson and Trainor, 2007; Pavlov et al., 2012]. Serotonin itself is removed from the synaptic cleft through the 5HT transporter (SCL6A4) and catabolized by monoamine oxidase A (MAOA), an enzyme that also catalyzes dopamine. The main metabolite of 5HT is 5-Hydroxyindoleacetic acid (5-HIAA), which is routinely used to measure serotonin levels. Serotonin has been implicated in several neurobiological mechanisms of aggression and violence more than any
| Gene name     | Variant major>minor | Allele; outcome | Measure of aggression (questionaire)* | Study type | Sample | N total or case/ctrl | Gender | Age mean | Ethnicity | First author, year |
|---------------|---------------------|----------------|---------------------------------------|------------|--------|---------------------|--------|----------|-----------|-------------------|
| TPH1          | rs1800532C>A        | C; pos. ass. (male) | General (NPI-D)                       | C          | AD     | N = 396             | 65     | 78       | CAUC      | Craig et al. [2004a] |
| TPH2 (haplotype) | rs186495G>A          | AGGTGA; pos. ass. (BDP) | Proactive (BDHI, BPAO, DAS-M)       | CC         | BPD, OPD, HC | N = 85/38             | 43.1   | 41.7     | CAUC      | Perez-Rodriguez et al. [2010] |
| HTR1A         | rs6295G>C            | No ass. | Proactive and reactive (STAXI, FAF)   | CC         | S, HC  | N = 722/443           | 58.1   | 45.6     | CAUC      | Serretti et al. [2007] |
| HTR1B         | rs6296G>C            | C; pos. corr. (children) | Proactive (ABS), reactive (BDHI)    | Other      | P      | N = 967              | 53.7   | NA       | CAUC      | Hakulinen et al. [2013] |
| HTR1B         | rs6296G>C            | No ass. | Aggression (CBCL, TRF)               | CC         | AC, HC | N = 50/50             | 16     | 10.1     | CAUC      | Davidge et al. [2004] |
| HTR1B         | rs130050A>T          | T; pos. ass. | Reactive (BDHI, BGHA)                | CC         | S, HC  | N = 338/358           | 18.9   | 38       | CAUC      | Zouk et al. [2007] |
| HTR2A         | rs6313G>T            | CC; pos. ass. | General (NPI)                        | CC         | AD, HC | N = 87/75             | NA     | 77.4     | ASI       | Lam et al. [2004] |
| HTR2A         | rs6313G>T            | T; pos. ass. | General (NPI)                        | C          | AD     | N = 96               | 61.5   | 76.7     | MIX       | Assal et al. [2004] |
| HTR2A         | rs6313G>T            | No ass. | General (NPI)                        | C          | AD     | N = 394              | 56     | 74.4     | CAUC      | Pritchard et al. [2008] |
| HTR2A         | rs6311G>T            | CC; pos. ass. | Reactive (STAXI, FAF)                | CC         | S, HC  | N = 203/363           | 66.5   | 40       | CAUC      | Giegling et al. [2006] |
| HTR2A         | rs732347A>T          | T; pos. ass. | Proactive (BPAO)                     | Other      | P      | N = 887              | 54.2   | 23.2     | CAUC      | Banlaki et al. [2015] |
| SLC6A4        | rs495541 S/L         | S; pos. ass. | Aggression (CBCL, TRF)               | FAM        | TW     | N = 1187             | 51.09  | NA       | CAUC      | Haberstick et al. [2006] |
| SLC6A4        | rs495541 S/L         | S; pos. ass. | Aggression (CBCL, TRF)               | CC         | AC, HC | N = 82/77             | 14.6   | 9.5      | NA        | Beitchman et al. [2006] |
| SLC6A4        | rs495541 S/L         | S; pos. ass. | Aggression (custom scales)           | ADOPT      | ADOPT  | N = 87               | 57.47  | NA       | CAUC      | Cadoret et al. [2006] |
| SLC6A4        | rs495541 S/L         | S; pos. ass. | General (criminal history, EIO)      | CC         | CD     | N = 72/81             | 0      | 34.7     | CAUC      | Retz et al. [2003] |
| SLC6A4        | rs495541 S/L         | L; pos. ass. (ADHD) | Aggression (CBCL, TRF)               | CC         | P, HC  | N = 50/50             | 16     | 10.1     | CAUC      | Davidge et al. [2004] |
| SLC6A4        | rs495541 S/L         | S; pos. ass. | Proactive (medical and criminal history) | CC         | OP, HC | N = 184/150           | 0      | 34.1     | CAUC      | Reif et al. [2007] |
| SLC6A4        | rs495541 S/L         | No ass. | General (BGHA, BIS)                  | CC         | S      | N = 216/223           | 70.37  | 36.8     | CAUC      | Baca-Garcia et al. [2004] |
| SLC6A4        | rs495541 S/L         | S; pos. ass. (DRD4 7r) | Aggression (CBCL, TRF)               | Other      | P      | N = 298              | 51.68  | NA       | CAUC      | Hohmann et al. [2009] |
| Gene name | Variant major>minor | Allele; outcome | Measure of aggression (questionaire)* | Study type | Sample | N total or case/ctrl | Gender | Age mean | Ethnicity | First author, year |
|-----------|---------------------|----------------|---------------------------------------|------------|--------|---------------------|--------|----------|-----------|-------------------|
| SLC6A3    | rs28363170 VNTR (3r-11r) | 9r; pos. ass. | Proactive (BDHI) | CC         | HU, HC  | N = 104/125          | NA     | NA      | CAUC      | Young et al. [2002] |
| SLC6A3    | rs28363170 VNTR (3r-11r) | 9r,9r; pos. ass. | Proactive (medical and criminal history) | CC         | OP     | N = 184/150         | 0      | 34.1    | CAUC      | Gerra et al. [2005] |
| DRD1      | rs4532A>G            | G,G; pos. ass. | General, CBRS subscale                 | C          | AD     | N = 275             | 66     | 73      | CAUC      | Reif et al. [2007]  |
| DRD2      | rs1801028C>G         | No ass.        | General, CBRS subscale                 | C          | AD     | N = 275             | 66     | 73      | CAUC      | Sweet et al. [1998] |
| DRD3      | DRD3 Bal1 polymorphism exon 3 VNTR | No ass.        | General, CBRS subscale                 | C          | AD     | N = 275             | 66     | 73      | CAUC      | Sweet et al. [1998] |
| DRD4      | rs1799978A>G         | GTT; pos. ass. | Aggression (CBCL, TRF)                 | CC         | AC, HC  | N = 144/144         | NA     | NA      | NA        | Zai et al. [2012a]  |
| DRD2      | (haplotype)          | rs1800497C>T   | Reactive (STAXI, SCIDI, SCIDII)        | CC         | S      | N = 149/328         | 64.42  | 40      | CAUC      | Rujescu et al. [2003]|
| COMT      | rs4680A>G            | A; pos. ass.   | Reactive (OAS)                         | C          | SZ     | N = 80              | 48.7   | NA      | CAUC      | Tosato et al. [2011]|
| COMT      | rs4680A>G            | A; pos. ass.   | Aggression (CBCL, TRF)                 | CC         | P (CBP), HC | N = 144/144 | 27.77  | 10.8    | CAUC      | Hirata et al. [2013]|
| COMT      | rs6269A>G            | AG; pos. ass.  | Aggression (CBCL, TRF)                 | CC         | P (CBP), HC | N = 144/144 | 27.77  | 10.8    | CAUC      | Hirata et al. [2013]|
| COMT      | rs6460A>G            | G; pos. ass.   | Reactive (STAXI)                       | C          | S      | N = 875             | 70.74  | 39.6    | CAUC      | Perroud et al. [2010]|
| MAOA      | 30 bp VNTR H/L allele | H; pos. ass.   | Reactive (LHA, BDHI)                   | Others     | P      | N = 110             | 0      | 45.2    | CAUC      | Manuck et al. [2000]|
| MAOA      | 30 bp VNTR H/L allele | H; pos. ass.   | Reactive (VIRA-R)                      | Others     | P (CBP) | N = 125              | 42.4   | 24.61   | CAUC      | Holz et al. [2014]  |
| MAOA      | 30 bp VNTR H/L allele | H; pos. ass.   | Aggression (CBCL, TRF)                 | CC         | PS, HC  | N = 50/50            | 0      | 9.5     | ?         | Beitchman et al. [2004]|
| MAOA      | 30 bp VNTR H/L allele | L-allele [early life stress] | Proactive (BPAQ subscale)              | CC         | PS, HC  | N = 90/145           | 68.89  | 32.18   | CAUC      | Frazzetto et al. [2007]|
| MAOA      | 30 bp VNTR H/L allele | H; pos. ass.   | Reactive (STAXI, LEIDS-R)              | others     | P      | N = 432             | 76.85  | NA      | CAUC      | Verhoeven et al. [2012]|
| MAOA      | 30 bp VNTR H/L allele | L; inv. corr. (provocation) | Reactive (FPI-R)                        | Others     | P      | N = 239             | 63.18  | 23.08   | CAUC      | Kuepper et al. [2013]|
| MAOA      | 30 bp VNTR H/L allele | L; inv. corr. (provocation) | Reactive (controlled experiment, hot Sauce Paradigm) | CC         | P      | N = 78              | 0      | NA      | ?         | McDermott et al. [2009]|

*Measure of aggression (questionaire): Aggression (CBCL), Proactive (BDHI), Reactive (STAXI, SCIDI, SCIDII), Aggression (CBCL, TRF), Reactive (LHA, BDHI), Aggression (CBCL, TRF), Reactive (OAS), Reactive (VIRA-R), Reactive (LHA, BDHI), Proactive (BDHI), Reactive (CBCL, TRF), Reactive (OAS), Reactive (STAXI, SCIDI, SCIDII), Reactive (CBCL, TRF), Reactive (LHA, BDHI), Proactive (OAS), Reactive (STAXI, SCIDI, SCIDII), Reactive (CBCL, TRF), Reactive (LHA, BDHI), Proactive (BDHI), Reactive (CBCL, TRF), Reactive (OAS), Reactive (STAXI, SCIDI, SCIDII), Reactive (CBCL, TRF), Reactive (LHA, BDHI), Proactive (OAS), Reactive (STAXI, SCIDI, SCIDII), Reactive (CBCL, TRF), Reactive (LHA, BDHI), Proactive (BDHI), Reactive (CBCL, TRF), Reactive (OAS), Reactive (STAXI, SCIDI, SCIDII), Reactive (CBCL, TRF), Reactive (LHA, BDHI), Proactive (OAS), Reactive (STAXI, SCIDI, SCIDII), Reactive (CBCL, TRF), Reactive (LHA, BDHI), Proactive (BDHI), Reactive (CBCL, TRF), Reactive (OAS), Reactive (STAXI, SCIDI, SCIDII), Reactive (CBCL, TRF), Reactive (LHA, BDHI), Proactive (OAS), Reactive (STAXI, SCIDI, SCIDII), Reactive (CBCL, TRF), Reactive (LHA, BDHI), Proactive (BDHI), Reactive (CBCL, TRF), Reactive (OAS), Reactive (STAXI, SCIDI, SCIDII), Reactive (CBCL, TRF), Reactive (LHA, BDHI), Proactive (OAS), Reactive (STAXI, SCIDI, SCIDII), Reactive (CBCL, TRF), Reactive (LHA, BDHI), Proactive (BDHI).
| Gene name | Variant major > minor | Allele; outcome | Measure of aggression (questionnaire)* | Study type | Sample | Sample size | Gender | Age mean | Ethnicity | First author, year |
|-----------|-----------------------|-----------------|---------------------------------------|------------|--------|-------------|--------|----------|-----------|-------------------|
| MAOA      | 30bp VNTR H/L allele  | H; pos. ass.    | Proactive (RPQ)                        | CC         | OP, HC | N = 18/13   | 0      | NA       | mixed     | Kolla et al. [2014] |
| MAOA      | 30bp VNTR H/L allele  | L; pos. ass.    | Aggression (TRF)                       | CC         | MC, HC | N = 73/41   | NA     | NA       | mixed     | Weder et al. [2009] |
| MAOA      | 30bp VNTR H/L allele  | L; pos. ass.    | Proactive (medical and criminal history) with adverse childhood | CC         | OP    | N = 184/150 | 0      | 34.1     | CAUC      | Reif et al. [2007] |
| MAOA      | rs1465108G>A          | A; pos. ass.    | Genotype [ACS, UPSS-P, Self-control scale] | Others     | P     | N = 277     | 50.9   | 18.88    | CAUC      | Chester et al. [2015] |
| CRHR1 [tag SNPs] | rs4458044G>C          | GGA; pos. ass.  | Proactive (criminal report)            | CC         | OP, HC | N = 177/282 | NA     | NA       | Asian     | Chen et al. [2014] |
| AVPR1A    | rs35369693G>C         | G; pos. ass.    | Aggressive behavioral subscale (CBCL, TRF) | CC         | AC, HC | N = 177/177 | 33.33  | 11.73    | CAUC      | Pappa et al. [2015] |
| AVPR1B    | rs35369693G>C         | C; inv. ass.    | Reactive [RSRPA]                       | C          | CBP    | N = 141     | 27.66  | 7.29     | CAUC      | Luppino et al. [2012b] |
| OXTR      | rs6270632G>T           | T; pos. ass.    | Aggressive behavioral subscale (CBCL, TRF) | CC         | AC, HC | N = 160/160 | 33.75  | 11.45    | CAUC      | Malik et al. [2012] |
| OXTR      | rs1042778C>A          | C; pos. ass.    | Proactive, reactive [RSRPA]            | CC         | AC, HC | N = 160/160 | 33.75  | 11.45    | CAUC      | Malik et al. [2012] |
| ABCG1     | rs225374C>G           | G; pos. ass.    | Reactive [STAXI, FAF]                  | CC         | S, HC  | N = 259/312 | 57.14  | 39.89    | CAUC      | Gietl et al. [2007] |
| ABCG1     | rs914189C>G           | G; pos. ass.    | Reactive [STAXI, FAF]                  | CC         | S, HC  | N = 259/312 | 57.14  | 39.89    | CAUC      | Gietl et al. [2007] |
| ApoE      | ApoE epsilon4 variant |                   | General [CBCL]                         | Others     | P     | N = 150     | 77     | NA       | CAUC      | Craig et al. [2011] |
| NR3C2 [tag SNPs] | rs2070951G>C       | CA; pos. ass.   | General [LEIDS-R subscale]              | Others     | P     | N = 150     | 77     | NA       | CAUC      | Klok et al. [2010] |
| AR        | rs5522A>G              | length inv. corr. | Proactive [ART, NART]                  | Others     | P     | N = 301     | 0      | 14.4     | CAUC      | Vermeersch et al. [2010] |
| AR        | rs5522A>G              | length inv. corr. | Proactive [criminal report]            | CC         | OP, HC | N = 645/271 | NA     | NA       | Indian    | Rajender et al. [2008] |
| AR        | GGC repeat S/L allele | S; pos. ass.    | Reactive [BDHI]                        | Others     | P     | N = 285     | 57.54  | NA       | CAUC      | Comings et al. [2002] |
| ESR1      | TA[n] repeat S/L      | L; pos. corr.   | Aggression [NA]                        | Others     | P     | N = 188     | 0      | NA       | MIX       | Vaillancourt et al. [2012] |
| NOS1      | ex1 VNTR S/L          | S; pos. ass.    | Proactive [SCIDI, SCIDII]              | CC         | S, OP, OPD, ADHD, HC | N = 1314 | NA     | NA       | CAUC      | Reif et al. [2009] |
TABLE II.  
Study type | Sample size | Ethnicity | Gene name | Variant | Measure of aggression (questionnaire) | Allele; measure of aggression (questionnaire) | Location | Ref. | Year |
|---------|-------------|-----------|-----------|----------|----------------------------------|------------------------------------------|--------|-----|------|
| CC      | S, NC       | CAUC      | NOS1      | rs693534A | G; pos. assoc. Reactive (STAXI; FAF) | CC S, HC N | 5q35.3 | Rujescu et al. [2008] | 2008 |
|         |             |           | NOS3      | rs2070744C | T; pos. assoc. Aggression (FAF) | CC S, HC N | 7q22   | Rujescu et al. [2008] | 2008 |
|         |             |           |           | rs1799983T | T | haplotype | cc | Guerin et al. [2007] | 2007 |
|         |             |           |           | rs891512G  | A; pos. corr. Aggression (5-item scale based on DSM-IV) | A, A; no assoc. | 5q21.2 | Wagner et al. [2010] | 2010 |

Other molecule in the brain [Miczek et al., 2007]. Indeed, there is consistent observation for both humans and animals that levels of 5-HIAA in cerebrospinal fluid (CSF) and blood or serotonergic activity inversely correlate with violent and AB [Birger et al., 2003; Coccaro et al., 1997; Coccaro et al., 1998; Chiavegatto et al., 2001]. Thus, candidate genes were selected based on their functional and biochemical role in the serotonin metabolism and signal transduction (Fig. 1).

Serotonergic candidate genes in aggression. Serotonin is synthesized from tryptophan. Tryptophan hydroxylases (TPH1 and TPH2) catalyze this rate-limiting step and are widely expressed in the brain [Zill et al., 2007]. The human TPH1 gene resides on chromosome 11p15.3-p14. SNP rs1800532C>A in intron 7 has been repeatedly associated with aggression, although with inconsistent findings: Men with Alzheimer’s disease and with rs1800532C alleles had a higher risk to present aggression and agitation as defined through the neuropsychiatric inventory with caregiver distress (NPI-D) [Craig et al., 2004a], whereas the number of A-alleles positively correlated with measures for aggression, anti-social behavior, and anger as assessed through the LHA, STAXI, and BDHI in a population-based cohort [Manuck et al., 1999]. When interpreting these associations, we need to consider the fact that activity of TPH2 and not TPH1 is anabolizing mainly all serotonin in the brain [Gutknecht et al., 2008]. However, KO of TPH1 in murine models is hypothesized to lead to insufficient serotonin levels in female reproductive tissues resulting in an impaired embryonal brain development [Halmøy et al., 2010].

For the human TPH2 gene, which is located on chromosome 12q21.1, a haplotype spanning 16 SNPs which potentially limits serotonin has been reported [Zhou et al., 2005]. Perez-Rodriguez et al. [2010] showed association of this haplotype with enhanced aggressiveness, suicidal behavior, and susceptibility for Bipolar disorder (BPD). Given that the authors have used different tagging SNPs we cannot conclude that the orientation of the associated haplotype exactly corresponded with the reported rate limiting haplotype. Thus, we cannot conclusively say if an increased expression of TPH2 enhances aggression or vice versa.

The large family of serotonin receptors (HTR) comprises seven types classified as a group of G protein-coupled receptors (types 1, 2, and 4–7) and ligand-gated ion channels (type 3). They both mediate serotonin-dependent excitatory and inhibitory neurotransmission in the central and peripheral nervous system [Hoyer et al., 1994]. The genes HTR1A and HTR1B encoding the inhibitory auto-receptors 1A and 1B are considered as major candidates for association with aggression in rodents and man [Bell et al., 1994; Olivier and van Oorschot, 2005]. The human HTR1A is intronless. It is located at 5q11.2-q13. Several polymorphisms in the coding sequence have been analyzed but only few studies investigated their association with human aggression. The functional variant (rs6295 C>G) leads to an increased HTR1A expression and subsequently to lower serotonin neurotransmission [Lemonde et al., 2003]. This variant has been related to increased anxiety- and depression-related personality traits but not to proactive anger hostility [Strobel et al., 2003]. Similarly, no association of rs6295 with aggressive-related behaviors in a cohort of
suicide attempters, completers, and healthy controls was reported. However, a significant gender x genotype effect on the STAXI scores for rs6295 as well as rs1423691T>C and rs878567T>C was mentioned [Serretti et al., 2007].

The HTR1B gene resides on chromosome 6q13. A most frequently studied and functional variant rs6296G>C alters the affinity of the ligand–receptor interaction. In contrast to previous findings [Davidge et al., 2004], a positive correlation between the

![Neural and molecular pathways involved in regulation of aggression. Dopaminergic, serotonergic and HPA signaling pathways are activating overlapping brain areas as well as similar signaling pathways. Brain areas involved in these pathways marked with darker borders. Circles beneath each brain region depict with which neurotransmitter system these areas are associated: upper-left segment, blue = Serotonin; lower, green segment = dopamine, upper-right, red segment = HPA-axis. Proteins shown in the signaling pathways are named according to their HGNC gene names (for full gene names see main text). Genes associated with aggression in human genetics or animal studies are marked by a black border. Pathways were generate from KEGG database entries [hsa04726 Serotonergic synapse; hsa04728 Dopaminergic synapse] as well as from literature reviews [Sardi, 2004; Krugers et al., 2010; Raabe and Spengler, 2013]. Neuronal brain connectivity pathways were adapted from previous publications [Scarr et al., 2013], brain sagittal vector image is provided by Lynch P and Jaffe C under Creative Commons Attribution 2.5 License 2006. AC: Adenylate-cyclase; Ca-Sig: Calcium signaling; DHEA/S: Dehydroepiandrosterone/sulfate; Glucocort.: Glucocorticoids; Horm.: Hormone; Min. cort.: Mineralocorticoid; PKA: Protein Kinase A Pathway; PLA: Phospholipase A; PLC: Phospholipase C; PPA Protein Phosphatase A Pathway; S. nigra: Substantia nigra; TA: Ventral tegmental area; VTA: Ventral tegmental area.](Image)
low-activity C-allele and proactive AB rated through parents but not anger or hostility in adults was reported recently [Hakulinen et al., 2013]. Another functional polymorphism rs130058A>T of HTR1B promoter region has been shown to modulate transcriptional activity by affecting a binding site for transcription factor AP1 [Duan et al., 2003]. An association study in a case–control cohort of suicide attempters revealed that the T-allele increased impulsive (reactive) ABs measured by the BDHI [Zouk et al., 2007]. Further evidence for HTR1B protein levels regulating aggression was provided by the identification of 3’UTR haplotypes that decrease translation presumably mediated via the minor G-allele of SNP rs13212041A>G which alters an miR-96 binding site. Men carrying the low expression alleles scored higher on LHA scale for anger and hostility [Jensen et al., 2009; Conner et al., 2010].

In contrast to type 1 serotonin receptors and serotonin transporters, which are involved in the negative control of serotonin signaling, type 2 receptors a positive mediators of serotonin transmission. Several polymorphisms are reported for gene HTR2A (Chr 13q14–q21). The C/C genotype of rs63113C>T is associated with increased agitation and aggression rated by subscales of the Chinese version of the neuropsychiatric inventory (NPI) in Alzheimer’s disease (AD) [Lam et al., 2004]. However, in Caucasian cohorts, either the T-allele was associated with aggression (NPI) in AD [Assal et al., 2004] or no association was reported [Assal et al., 2004; Pritchard et al., 2008]. A second well-studied variant is the rs6311C>T, a functional promoter SNP, has been associated with increased impulsivity in healthy individuals [Nomura and Nomura, 2006; Nomura et al., 2006] and alcohol use disorder [Preuss et al., 2001]. In addition, Giegling et al. [2006] observed in a cohort of suicide attempters and healthy controls a significant association between rs6311 C/C homozygotes and anger- and aggression-related behavior (STAXI and FAF, respectively). Recently, the T-allele of intronic SNP rs7322347A>T of gene HTR2A showed significant association with BPAQ subscales for hostility, anger, and physical (proactive) aggression in a non-clinical adult population [Banlaki et al., 2015]. This T-allele, according to the miRBase registry, disrupts a potential miRNA binding site [Griffiths-Jones, 2006; Griffiths-Jones et al., 2008] and may thus alter translation. Similarly, a recent study associated the miR-668 binding site variant rs1046322G>A of the Wolframin gene WSI with elevated aggression levels in a population cohort [Kovacs-Nagy et al., 2013]. A population-specific stop codon in the HTR2B gene (2q36.3–q37.1) leading to a blocked expression of respective protein has been associated with severe impulsivity in a cohort of Finnish violent offenders and arsonists [Bevilacqua et al., 2010]. However, a recent candidate gene analysis in two independent cohorts of Finnish prisoners did not find any strong association signal (P ≥ 1 × 10^-5) of this HTR2B stop codon with violent offending [Thihonen et al., 2015].

An additional negative regulation occurs through reuptake of 5HT by the serotonin transporter (5HTT). The encoding gene SLC6A4 is located on chromosome 17q11.1–q12. One of the most studied variants of this gene, a SLC6A4 linked polymorphic region (rs4795541) named 5HTT-LPR, resides within the promoter region. The short (S) allele in contrast to the long (L) allele of SLC6A4 lacks a 44-bp sequence leading to low expression, or high expression of the transporter, respectively, and consequently, to a reduced re-uptake of serotonin [Lesch et al., 1996; Hanna et al., 1998]. In addition, the 5HTT-LPR variant changes SCL6A4 expression in interaction with rs25531A>G, where the G-allele brings expression levels of L-allele carriers back to normal levels [Praschak-Rieder et al., 2007]. The S-allele showed significant association with increased aggression and impulsivity in different cohorts including children [Davidge et al., 2004; Beitchman et al., 2006; Haberstick et al., 2006], adoptees [Cadoret et al., 2003], and criminal defendants [Retz et al., 2004], whereas aggressive children especially with ADHD were significantly more likely to have either one or two copies of the L-allele than those without ADHD [Davidge et al., 2004]. This S-allele was also shown to modulate violent behavior in dependence of adverse childhood events [Reif et al., 2007]. In suicide attempters or individuals with CD no association of the serotonin VNTR with any aggressive measures was observed [Baca-Garcia et al., 2004; Monuteaux et al., 2009]. The genetic effect of the 5HTT-LPR on aggressivity is conserved in primates (reviewed in Barr and Driscoll [2014]), strengthening its association with AB. Interestingly, a significant interaction between the short allele and a DRD4 repeat on aggressive and/or delinquent behavior was observed [Hohmann et al., 2009].

Serotonin is catabolized to 5HIAA through the monoamine oxidase enzymes MAOA and MAOB. Both enzymes are also involved in the degradation of dopamine and are, thus, reported at the end of the dopamine section.

**Dopamine pathway.** Dopamine is part of the neural reward system including behavioral activation, motivated behavior, and reward processing. Dopamine is transmitted via (1) the nigrostriatal pathway between the substantia nigra to the caudate nucleus-putamen (neostriatum) responsible for motor control, (2) the mesolimbic/mesocortical pathways from ventral tegmental area to nucleus accumbens, amygdala, hippocampus, and prefrontal cortex (memory, motivation, emotion, reward, desire, addiction), and (3) the tuberoinfundibular pathway from hypothalamus to pituitary gland for hormone regulation, nurturing behavior, pregnancy, sensory processes. Thus, dopamine is connecting stress response and reward processing [Pivonello et al., 2007]. Dopamine is anabolized from L-Tyrosin mainly in presynapses. Once released, postsynaptic dopamine receptors D1–D5 (DRD1–5) can be activated. Upon activation, the G-protein coupled DRD1 and DRD5 stimulate the adenyl cyclase (AC) cascade. In addition, DRD1 induces Ca++ release from the endoplasmic reticulum and DRD5 activates downstream phospholipase (PL) C signaling. Receptors D2, D3, and D4 are members of the D2-like subfamily and coupled to a second set of G proteins that inhibit AC upon stimulation. DRD2 can also activate protein phosphatase A pathways, whereas G-proteins activated by DRD3 and DRD4 co-stimulate a potassium channel (GIRK) and PLC signaling (Fig. 1; reviewed in Pavlov et al. [2012]). In addition DRD2, has an auto-receptor function generating a negative feedback loop inhibiting additional dopamine release. Another rate limiting transporter, SLC6A3/DAT1 (dopamine transporter 1) clears dopamine from the synaptic cleft. Dopamine is catabolized through Catechol-O-methyltransferase (COMT) and the monoamine oxidase enzymes (MAOA/B) that also catalyze serotonin.

Dopaminergic innervation of the striatum is proposed to mediate behaviors such as impulsivity and temperament, suggesting
that functional variants of genes regulating dopaminergic activity could therefore modulate aggression-related traits. Indeed, several human and animal studies (detailed below) demonstrated a functional relation of this neurotransmitter system to aggression. In humans, dopamine has been linked to the recognition and experience of aggression, and further evidence of enhanced impulsive behavior by elevated dopaminergic function has been provided. This is endorsed by studies where pharmacologically manipulated dopamine levels have been shown to influence AB (reviewed in Seo et al. [2008]). An involvement of dopaminergic genes in the etiology of pathological aggression was explained by an impaired sensitivity of the reward neurotransmitter system [Chen et al., 2005].

**Dopaminergic candidate genes in aggression.** The gene coding for the rate limiting DAT1 transporter, that is, SLC6A3, resides on chromosome 5p15.3 and contains 15 exons. The 3'UTR of this gene contains a 40 bp variable number tandem repeat (VNTR, rs28363170). This variant can be present in 3–11 copies (3r–11r) where the alleles 9r and 10r are most common. The length of the VNTR is positively correlated with SLC6A3 expression levels [Van Ness et al., 2005] and subsequently inversely correlated with the activation of dopamine-stimulated regions such as the ventral striatum [Dreher et al., 2009]. Association between the SLC6A3 9r-allele and externalizing subscales of the CBCL has been demonstrated in a cohort of N = 790 children from a longitudinal twin study [Young et al., 2002]. Furthermore, carriers of the SLC6A3 9r/9r genotype showed a significant increase (6–10 times) to irritability and direct aggressiveness (BDHI) scores compared with 9r/10r-carriers in a cohort of N = 104 drug users [Gerra et al., 2005]. In contrast, a study in 184 adult men from an offender population did not find any association between SLC6A3-40 bp VNTR and the liability for committing violent crimes [Reif et al., 2007], a form of proactive aggression behavior. However, with respect to aggression, the differentiation between violent and non-violent crimes could bias conclusions toward AB in general, as committing non-violent crimes may also relate to covert forms of AB.

The post-synaptically expressed D1-like subfamily receptors DRD1 and DRD5 are located on Chr 5q35.1 and 10p16.1. DRD2 is coded on Chr 11q23, with the two known splicing isoforms showing a tissue-specific expression. The short variant is expressed in presynaptic neurons with auto-receptor function for regulating neurotransmission, whereas the long DRD2L resides in postsynaptic neurons acting in the classical neurotransmission pathway [Sedaghat et al., 2006]. Receptors DRD3 (Chr 3q13.3) and DRD4 (Chr 11q15.5) are both activating the canonical neurotransmitter pathways at postsynaptic membranes [Pitonello et al., 2007].

Sweet et al. [1998] investigated selected polymorphisms in the dopamine receptor genes DRD1, DRD2, DRD3, and DRD4 in a cohort of AD patients. Physical aggression was more prevalent in AD patients who were homozygous for the G-alleles of the DRD1 rs45532A>G polymorphism. However, no association with aggression was found for variants on the DRD2, DRD3, or DRD4. A further study in DRD2 revealed an association between SNPs rs1799978A>G, rs1800497C>T, and rs1079598C>T with perva- sive aggression in children [Zai et al., 2012a]. Rs1799978A>G lies within the promoter sequence of the gene. Rs1800497T, although it is located 10kb downstream of DRD2, was reported to reduce receptor density in the striatum [Pohjalainen et al., 1998]. Rs1800497 is intronic and currently no functional impact is known. Interestingly, Hohmann et al. [2009] reported an epistatic effect of DRD4 exon three VNTR and the 5HTT-LPR polymorphism. Carriers of two copies of the 5HTT-LPR short allele and the DRD4 7r variant scored highest on aggressive and/or delinquent behavior compared to other genotypes. No studies have been published associating DRD5 with AB.

Dopamine is degraded in the synaptic cleft and adjacent cells after reuptake to homovanillic acid catalyzed by the Catechol-O-methyl transferase (COMT) and MAOA/B. In addition, dopamine can be converted to noradrenaline (NE) by the dopamine-β-hydroxylase (DBH) which is strongly related to aggression in mice [Marino et al., 2005]. COMT is acting as an intracellular, membrane-bound enzyme in the presynaptic neuron, as well as in the synaptic cleft in soluble form and is, thus, again a rate limiting enzyme. Studies in knockout mice have revealed an increase in AB in heterozygous COMT-deficient males [Gogos et al., 1998] indicating a role for COMT in emotional and social behavior.

The human COMT gene is localized on chromosome 22q11.1–q11.2. Genetic studies in humans mainly focused on the functional SNP Val158Met (rs4680A>G), which reduces the activity of the enzyme by almost twofold compared to the Val158 allele [Lachman, 2008]. Several studies have reported an association between the Met158 allele and aggressive personality traits in adults [Rujescu et al., 2003], AB in schizophrenia patients [Tosato et al., 2011], and aggression in children [Perroud et al., 2010; Hirata et al., 2013]. Perroud et al. [2010] have shown that Val158Met polymorphism modulates the association between childhood sexual abuse and adulthood anger-trait level resulting in reactive AB. COMT Val158Met is likely to play a pathophysiological role in context of AB due to an increased catecholamine level in Met/Met homozygotes and a reduced degradation of these hormones by the low activity of Met158 variant. In addition, COMT promoter SNP rs6269 was correlated with early childhood aggression rated by a combination of CBCL and TRF [Hirata et al., 2013]. Interestingly, Monuteaux et al. [2009] reported that COMT was associated with an increase in aggressive conduct disorder (CD) symptoms but not with risk for CD itself. Dopamine and NE decrease the threshold for aggressive reaction in response to outer stimuli, while an excess of these hormones increase the vulnerability and the risk of uncontrolled responses against stress [Volavka et al., 2004]. Thus high levels of dopamine may also be causally related to reduced NE conversion of dopamine. The DBH gene lies on chromosome 9q34 and harbors a functional SNP rs1611115C>T in the promoter region which reduces plasma levels of DBH [Zabetian et al., 2001, 2003]. The rs1611115T allele is associated with personality features related to impulsiveness and aggressive hostility, that is, reactive and proactive aggression, in a cohort of male ADHD patients [Hess et al., 2009].

The Monoamine Oxidases are mitochondrial enzymes and encoded by two paralogs MAOA and MAOB on the X Chromosome that catalyze monoamines [Shih et al., 1999]. Serotonin is mostly degraded by MAOA which is coded on the X chromosome (Xp11.23–11.4), whereas dopamine is catalyzed by both, MAOA and to a lesser extent by MAOB [Kalikutkar et al., 2001]. Both enzymes have been studied in context of behavioral genetics.
although with a strongly biased toward MAOA, and significant associations with aggression were only reported for MAOA.

In humans, a stop-mutation in the MAOA gene has been correlated with heightened levels of aggression [Brunner et al., 1993] suggesting a key role of this enzyme in the regulation of aggression. Among several variants in MAOA, a VNTR polymorphism, first reported by Sabol et al. [1998], has been studied in context of aggression and violent behavior. This VNTR is located 1.2 kb upstream of the coding region, comprises a 30-bp repeated sequence and has been shown to be present as 2, 3, 3.5, 4, or 5 copies [Sabol et al., 1998]. The 3r and 4r repeat variants are the most prevalent forms in Caucasians where the 2r and 3r lead to a 2- to 10-fold reduced transcriptional activity, whereas the 3.5r and 4R-variants have been found to be more active [Sabol et al., 1998; Deckert et al., 1999; Guo et al., 2008]. The role of the least frequent 5r allele is not convincingly clarified, as Deckert et al. [1999] showed increased expression, while Sabol and associates reported a decrease in MAOA activity [Sabol et al., 1998]. It has to be noted that males carry only one allele, in contrast to females, that is, they are X-chromosomal hemizygous. However, the results for MAOA are inconsistent: Some studies reported a positive association between expression levels and ABs, such as reactive aggression [Manuck et al., 2000; Verhoeven et al., 2012; Holz et al., 2014], pervasive AB [Beitchman et al., 2004] or early life stress induced AB [Frazzetto et al., 2007]. Other studies reported an inverse correlation, for example, low-activity alleles increased measures for reactive aggression [McDermott et al., 2009; Kuepper et al., 2013] and proactive aggression [Kolla et al., 2014] or violent offending [Tiibonen et al., 2015].

In addition gene x environment interaction has been reported for MAOA. One well studied environmental risk factor for developing antisocial behavior is early childhood abuse [Kelley et al., 2001]. In addition, infants of parents with antisocial personalities are at increased risk for developing ABs, such as reactive aggression [McDermott et al., 2009; Kuepper et al., 2013] and proactive aggression [Kolla et al., 2014] or violent offending [Tiibonen et al., 2015].

Summarizing across studies, it appears that the promoter region of the MAOA gene is associated with high aggression; however, it is unclear whether the VNTR itself, or in interaction with environmental factors or another nearby DNA variant, is functionally responsible for the manifestation of aggression [Beitchman et al., 2004].

Neuroendocrine pathways. The stress response mediating HPA axis involves hormonal signaling between hypothalamus, pituitary gland, and adrenal-cortex. Corticoid releasing hormone (CRH) signaling from the hypothalamus to the pituitary gland triggers the release of adrenocorticotrophic hormone (ACTH) into the blood stream. ACTH activates glucocorticoid, mineralocorticoid, and sex-steroid production in the adrenal cortex, all of which activate receptors that act as nuclear transcription factors and regulate expression of target genes that harbor respective recognition elements. These hormonal pathways induce biological responses in peripheral systems such as the immune system. In addition, glucocorticoids and mineralocorticoids regulate CRH production and form activating and inhibitory frontal-hippocampal feedback-loops (Fig. 1); low reactive cortisol has consistently been found in individuals with high AB [Platje et al., 2013]. Thus, genetic variants involved in stress response may, therefore, be implicated in aggression [Craig, 2007].

Although animal models show a strong relation between the HPA axis and aggression only few genetic association studies in human individuals have been performed. In a Chinese southwest Han population, a single marker and haplotype analysis of three variants (rs4458044G>C, rs242924T>G, and rs17689966G>A) of the CRHR1 gene showed significant association of the G-G-A haplotype with an increased susceptibility of AB toward others [Chen et al., 2014]. This receptor is located on the cells of the pituitary gland and activates a protein kinase A (PKA) signaling cascade triggering pro-opiomelanocortin (POMC) transcription. No genetic association study for POMC and aggression is known so far, but evidence for direct involvement in regulation of aggression comes from KO animal models as detailed below.

Corticotrophic-hormone release is also modulated through Arginine-Vasopressin (AVP) [Koshimizu et al., 2012]. In addition, AVP activates and regulates neuronal nitric oxide and catecholamine signaling. This nona-peptide is produced in the hypothalamus and its gene overlaps with that of the pro-social neuropeptide oxytocin (OXT) gene [Gimpl and Fahrenholz, 2001]. AVP levels in cerebrospinal fluids were positively correlated with lifetime history of aggression [Coccaro et al., 1998]. Variant rs35369693G>C of the AVP receptor gene AVPR1B, localized on Chr 1q32 was significantly associated in two independent studies with reactive aggression in children [Zai et al., 2012b; Luppino et al., 2014]. No association study has been reported for the AVP receptor AVPRIA (Chr 12q14–q15) with human AB so far. The OXT system is mostly known as regulator of social interaction and maternal bonding. Two SNPs of the OXT Receptor (OXTR), rs6770632G>T and rs10427778C>A, were significantly associated with extreme, persistent and pervasive ABs [Malik et al., 2012].

The hypothalamic factors CRH and AVP stimulate ACTH release from the pituitary gland which further stimulates steroid production from cholesterol in the adrenal cortex. Free cholesterol
levels were inversely correlated with aggression in individuals taking psychiatric medication [Sahebzamani et al., 2013]. However, it is unclear if the reduced levels were causally related to high aggression. Interestingly, the minor alleles of variants rs225374C>G and rs914189C>G of the cholesterol transporter ABCG1 gene (ABCG1), mapped to Chr 21q22.3 which regulates intracellular availability of cholesterol, increased spontaneous and reactive aggression [Gietl et al., 2007]. In patients with Alzheimer’s disease (AD), the AD associated epsilon4 variant of a key regulatory enzyme in cholesterol metabolism, apolipoprotein E (APOE), also influenced AB [Craig et al., 2004b]. Gluco- and mineralocorticoids as well as sex-steroid hormones synthesized from cholesterol are released into the blood stream and target peripheral organs including the brain and the immune system or the gonads. Interestingly, pathologically relevant exposure to stress that has been found to be related to AB such as early life events influence epigenetic markers of immune-system-related genes (see Epigenetics section below). Several studies found a correlation between lower basal saliva cortisol and increased impulsivity in adolescents and young men [Shirtcliff et al., 2005; Loney et al., 2006; Popma et al., 2007]. Interestingly, Yu and Shi [2009] found lower basal cortisol levels in aggressive male adolescents, but higher basal testosterone levels in girls showing AB. Upon chronic stress cortisol is reduced in non-aggressive individuals due to a potential long-term stress-induced impairment in the HPA axis function [Kudielka and Wüst, 2010; Pavlov et al., 2012]. It has been hypothesized that the susceptibility toward abnormal aggression is less dependent on cortisol levels per se, but on the ratio and interplay between corticosteroid hormones such as testosterone and cortisol (see review Pavlov et al., 2012). Gender-specific differences in AB in humans probably result from different aggression strategies acquired during evolution linked to sexual hormones, for example, testosterone. Although in numerous animal studies a strong correlation between testosterone levels and aggression has been observed, the relationship in humans is much less clear. A positive correlation between saliva testosterone levels and serious aggression in boys but not in girls was reported [Sánchez-Martín et al., 2000]. This finding is supported by other researchers who found evidence of positively correlated testosterone levels and aggressiveness in male volunteers [Brown et al., 2008] and prisoners [Chichinadze et al., 2010], as well as in female and male adolescents [Yu and Shi, 2009].

Steroid receptors act as nuclear transcription factors by inducing the biological responses within the peripheral organs. Cortisol is bound by the nuclear receptor 3C1 (NR3C1), also named glucocorticoid receptor (GCR). Through interaction with glucocorticoid response units (GRU), it can activate transcription of genes related to gluconeogenesis, energy metabolism, or inhibit immune response and reduce corticotrophin releasing hormone levels in the hypothalamus and pituitary gland [Schoneveld et al., 2004]. Currently, known variants have not been reported in the context of AB. However, stress-dependent epigenetic changes of the NR3C1 gene (Chr 5q31.3) were reported as detailed below.

Besides the primary agonist aldosterone, the mineralocorticoid receptors (MCRs), encoded by the NR3C2 gene (Chr 4q31.1), can also bind cortisol. MCRs activate transcription of proinflammatory genes, and regulate corticotrophin pathways. A female-specific association of a NR3C2 promoter haplotype including eight variants tagged by the functional SNPs rs2070951G>C and rs5522A>G was significantly associated with lower Leiden Index Scores (LEIDS-R) for aggression in a female control cohort. The associated haplotype reduced the promoter activity of the NR3C2 gene. Probably due to the smaller cohort size, this effect was not observed in the male individuals studied [Klok et al., 2011].

The androgen receptor (AR) is in terms of sex determination a highly polymorphic and functional locus on Chromosome Xq11-12 comprising eight exons. The AR embraces two trinucleotide repeats. The first, a CAG repeat, encodes for a polyclutammine stretch and has a potential influence on the transcription-factor function of the AR protein. It has been shown that long fragments inhibit the interaction with transcriptional activators [Chamberlain et al., 1994; Callewaert et al., 2003]. The length of the second variant, a GGN repeat encoding for a polyglycine stretch, also correlates with the transcriptional activity of the receptor but with inconsistent functional results [Dunning et al., 2004; Brockschmidt et al., 2007; Lundin et al., 2007].

At genetic levels, the shorter and putatively higher active CAG repeat was associated with aggressive risk taking behavior in adolescent males. In addition, a significant interactive effect on dominance as well as on non-aggressive and aggressive risk behavior between the length of the CAG-repeat and free testosterone levels was identified: Free testosterone was more strongly related to risk-taking (aggressive and non-aggressive) in boys with high-active AR alleles [Vermeersch et al., 2010]. By now, several studies in Europeans and Asians have confirmed these observations showing a correlation between the short CAG repeat allele and antisocial behavior [Prichard et al., 2007] and proactive aggression [Comings et al., 2002] as well as positive correlation between the short GGC repeat allele and reactive aggression [Rajender et al., 2008]. Furthermore, both, the CAG and GGN repeat, were implicated in impulsivity of inmates [Aluja et al., 2011].

Testosterone levels were confirmed to be weakly associated with aggression in a meta-analysis based on 45 independent studies, showing significant confounder effects for age of the study participants and the time-point of sample collection [Book et al., 2001]. The age-related effect corroborates the hypothesis of the “young male syndrome,” proposed by Wilson and Daly [1985]. This theory is explaining the enhanced AB of young adult men between the ages of 12–25 due to the increase in testosterone levels that happens in early adolescence, supporting reproductive physiology and respective behavior [Book et al., 2001].

Similarly, the estrogen receptors are transcriptional regulators and are encoded by ESR1 (Chr 6q25.1) and ESR2 (Chr 14q23.2) with several polymorphisms reported (reviewed in Pavlov et al., 2012). One study within the context of depression showed that the length of a TA[n] repeat in the promoter region of ESR1, which alters ESR1 expression, is inversely associated with physical aggression in healthy male students, and lowest in those men with large differences between the two carried alleles [Vallancourt et al., 2012]. In addition, several studies have associated ESR1 polymorphisms with impulsivity-related traits [Comings et al., 1999; Ryan et al., 2011], or antisocial behavior in men [Prichard et al., 2007].
**Additional signaling pathways.** Besides the most commonly described serotonergic, dopaminergic and endocannabinoid pathways involved in aggression, studies have emerged that implicated signaling mechanisms that connect all three pathways, such as nitric oxide signaling, or BDNF signaling.

Nitric oxide (NO) is a central second messenger in neurons activating kinase and calcium signaling pathways. NO is enzymatically synthesized from arginine via the nitric oxide synthetases (NOS). Neuronal NOS (NOS1) binds to the postsynaptic density and is closely linked to the glutamatergic signaling pathways. Reif et al. [2009] described a novel functional promoter polymorphism (ex1 VNTR) of the NOS1 gene (Chr 12q24.22) which is associated with traits related to proactive ABs. In addition, the NOS1 rs693534G allele increased reactive aggression in German suicide attempters. The same study also showed that a T–T–G haplotype (rs2070744-rs1799983-rs891512) of the NOS3 gene (Chr 7q36) was associated with increased aggression [Rujescu et al., 2008].

Brain-derived neurotrophic factor (BDNF) signaling regulates neuronal survival, morphogenesis, and plasticity by activating tyrosine receptor kinase B (TRKB) and mitogen-activated kinase (MAPK/ERK), phospholipase Cγ (PLCγ), and phosphoinositide 3-kinase (PI3K) pathways. The same mechanisms are activated via dopaminergic and serotonergic signaling [Numakawa et al., 2010]. A very well studied polymorphism in the BDNF gene (Chr 11p13) changes the amino acid valine at position 66 to methionine (V66M, rs6265G>A). Interestingly, significant interactions of the V66M allele with environmental risk factors were identified: V66M modulates the impact of childhood sexual abuse on impulsive aggression (BDHI-sub scores) of patients with borderline personality disorder [Wagner et al., 2010]. Carriers of the Met–Met variant compared to Val–Val carriers showed increased risk for being aggressive in adolescence if affiliated with aggressive peers in childhood compared to Val–Val carriers [Kretschmer et al., 2014]. However, no association was reported between BDNF variants V66M, C270T or a GT[n] repeats with exhibition of aggression in children [Guerin et al., 2007].

**Animal Models for Aggressive Behavior**

Animal models are a crucial tool to generate hypotheses about aggression in humans. However, the generalization to human behavior is limited in that complex communication or ethological aspects remain mostly unexplored. Here, we will summarize, with no claim of completeness, aggression studies in rodents, primates and insects. For a more complete review, we recommend reading an extensive review on neurogenetics of rodents [Takahashi and Miczek, 2014].

Animal studies focus on single well defined patterns of AB that can be quantified (e.g., latency to attack or number of lunge and attacks) to allow operationalization of clearly defined aggressive traits. For example, reactive AB can be induced through (1) introduction of “intruders” into the home territory (resident–intruder test; R1), (2) isolation, in which a single individual is isolated in a cage and then exposed to an intruder, or (3) painful stimuli produced by electric shocks. Proactive aggression can be observed through (1) food deprivation leading to predation (2) operant conditioning, aimed at extinction or (3) within social cohesion of a colony to maintain hierarchical structures, for example, dominant behavior in general. Female aggression is parametrized, for example, through maternal aggression, exposing lactating females in the presence of the offspring (mainly in rodents) to non-familiar intruders; trough measures of attacks during female dominant behavior in non-human primates or hierarchical dominance of queens of mole rat colonies [reviewed in Ramirez, 2000].

Based on the hypothesis that aggression is a normally distributed biological behavior, mice strains were selectively inbred for (mostly reactive) aggressive traits such as the time between exposure to an intruder and the actual attack (latency). Three strains have emerged so far: the Short Attack Latency (SAL) and Long Attack Latency (LAL) [van Oortmerssen and Bakker, 1981], the Turku Aggressive (TA) and Turku Non-Aggressive (TNA) [Kenneth Sandnabba, 1985], as well as the North Carolina Aggressive (NC900) and North Carolina Non-Aggressive (NC100) [Cairns et al., 1983; Gariépy et al., 1988] mouse strains. SAL mice showed consistently lower ACTH levels, but similar corticosterone levels compared to LAL animals. Under stress conditions, rise in ACTH levels was similar, but corticosterone levels were higher in LAL mice, supporting the link between reactive aggression, stress coping mechanisms, and the HPA axis [Veneema and Neumann, 2007]. TA mice were selectively inbred for isolation-induced intermale aggression. It was shown that this increase is correlated with levels of predatory aggression in males as well as in postpartum aggression in females supporting a genetic link between these biologically relevant behaviors [Sandnabba, 1993, 1995]. High aggressive NC900 female animals showed high postpartum aggression upon exposure to male intruders with no differences in freezing behavior compared to non-selected animals, whereas low aggressive NC100 displayed increased freezing behavior, which is usually related to anxiety [Lewis et al., 1994].

Rats selected for extreme traits of anxiety behavior (Low Anxiety Behaviour LAB; High Anxiety Behaviour; HAB) resulted in animals with high levels of reactive aggression compared to non-selected rats as assessed in resident–intruder assays, where LAB strain scored highest. In addition, LAB males showed abnormally increased ABs like attacks towards vulnerable body parts, females or narcotized males, that is, proactive aggression [Beiderbeck et al., 2012].

Systematic analysis of mouse models, including KO mice, also presents strong evidence for an interaction of the serotonergic, the dopaminergic system as well as the HPA stress response axis. Similar to human genetic studies, recent system wide analyses suggest additional not yet extensively studied pathways for aggression such as the nitric oxide signaling or the oxidative stress system.

Cross breeding of animals with different aggression levels allowed identifying genetic loci for aggression. A genome-wide scan in an F2 population of male mice bred from the highly aggressive BALB/cJ strain and the normal to low aggressive A/J mouse strains linked aggression to chromosomes 5, 10, and 15. Three positional candidate genes on chromosome 10 were identified in this study: The protein tyrosine phosphatase, receptor type, f polypeptide (PTPRF), interacting protein (liprin), alpha 2 (PPIA2), the citrate synthase (CS), and the epidermal growth factor receptor erb-b2 receptor tyrosine kinase 3 (ERBB3) [Dow...
that high aggression is associated with altered NF-κB and the MAPK pathways [Malki et al., 2014]. Similar results, associating the ERK/MAPK and Calmodulin pathways with aggression, were found in the hippocampus of LAL/SAL mouse models [Feldker et al., 2003].

These few genome-wide analyses did not identify genes belonging to the classical pathways for aggression. However, targeted approaches that included mostly knockout (KO), targeted expression studies, or pharmacological intervention studies have again been corroborating the implication of the dopamine, the serotonin, and the endocrine systems in aggression.

**Dopamine and serotonin pathways in animal models for aggression.** Similar to human studies, strongest evidence as modulator of aggression is presented for serotonin. In the inbred SAL (high aggression) and LAL (low aggression), mouse strains differences in stress responsivity were observed in association with significantly altered HPA regulation, serotonin neurotransmission, and hippocampal cell proliferation rate [Veneema et al., 2004]. In Drosophila, specific inhibition of neurotransmission of serotonergic and dopaminergic neurons simultaneously abolished mid- and high-level aggression. Although disruption of any of the two pathways individually did not replicate the phenotype, the inhibition of the serotonergic pathway alone produced less aggressive animals [Alekseyenko et al., 2010]. It was hypothesized that aggression is negatively modulated through the inhibitory input from 5HT1A receptor, which can be released by activation of 5HT secretory neurons located in the posterior lateral protocerebrum [Alekseyenko et al., 2014]. In a female rhesus monkey model, the serotonin transporter 5HTT-LRP variant impaired the anxiolytic action of Estrogen (E2; see also paragraph below).

Cross breeding of highly aggressive wild-mouse strain MSM/Ms with the less aggressive inbred lab strain BL6 as well as generation of consomic mouse strains (i.e., a BL6 mouse harboring a complete MSM/Ms derived chromosome) allowed linking reactive AB as measured through the resident–intruder test to chromosomes 4 and 15. Interestingly, tryptophan hydroxylase 2 (TPH2), a metabolic enzyme in the serotonin anabolism, was increased in the Chr4 consomic strain as well as in the MSM/Ms strain compared to wild-type BL6 mice. TPH2 mRNA levels were correlated with ABs [Takahashi et al., 2014]. A C1473G polymorphism altering the enzyme activity of the TPH2 gene has been associated with aggression intensity and immobility in a forced swim test [Osipova et al., 2009] and TPH2 KO mice showed increased aggression and increased expression of serotonin auto-receptors HTR1A and HTR1B [Lesch et al., 2012].

Central administration of brain-derived neurotrophic factor (BDNF) to high aggressive AKR mice induced proactive AB (aggressive attacks toward young mice) and reduced HTR1A and HTR2A receptor mRNA levels in the frontal cortex as well as TPH-2 mRNA level in the midbrain. When transferring a fragment of chr13 from low aggressive CBA mice carrying the low expression variant of the HTR1A receptor gene to the AKR background, BDNF exposure was attenuating the increased expression of HTR1A, HT2RA, and TPH genes and decreased functional activity of 5HT2A receptors. BDNF administration did, however, restore social deficiency observed in the partially consomic mouse strain [Naumenko et al., 2014].

Caramaschi et al. observed an up-regulation of somatodendritic HTR1A and terminal HTR1B in highly aggressive LAB rats, followed by an increase of victorious aggressive experiences. Such up-regulation may be part of a normal compensatory mechanism to the elevated serotonergic activity in such aggressive animals [Caramaschi et al., 2007], although both receptors probably differentially contribute in specific brain areas to the inhibitory postsynaptic effects of 5HT on aggression [Nelson and Trainor, 2007].

Mice lacking the 5HT transporter SLC6A4 showed reduced aggression and locomotor activity, probably mediated by dysregulation of HTR1A and HTR1B genes [Holmes et al., 2002]. Pharmacological inhibition of serotonin transporters with fluoxetine, a selective serotonin reuptake inhibitor (SSRI) in gold hamsters, increased attack latency and reduced attack frequency [Ferris et al., 1997]. In naked mole rats, the only mammal that displays eusocial behavior, fluoxetine treatment decreases aggression in dominant naked mole-rats when paired with unfamiliar animals and decreases digging behavior in subordinate naked mole-rats when in their home colony [Mongillo et al., 2014].

Similarly, strong evidence is provided for the dopaminergic system; at neurobiological levels, Beiderbeck et al. [2012] report that the selectively bred LAB but not HAB rats showed an increased dopamine release as well as specific neuronal activation in the nucleus accumbens. Interestingly, LAB rats, in contrast to SAL mice, also showed an increased HPA response. However, both aggressive strains show high activation of the central amygdala, reduced activation of the lateral septum, impaired vasopressin systems and an increased serotonergic neurotransmission [Veneema and Neumann, 2007]. Similarly, an earlier study in the Northern Carolina mouse strains NC100 and NC900 showed that the high aggressive NC900 mice have higher dopamine concentrations in the nucleus accumbens [Lewis et al., 1994]. In LAB-rats pharmacological inhibition of D2 but not D1 receptors reduced aggression [Beiderbeck et al., 2012]. Over-activation of D1 receptors as induced in a transgenic mouse model expressing choleratoxin under the control of the DRD1 promoter decreased AB in the resident–intruder aggression assay [Campbell et al., 1999].

The amide signaling pathways are connected through their katabolic enzymes MAOA [Shih and Thompson, 1999]. Studies in MAOA gene KO mice have revealed an increase in aggression levels of the animals and AB could be normalized by restoring MAOA expression [Vishnivetskaya et al., 2007; Scott et al., 2008] or by acute treatment with fluoxetine [Godar et al., 2014]. Interestingly, only the complete MAOA KO but not introduction of hypomorphic MAOA alleles in mice led to an increased resident–intruder aggression [Bortolato et al., 2011]. MAOA expression, was also altered in mice lacking the cannabinoid receptor 1 (CB1R). KO of CB1R induced higher levels of offensive/proactive aggression together with an increase in 5HT1BR, COMT, and MAOA expression in the amygdala, with an increase in COMT expression in dorsal raphe and median raphe as well as with...
decreases of MAOA level in median raphe. The CBRI KO strain showed no isolation-induced aggression in contrast to wild-type animals. Blocking CBRI using the antagonist ACEA (Arachidonyl-2'-chloroethylamide) significantly reduced aggression levels in an outbred strain (OF1). This study is linking CBRI-dependent modulation of aggression to the amidic and specifically to the serotonin pathways [Rodriguez-Arias et al., 2013].

**Endocrine pathways.** The HPA axis has been shown above to be involved in aggression in humans. In mice, KO of the prohormone Proopiomelanocortin (POMC), a precursor for Adrenocorticotropic hormone (ACTH) reduced freezing behavior in favor of aggressive traits with normal clinching behavior when exposed to an aggressive dominant conspecific mouse [Vaanholt et al., 2003]. Mice lacking the ACTH stimulating hormone CRH showed a reduced stress-induced cortisol response and abnormal lung morphology. However, the behavioral phenotypes were normal [Muglia et al., 1995; Venihaki and Majzoub, 2002].

Injection of the neuropeptide AVP (Arginine-vasopressin), another regulator of POMC expression, into the anterior hypothalamus of gold hamster shortened the latency times of attacks and administration of fluoxetine could inhibit the AVP induced aggression [Ferris et al., 1997]. Selective inhibition of the AVP receptor also reduced AB in hamster [Ferris et al., 2006]. In contrast to this finding, repeated administration of clinically relevant doses of fluoxetine during adolescent development of gold hamsters directly stimulates AB and resulted in aberrant 5HT and Vasoressin (AVP)-dependent development. However, only alterations in AVP afferent neuronal development within the latero-anterior hypothalamus correlated with the fluoxetine-induced AB phenotype [Ricci et al., 2012].

Males lacking the Vasopressin Receptor AVPR1B display a longer latency to attack and less agonistic behavior toward intruder males. In addition, juvenile animals showed higher testosterone levels compared to homozygous litters. This effect is not visible in adults animals [Wersinger et al., 2002]. Mice lacking the social bonding hormone Oxytocin show reduced aggression and spend less time in aggressive interactions in an open arena test with less prominent effects in a resident–intruder assay [Young et al., 1998].

Interesting studies have been provided for sexual hormone receptors: KO of the estrogen receptor 1 reduced offensive aggression as well as reactive aggression (RI-test) of males [Ogawa et al., 1997, 2000]. In contrast, younger, sexually naïve male mice lacking the estrogen receptor 2, showed an increased aggression towards intruder males [Ogawa et al., 2000]. In female mice, estrogen-dependent aggression between dames has been observed: wild-type females exhibit higher levels of aggression toward gonadectomized and steroid-primed female intruders; however, ERI KO inhibits this female aggression [Ogawa et al., 1998]. Interestingly, in rhesus monkeys, estrogen increases affiliate behaviors in female, ovariectomized individuals, with even more of this prosocial behavior directed toward a dominant female. Dominant females of this group had higher levels of oxytocin than subordinate animals while estrogen administration increased immunoreactive serum oxytocin in all females [Michopoulos et al., 2011].

Testosterone exposure of female high aggressive inbred TA mice increased aggression similar to female TA mice after isolation, but had no effect on the inbred non-aggressive TNA strain. The induced aggression in females was comparable to that observed in males, suggesting that differences in testosterone reactivity of target organs, other than those which are Y chromosome determined are responsible for the aggressiveness [Sandnabba et al., 1994].

**Additional signaling pathways associated with aggression in animal models.** Takahashi and Miczek [2014] in an extensive review on neurogenetics of AB in rodents summarize that aggressive traits in rodents are also attributed to an imbalance between glutamatergic excitation and GABAergic inhibition in limbic areas. NMDA ionotropic glutamatergic receptor subunit expression positively correlates with levels of aggression [Zhao et al., 2009; Bortolato et al., 2012]. In addition, AB of MAOA-KO mice is suggested to be mediated through altered expression of NMDA receptors [Bortolato et al., 2011]. Similarly, AMPAR subunit availability correlates with male specific aggression in mice [Vekovscheva et al., 2004] and hamster [Fischer et al., 2007]. Animals lacking the Kainate receptor GRK2 showed a broad range of psychopathologies including enhanced aggression toward males reversed by lithium administration [Shaltiel et al., 2008].

Similarly, altered metabotropic glutamatergic signaling pathways alters AB. Inhibition of the excitatory GRM1 [Navarro et al., 2008] or GRM5 [Navarro et al., 2006; Newman et al., 2012] reduced aggression, while activation of the inhibitory group II GRM2/3 receptors or group III GRM7 receptors also reduced aggression [Ago et al., 2012; Newman et al., 2012].

Evidence for impaired glutamatergic connectivity comes from hamster models treated with AAS (anabolic androgen steroids). This resulted into highly aggressive animals that showed a significant increase in the projections of VGLUT2 (vesicular glutamate transporter 2) positive cells from the latero-anterior hypothalamus (LAH) to the bed nucleus of the stria terminalis (BNST) [Fischer et al., 2007].

When interfering with the inhibitory GABAergic signaling pathway, a reduction in GABA_A receptor function may predispose individuals to initiate ABs, whereas over-expression or over-activation, for example, through benzodiazepine (GABA_A agonists) administration, clearly has dose-dependent effects. Similar inverse U-shaped effects are known from ethanol, a GABA-positive allosteric modulator [reviewed in Takahashi and Miczek, 2014].

A very recent finding in adult mice showed that the increased aggression and impaired social recognition as triggered by early life stress is accompanied by increased expression of the postsynaptic density protein Neuriligin 2 (NLGN2) in the hippocampus. NLGN2 is a cell adhesion molecule strengthening synaptic connections of inhibitory GABAergic synapses. Ectopic overexpression of NLGN2 in the hippocampus of adult animals mimicked early-life stress-induced alterations in social behavior and social cognition. Moreover, knockdown of Neuriligin-2 in the adult hippocampus attenuates the observed behavioral changes [Kohl et al., 2015]. Interestingly, KO of the X-linked FMRI gene, a downstream effector of synaptic plasticity which is regulated through GABAergic and glutamatergic signaling, in males leads to a reduced dominance compared with wild-type mice [Pacey et al., 2011]. In addition, an increased tendency to attach juvenile mice [Pietropaolo et al., 2011] in C57BL/6 but not FVB mouse
strains was reported, emphasizing the importance of the specific genetic background.

Glutamatergic signaling is also coupled to the nitric oxide NO second messenger system. Mice lacking NOS1, the main enzyme synthesizing NO, show a reduced AB as measured in male intruder assays and in females during postpartum maternal aggression [Gammie and Nelson, 1999; Le Roy et al., 2000].

Besides classical neurotransmitter pathways, aggression was also related to oxidative stress. Male mice with experimentally elevated sensitivity to oxidative stress as induced through KO of the copper–zinc superoxide dismutase (SOD1), a scavenger enzyme of reactive oxygen species (ROS), showed higher proactive (initiation of fights and reduced attack latency) behavior than both wild-type males and heterozygous KO males [Garratt et al., 2015]. Targeting the ROS producing oxidative phosphorylation (OXPHOS) pathway in bees through inhibition of cytochrome complexes I or V also resulted in an increased aggression. Interestingly, manipulating social structures of honey bee colonies which lead to a decreased individual aggression also attenuated the effects of OXPHOS inhibition on aggression, demonstrating a specific effect of the social environment on brain function. The same study also showed that a cell-specific RNAi-knockdown of complex I in neurons of Drosophila melanogaster resulted in increased aggression, but knockdown in glia had no effect.

**Epigenetics of Aggression**

Twin, targeted genetic, and animal studies suggest that aggression is the product of genetic predisposition and environmental (mainly non-shared) risk factors.

Current hypotheses of environmental factors influencing biological mechanisms include changes of epigenetic patterns. Epigenetic regulation of gene expression includes structural modification of chromatin, post-translational modification of histones including acetylation and methylation, chemical modification of DNA through methylation or hydroxymethylation of cysteins, as well as expression of interfering non-coding RNAs including miRNAs and long-non-coding RNAs. These mechanisms allow reprogramming of the genome upon environmental inputs at specific time-points during development. Among them, predomnately DNA-methylation has been in the focus of stress and aggression research. Studies on post-traumatic stress disorder and on early life-time stress events show a strong effect at the level of DNA-methylation. Provençal and associates have recently published a comprehensive review on the biological origins of physical aggression where they summarized epigenetic changes upon early adversity and significant changes associated with AB itself [Booij et al., 2015]. The authors specifically emphasize the association of chronic physical aggression in men with an elevated level of methylation of regulatory elements of transcription factors and cytokines (e.g., IL-6 interleukin 6) [Provençal et al., 2013a,b]. Association of the inflammatory pathways was also reported to be associated with early-life-time-dependent environmental factors associated with AB such as maternal deprivation in rhesus monkeys, child abuse, socioeconomic status, or PTSD [reviewed in Provençal and Binder, 2015]. Genome-wide approaches performed by Provençal and colleagues associated methylation levels of several gene promoters with chronic physical aggression. Among the most interesting genes, they identified candidates of the serotonergic system (e.g., HTR1D), the dopaminergic system (DAT; SLC63A), the HPA axis (AVPR1A), the glutamatergic system (GRM5) as well as the inflammatory and immune response pathways [Provençal et al., 2014] which were partly overlapping with findings of studies on chronic physical aggression in females. Female-specific differences in methylation patterns were found for HPA associated genes (NR3CI and CRHBP), underlining the gender-specific differences in aggression and stress coping [Guillemin et al., 2014].

Targeted analysis of genes known to be involved in modulation of AB suggests that hypermethylation of the serotonin transporter gene leads to a decreased expression of SLC6A4 and increase the risk for abnormal impulsive aggression [Beach et al., 2011]. Interestingly, this methylation pattern interacts with the 5HTT-LPR genotype risk for abnormal impulsive aggression [Beach et al., 2011]. This directly links maternal stress to epigenetic changes in the HPA system and serotonin signaling. In rats, maternal stress also increased methylation of the promoter of the glucocorticoid receptor which had direct effects on stress responses in the offspring [Meaney and Szyf, 2005].

Peripubertal stress in male rats increased reactive aggression and MAOA expression which was found to be induced through an increased histone-3 but not histone-4 acetylation at the promoter region of the gene. This modification is known to lead to an increased accessibility for transcription factors [Márquez et al., 2013].

In a longitudinal study, comparing monozygous twins discordant for bullying victimization, only siblings that have been bullied showed an increasing methylation of the 5HTT promoter over time, but no increase was observed in the non-bullied siblings. In addition, siblings with higher 5HTT methylation levels had blunted cortisol responses to stress again linking 5HT signaling and HPA response [Ouettel-Morin et al., 2013].

The interaction of genetic risk factors with epigenetic markers has also been identified for the stress response regulatory gene FKBP5 (FK506 binding protein 5). Here, an rs1360780 allele-specific trauma-dependent demethylation of the promoter region is linked to long-term dysregulation of the stress hormone system. In addition, this demethylation had effect on immune cell function and brain areas related to stress coping mechanisms [Klengel et al., 2013]. Similarly, a genetic variant in the GCR gene may directly modify its epigenetic signatures and potentially change its accessibility. Maternal care triggers serotonergic signaling which activates the NGFIA transcription factor. This transcription factor recruits histone acetyl transferase CBP and a DNA modulating protein MBD2 to its targets.
[Hellstrom et al., 2012]. The GR gene harbors such a NGFIA binding site and a functional variant within this region may thus interfere with NGFIA recruitment and explain the association of stress and epigenetic changes in dependence of genotypes [Vukojevic et al., 2014]. This hypothesis is underpinned by the fact that 23–37% of heterozygous SNPs near CpG islands were quantitative methylation loci, that is, an allele-specific methylation level, connecting genetic variation with the epigenome [Shoemaker et al., 2010] and, thus, providing a clue toward genetic predispositions to present abnormal AB upon stress or trauma experiences.

CONCLUSION

Pathological aggression in terms of an extreme end of an evolutionary conserved behavior is not a single factor, but a composite of different behavioral aspects which in combination define reactive and proactive aggression of an individual. From a genetic perspective, we have summarized here that proactive and reactive aggression differ in heritability and, thus, it is very likely that different genetic mechanisms are involved. Here, we have reported functional studies in humans and animals suggesting a model were an overstimulation of the serotonergic and dopaminergic pathways increase measures for aggression that can potentially be attributed to both proactive and reactive aggression. A specific increase in dopamine within the reward associated nucleus accumbens supports the hypothesis that proactive aggression might be related to increased reward anticipation. In parallel, the endocrine systems and specifically the HPA pathway are involved in regulation of impulsivity and stress response, two behavioral aspects closely related to regulation of reactive aggression. Targeted genetic analyses suggest that the overstimulation of the aminergic systems is mainly driven by reduced functionality of the inhibitory pathways, that is, lowered expression of catabolic enzymes and transporters. Similarly, disruption of the endocrine pathways decreases hormonal stress responses. The interaction and fine-tuning of these systems is regulated via direct connections of the transmitter specific brain areas: The dopaminergic system is directly connected to the HPA axis through the tubero-infundibular neurons, and both, the serotonergic and dopaminergic systems signal into hippocampal and cortical areas and are thus directly involved in modulating HPA responses. In addition, the excitatory and inhibitory neurons (i.e., glutamate and gamma-aminobutyric-acid, GABA) connect several brain areas and modulate regional activity. Clear evidence is provided by the fact that ethanol, a positive allosteric modulator of GABA-A receptors, can induce AB in a subset of predisposed individuals [Heinz et al., 2011]. To conclusively state that aminergic pathways are associated with both proactive and reactive forms of aggression while the endocrine system modulates reactive aggression further experimental evidence needs to be presented. To clearly understand pathways-specific effects on selected aspects of AB, the connection between these systems has to be taken into account.

In aggression, twin studies revealed that non-shared environmental factors are as important as genetic factors. In addition, the genetic etiology might be different across age groups. Recent studies try to investigate how these non-genetic risk factors can be translated into biological function. The identification of epigenetic changes triggered by early life events delivered a valuable hypothesis of the environmentally induced behavioral changes. In order to understand, and finally translate into the clinical setting, the genetic architecture behind the stress response and related coping mechanisms need to be investigated, by linking epigenetic and genetic data.

Thus, reviewing the current literature of genetics in aggression, we conclude that the current targeted genetic approaches need to be supported by quantitative and adequately powered, hypotheses free, genome wide SNP, sequencing and epigenetic analyses, including several age groups. This will allow identifying the molecular biology behind multigenic AB. These studies also need to include specific operationalized measures for reactive and proactive aggression and their underlying personality traits such as impulsivity given the potential to elicit a different genetic architecture.

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CONFLICTS OF INTEREST

None of the authors has any conflicts of interest to declare that interfere with any part of this manuscript.

REFERENCES

Ago Y, Araki R, Yano K, Kawasaki T, Chaki S, Nakazato A, Onoe H, Hashimoto H, Baba A, Takuma K, Matsuda T. 2012. The selective metabotropic glutamate 2/3 receptor agonist MGS0028 reverses isolation rearing-induced abnormal behaviors in mice. J Pharmacol Sci 118:295–298.

Ahmed AA, Ma W, Ni Y, Zhou Q, Zhao R. 2014. Embryonic exposure to corticosterone modifies aggressive behavior through alterations of the hypothalamic pituitary adrenal axis and the serotoninergic system in the chicken. Horm Behav 65:97–105.

Alekseyenko OV, Chan YB, Fernandez Mde L, Bülow T, Pankratz MJ, Kravitz EA. 2014. Single serotoninergic neurons that modulate aggression in Drosophila. Curr Biol 24:2700–2707.

Alekseyenko OV, Lee C, Kravitz EA, McCabe BD. 2010. Targeted manipulation of serotoninergic neurotransmission affects the escalation of aggression in adult male Drosophila melanogaster. PLoS ONE 5:e10806.

Aluja A, Garcia LF, Blanch A, Fiba J. 2011. Association of androgen receptor gene, CAG and GGN repeat length polymorphism and impulsivity in alcohol dependent patients. Alcohol Alcohol 46:540–545.

Anney RJ, Ladey-Su J, O’Díushláine C, Kenny E, Neale BM, Mulligan A, Frawley B, Zhou K, Chen W, Christiansen H, Arias-Vásquez A, Banaszewski T, Buitelaar J, Ebstein R, Miranda A, Mulas F, Oades RD, Roeyers H, Rothenberger A, Sergeant J, Sonuga-Barke E, Steinhausen H, Asherson P, Pariante CM, Gill M, Anney Richard J L, O’Díushláine C. 2008. Conduct disorder and ADHD: evaluation of conduct problems as a categorical and quantitative trait in the international multicentre ADHD genetics study. Am J Med Genet Part B 147B:1369–1378.

Ashkal F, Alarcón M, Solomon EC, Masterman D, Geschwind DH, Cummings JL. 2004. Association of the serotonin transporter and receptor gene polymorphisms in neuropsychiatric symptoms in Alzheimer disease. Arch Neurol 61:1249–1253.

Baca-Garcia E, Vaquero C, Díaz-Sastre C, García-Resa E, Saiz-Ruiz J, Fernández-Piqueras J, de Leon J. 2004. Lack of association between the...
serotonin transporter promoter gene polymorphism and impulsivity or aggressive behavior among suicide attempters and healthy volunteers. Psychiatry Res 126:99–106.

Baker LA, Raine A, Liu J, Jacobson KC. 2008. Differential genetic and environmental influences on reactive and proactive aggression in children. J Abnorm Child Psychol 36:1265–1278.

Banlaki Z, Elek Z, Nanasi T, Szekely A, Nemoda Z, Sasvari-Szekely M, Ronai Z, Siegel A. 2015. Polymorphism in the serotonin receptor 2a (HTR2A) gene as possible predispositional factor for aggressive traits. PLoS ONE 10:e0117792.

Barr CS, Driscoll C. 2014. Neurogenetics of aggressive behavior: Studies in primates.Curr Top Behav Neurosci 17:45–71.

Barrett TD, Marcus DK, Barry CT, Coccaro EF. 2013. The latent structure of impulsivity. Nature 468:1061–1066.

Beitchman JH, Mik HM, Ehtesham D, Kennedy JL. 2006. Serotonin transporter polymorphisms and persistent, pervasive childhood aggression. Am J Psychiatry 163:1103–1105.

Beitchman JH, Mik HM, Ehtesham S, Douglas L, Kennedy JL. 2004. MAOA and persistent, pervasive childhood aggression. Mol Psychiatry 9:546–547.

Bell R, Hobson H, Bell R, Hobson H. 1994. 5-HT1A receptor influences on rodent social and agonistic behavior: A review and empirical study. Neurosci Biobehav Rev 18:325–338.

Bevilacqua L, Doly S, Kaprio J, Yuan Q, Tikkanen R, Paunio T, Zhou Z, Bell R, Hobson H. 1994. 5-HT1A receptor influences on the impact of child sex abuse on women’s antisocial behavior: an examination of the Iowa adoptee sample. Psychosom Med 73:83–87.

Banlaki Z, Elek Z, Nanasi T, Szekely A, Nemoda Z, Sasvari-Szekely M, Ronai Z, Siegel A. 2015. Polymorphism in the serotonin receptor 2a (HTR2A) gene as possible predispositional factor for aggressive traits. PLoS ONE 10:e0117792.

Barr CS, Driscoll C. 2014. Neurogenetics of aggressive behavior: Studies in primates. Curr Top Behav Neurosci 17:45–71.

Barrett TD, Marcus DK, Barry CT, Coccaro EF. 2013. The latent structure of impulsivity. Nature 468:1061–1066.

Beitchman JH, Mik HM, Ehtesham S, Douglas L, Kennedy JL. 2004. MAOA and persistent, pervasive childhood aggression. Mol Psychiatry 9:546–547.

Bell R, Hobson H, Bell R, Hobson H. 1994. 5-HT1A receptor influences on rodent social and agonistic behavior: A review and empirical study. Neurosci Biobehav Rev 18:325–338.

Bevilacqua L, Doly S, Kaprio J, Yuan Q, Tikkanen R, Paunio T, Zhou Z, Wedenjoko J, Maroteaux L, Diaz S, Belmer A, Hodgkinson CA, Dell’osso L, Suvisaari J, Coccaro E, Rose RJ, Peltonen L, Virkkunen M, Goldman D. 2010. A population-specific HTR2B stop codon predisposes to severe impulsivity. Nature 468:1061–1066.

Birger M, Swartz M, Cohen D, Alesh Y, Grishpan C, Kotler M. 2003. Aggression: The testosterone-serotonin link. Isr Med Assoc J 5:653–658.

Booij L, Tremlay RE, Kotelr M. 2003. Abnormal behavior associated with a point mutation in the structural gene for monoamine oxidase A. Science 262:578–580.

Burt SA, Donnellan MB. 2009. Development and validation of the subtypes of antisocial behavior questionnaire. Agress Behav 35:376–398.

Burt SA, Klump KL. 2012. Ethological distinctions between aggressive and non-aggressive antisocial behavior: Results from a nuclear twin family model. J Abnorm Child Psychol 40:1059–1071.

Burt SA. 2009. Are there meaningful ethological differences within antisocial behavior? Results of a meta-analysis. Clin Psychol Rev 29:163–178.

Cadoret RJ, Langbehn D, Caspers K, Troughton EP, Yucuis R, Sandhu HK, Philibert R. 2003. Associations of the serotonin transporter promoter polymorphism with aggressiveness, attention deficit, and conduct disorder in an adoptee population. Compr Psychiatry 44:88–101.

Cairns RB, MacCombie DJ, Hood KE. 1983. A developmental-genetic analysis of aggressive behavior in mice: I. Behavioral outcomes. J Comp Psychol 97:69–89.

Callewaert L, Christiaens V, Haedens A, Verrijdt G, Verhoeven G, Claessens F. 2003. Implications of a polyglutamine tract in the function of the human androgen receptor. Biochim Biophys Acta 1606:46–52.

Campbell KM, de Leece L, Severynse DM, Caron MG, McGrath MJ, Sparber SB, Sun LY, Burton FH. 1999. OCD-Like behaviors caused by a neuropotentiating transgene targeted to cortical and limbic D1+ neurons. J Neurosci 19:5044–5053.

Caramaschi D, de Boer SF, Koolhaas JM. 2007. Differential role of the 5-HT1A receptor in aggressive and non-aggressive mice: An across-strain comparison. Physiol Behav 90:590–601.

Caspri A, McCauley J, Moffitt TE, Mill J, Martin J, Craig IW, Taylor A, Poulton R. 2002. Role of genotype in the cycle of violence in maltreated children. Science 297:851–854.

Chamberlain NL, Driver ED, Miesfeld RL. 1994. The length and location of CAG trinucleotide repeats in the androgen receptor N-terminal domain affect transcription function. Nucleic Acids Res 22:3181–3186.

Brown GL, McGarvey EL, Shirliff EA, Keller A, Granger DA, Flavin K. 2008. Salivary cortisol, dehydroepiandrosterone, and testosterone inter-relationships in healthy young males: A pilot study with implications for studies of aggressive behavior. Psychiatry Res 159:67–76.

Brunner HG, Nelen M, Breakefield XO, Ropers HH, van Oost BA. 1993. Abnormal behavior associated with a point mutation in the structural gene for monoamine oxidase A. Science 262:578–580.

Brown GL, McGarvey EL, Shirliff EA, Keller A, Granger DA, Flavin K. 2008. Salivary cortisol, dehydroepiandrosterone, and testosterone inter-relationships in healthy young males: A pilot study with implications for studies of aggressive behavior. Psychiatry Res 159:67–76.
Chichinadze KN, Domianidze TR, Matitaishvili TT, Chichinadze NK, Lazarashvili AG. 2010. Possible relation of plasma testosterone level to aggressive behavior of male prisoners. Bull Exp Biol Med 149:7–9.

Coccaro EF, Kavoussi RJ, Hauger RL, Cooper TB, Ferris CF. 1998. Cerebrospinal fluid vasopressin levels: Correlates with aggression and serotonin function in personality-disordered subjects. Arch Gen Psychiatry 55:708–714.

Coccaro EF, Kavoussi RJ, Trestman RL, Gabriel SM, Cooper TB, Siever LJ. 1997. Serotonin function in human subjects: Intercorrelations among central 5-HT indices and aggressiveness. Psychiatry Res 73:1–14.

Comings DE, Mulheiman D, Johnson JP, MacMurray JP. 2002. Parent-daughter transmission of the androgen receptor gene as an explanation of the effect of father absence on age of manarche. Child Dev 73:1046–1051.

Comings DE, Mulheiman D, Johnson P, MacMurray JP. 1999. Potential role of the estrogen receptor gene (ER1) in anxiety. Mol Psychiatry 4:374–377.

Conner TS, Jensen KP, Tennen H, Furneaux HM, Kranzler HR, Covault J. 2010. Functional polymorphisms in the serotonin 1B receptor gene (HT1RB) predict self-reported anger and hostility among young men. Am J Med Genet Part B 153B:67–78.

Craig D, Hart DJ, Carson R, McLlroy SP, Passmore A, Passmore AP. 2004a. Allelic variation at the A218C tryptophan hydroxylase polymorphism influences agitation and aggression in Alzheimer’s disease. Neurosci Lett 363:199–202.

Craig D, Hart DJ, McCool K, McIlroy SP, Passmore AP. 2004b. Apolipoprotein E e4 allele influences aggressive behaviour in Alzheimer’s disease. J Neurol Neurosurg Psychiatry 75:1327–1330.

Craig IW, Halton KE. 2009. Genetics of human aggressive behaviour. Hum Genet 126:101–113.

Craig IW. 2007. The importance of stress and genetic variation in human aggression. Bioessays 29:227–236.

Crapanzano AM, Frick PJ, Terranova AM. 2010. Patterns of physical and relational aggression in a school-based sample of boys and girls. J Abnorm Child Psychol 38:433–445.

Davidge KM, Atkinson L, Douglas L, Lee V, Shapiro S, Kennedy JL, Beitchman JH. 2004. Association of the serotonin transporter and SHT1Dbeta receptor genes with extreme, persistent and pervasive relational aggression in a school-based sample of boys and girls. J Abnorm Child Psychol 38:433–445.

Deichert J, Catalano M, Syagailo YV, Bosi M, Okladnova O, Di Bella D, Kelemen L, Ogata S, Pharoah PD, Easton DF, Day NE, Ponder BA. 2004. Polymorphisms associated with circulating sex hormone levels in postmenopausal women. J Natl Cancer Inst 96:936–945.

Feldker DE, Datson NA, Veneema AH, Meulmeester E, de Kloet ER, Vreugdenhil E. 2003. Serial analysis of gene expression predicts structural differences in hippocampus of long attack latency and short attack latency mice. Eur J Neurosci 17:379–387.

Ferris CF, Lu S, Messenger T, Guillon CD, Heindel N, Miller M, Koppel G, Robert Bruns F, Simon NG. 2006. Orally active vasopressin V1a receptor antagonist, SRX251, selectively blocks aggressive behavior. PharmacoBiosci Behav 83:169–174.

Ferris CF, Melloni RH, Koppel G, Perry KW, Fuller RW, Delville Y. 1997. Vasopressin/serotonin interactions in the anterior hypothalamus control aggressive behavior in golden hamsters. J Neurosci 17:4331–4340.

Fischer SG, Ricci LA, Melloni RH. 2007. Repeated anabolic/androgenic steroid exposure during adolescence alters phospho-activated glutaminase and glutamate receptor 1 (GluR1) subunit immunoreactivity in Hamster brain: Correlation with offensive aggression. Behav Brain Res 180:77–85.

Frazzetto G, Di Lorenzo G, Carola V, Proietti L, Sokolowska E, Siracusano A, Gross C, Troisi A. 2007. Early trauma and increased risk for physical aggression during adulthood: The moderating role of MAOA genotype. PLoS ONE 2:e486.

Fung AL, Raine A, Gao Y. 2009. Cross-cultural generalizability of the reactive-proactive aggression questionnaire (RPQ). J Pers Assess 91:473–479.

Gammie SC, Nelson RJ. 1999. Maternal aggression is reduced in neuronal nitric oxide synthase-deficient mice. J Neurosci 19:8027–8035.

Gariépy JL, Hood KE, Cairns RB. 1988. A developmental-genetic analysis of aggressive behavior in mice (Mus musculus): III. Behavioral mediation by heightened reactivity or immobility? J Comp Psychol 102:392–399.

Garratt M, Brooks RC, Garratt M, Brooks RC. 2015. A genetic reduction in antioxidant function causes elevated aggression in mice. J Exp Biol 218:223–227.

Georgiev AV, Klimczuk Amanda CE, Traficante DM, Maestripieri D. 2013. When violence pays: A cost-benefit analysis of aggressive behavior in animals and humans. Evol Psychol 11:678–699.

Gerra G, Garofano L, Pellegrini C, Bosari S, Zaimovic A, Miot G, Avanzini P, Talarico E, Gardini F, Donnini C. 2005. Allelic association of a dopamine transporter gene polymorphism with antisocial behaviour in heroin-dependent patients. Addict Biol 10:275–281.

Giegling I, Hartmann AM, Möller H, Rujescu D. 2006. Anger- and aggression-related traits are associated with polymorphisms in the 5-HT-2A gene. J Affect Disord 96:75–81.

Gietl A, Giegling I, Hartmann AM, Schneider B, Schnabel A, Maurer K, Kohler H, Rujescu D, Moller H, Rujescu D. 2007. Genetic dissection of intermale aggressive behavior in BALB/cj and A/J mice. Genes Brain Behav 10:57–68.

Gimel F, Dreyer J, Kohn P, Kolachana B, Weinberger DR, Berman KF. 2009. Variation in dopamine genes influences responsivity of the human reward system. Proc Natl Acad Sci USA 106:617–622.

Gogos JA, Morgan M, Luine V, Santha M, Ogawa S, Pfaff D, Karayiorgou M. 1998. Catechol-O-methyltransferase-deficient mice exhibit sexually dimorphic changes in catecholamine levels and behavior. Proc Natl Acad Sci USA 95:9991–9996.

Gorodetsky E, Bevilacqua L, Carli V, Sarchiapone M, Roy A, Goldman D, Enoch M. 2014. The interactive effect of MAOA -LPR genotype and childhood physical neglect on aggressive behaviors in Italian male prisoners. Genes Brain Behav 13:543–549.
Griffiths-Jones S, Saini HK, van Dongen S, Enright AJ. 2008. MiRBase: Tools for microRNA genomics. Nucleic Acids Res 36:D154–D158.

Griffiths-Jones S. 2006. MiRBase: The microRNA sequence database. Methods Mol Biol 342:129–138.

Guerin AA, Beitchman JH, Strauss J, Kennedy JL. 2007. Association study of the brain-derived neurotrophic factor gene and childhood aggression. Psychiatr Genet 17:7–8.

Guillen C, Provençal N, Suderman M, Coté SM, Vitaro F, Hallett M, Tremblay RE, Szyf M, Marois CJ. 2014. DNA methylation signature of childhood chronic physical aggression in T cells of both men and women. PLoS ONE 9:e86822.

Guo G, Ou X, Roettger M, Shih JC. 2008. The VNTR 2 repeat in MAOA and delinquent behavior in adolescence and young adulthood: associations and MAOA promoter activity. Eur J Hum Genet 16:626–634.

Gutknecht L, Waider J, Kraft S, Kriegebaum C, Holmstén B, Reif A, Schmitt A, Lesch K. 2008. Deficiency of brain 5-HT synthesis but serotonergic neuron formation in Tph2 knockout mice. J Neurotransm 115:1127–1132.

Haberstick BC, Smolen A, Hewitt JK. 2006. Family-based association test of the 5HTTLPR and aggressive behavior in a general population sample of children. Biol Psychiatry 59:836–843.

Hakulinen C, Jokela M, Hintsenan M, Merjionen P, Pulikki-Räback A, Seppälä I, Lyytiäinen L, Lehtimäki T, Kähönen M, Viikari J, Raitakari OT, Keltikangas-Järvinen L. 2013. Serotonin receptor 1B genotype and hostility, anger and aggressive behavior through the lifespan: The Young Finns study. J Behav Med 36:583–590.

Halmøy A, Johansson S, Winge I, McKinney JA, Knappskog PM, Haavik J. 2013. Serotonin receptor 1B genotype and hostility, anger and aggressive behavior through the lifespan: The Young Finns study. J Behav Med 36:583–590.

Hallerie CM, Langley K, Martin J, Agha SS, Stergiakoulou E, Anney RJ, Builetta J, Faraone SV, Lesch K, Neale BM, Franke B, Sonuga-Barke E, Asherson P, Merwood A, Kuntsi J, Medland SE, Ripke S, Steinhausen H, Freitag C, Harmony N, Mauri P, Wiesmann U, Kokkevi A, Huizinga A, Rothenberger A, Banaschewski T, Aukes RD, McGough JJ, Kent L, Williams N, Owen MJ, Holmans P, O’Donovan MC, Thapar A, Biederman J, Doyle AE, Hakonarson H, Rothenberger A, Banaschewski T, Oades RD, Kranzler HR, Furneaux HM. 2009. A common polymorphism in serotonin receptor 1B mRNA regulates regulation by miR-96 and associates with aggressive human behaviors. Mol Psychiatry 14:381–389.

Kalugutkar AS, Dalvie DK, Castagnoli N, Taylor TJ. 2001. Interactions of nitric-oxide containing xenobiotics with monoamine oxidase (MAO) isoenzymes A and B: SAR studies on MAO substrates and inhibitors. Chem Res Toxicol 14:139–146.

Kelley MK, Howe TR, Dodge KA, Bates JE, Petts GS. 2001. The timing of child physical maltreatment: A cross-domain growth analysis of impact on adolescent externalizing and internalizing problems. Dev Psychopathol 13:891–912.

Kempes M, Matthys W, de Vries H, van Engeland H. 2005. Reactive and proactive aggression in children—a review of theory, findings and the relevance for child and adolescent psychiatry. Eur Child Adolesc Psychiatry 14:11–19.

Kendler KS, Aggen SH, Patrick CJ. 2013. Familial influences on conduct disorder reflect 2 genetic factors and 1 shared environmental factor. JAMA Psychiatry 70:78–86.

Kenneth Sandnabba N. 1985. Differences in the capacity of male odours to affect investigatory behaviour and different urinary marking patterns in two strains of mice, selectively bred for high and low aggressiveness. Behav Processes 11:257–267.

Kim-Cohen J, Caspi A, Taylor A, Williams B, Newcombe R, Craig IW, Moffitt TE. 2006. MAOA, maltreatment, and gene-environment interaction predicting children’s mental health: New evidence and a meta-analysis. Mol Psychiatry 11:903–913.

Klingel T, Mehta D, Anacker C, Rex-Haffner M, Pruessner JC, Pariente CM, Pace TW, Mercer KB, Mayberg HS, Bradley B, Nemeroff CB, Holbofer F, Heim CM, Ressler KJ, Rein T, Binder EB. 2013. Allele-specific FKB5P3 DNA demethylation mediates gene-childhood trauma interactions. Nature Neurosci 16:33–41.

Klok MD, Giltay EJ, Van der Does AJW, Geleijnse JM, Antypa N, Penninx BW, de Geus EJ, Willemgen G, Boomsma DI, van Leeuwen N, Zitman FG, de Kloet ER, DeRijk RH. 2011. A common and functional mineralocorticoid receptor haplotype enhances optimism and protects against depression in females. Transl Psychiatry 1:e62.

Kohl C, Wang X, Grosse J, Fournier C, Harbich D, Westerholz S, Li J, Baqc A, Sippel C, Hausch F, Sandi C, Schmidt MV. 2015. Hippocampal neuroligin-2 Links early-life stress with impaired social recognition and...
increased aggression in adult mice. Psychoneuroendocrinology 55:128–143.

Kolla NJ, Attard S, Craig G, Blackwood N, Hodgins S. 2014. Monoamine oxidase A alleles in violent offenders with antisocial personality disorder: high activity associated with proactive aggression. Crim Behav Ment Health 24:368–372.

Koshimizu T, Nakamura K, Egashira N, Hiroyama M, Nonoguchi H, Tanoue A. 2012. Vasopressin V1a and V1b receptors: From molecules to physiological systems. Physiol Rev 92:1813–1864.

Kovacs-Nagy R, Elek Z, Szekely A, Nanasi T, Sasvari-Szekely M, Ronai Z. 2013. Association of aggression with a novel microRNA binding site polymorphism in the wolframin gene. Am J Med Genet Part B 162B:404–412.

Kretschmer T, Vitaro F, Barker ED. 2014. The association between peer and own aggression is moderated by the BDNF val–met polymorphism. J Res Adolesc 24:177–185.

Krugers HJ, Hoogenraad CC, Groc L. 2010. Stress hormones and AMPA receptor trafficking in synaptic plasticity and memory. Nature reviews. Neuroscience 11:675–681.

Kudiela BM, Wüst S. 2010. Human models in acute and chronic stress: assessing determinants of individual hypothalamus-pituitary-adrenal axis activity and reactivity. Stress 13:1–14.

Kuepper Y, Grant P, Wiel pactz C, Henning J. 2013. MAOA-uVNTR genotype predicts interindvidual differences in experimental aggressiveness as a function of the degree of provocation. Behav Brain Res 247:73–78.

Lachman HM. 2008. Does COMT Val158met affect behavioral phenotypes? Yes, no, maybe? Neuropsychopharmacology 33:3027–3029.

Lacourse E, Boivin M, Brendgen M, Petitclerc A, Girard A, Vitaro F, Paquin S, Ouellet-Morin I, Dionne G, Tremblay RE. 2014. A longitudinal twin study of physical aggression during early childhood: Evidence for a developmentally dynamic genome. Psychol Med 44:2617–2627.

Lam LCW, Tang NLS, Ma SL, Zhang W, Chiu HFK. 2004. 5-HT2A T102C receptor polymorphism and neuropsychiatric symptoms in Alzheimer’s disease. Int J Geriatr Psychiatry 19:523–526.

Le Roy I, Pothion S, Mortaud S, Chabert C, Nicolas L, Cherfouh A, Roubertoux PL. 2000. Loss of aggression, after transfer onto a C57BL/6J background, in mice carrying a targeted disruption of the neuronal nitric oxide synthase gene. Behav Genet 30:367–373.

Lemonde S, Turecki G, Bakish D, Du L, Hrdina PD, Sequeira A, Kushwaha N, Morris SJ, Basak A, Ou X, Albert PR. 2003. Impaired repression at a 5-hydroxytryptamine 1A receptor gene polymorphism associated with major depression and suicide. J Neurosci 23:8788–8799.

Lesch K, Araragi N, Waider J, van den Hove D, Gutknecht L, Lesch K, Araragi N, Waider J, van den Hove D, Gutknecht LK. 2012. Targeting brain serotonin synthesis: Insights into neurodevelopmental disorders with long-term outcomes related to negative emotionality, aggression and antisocial behaviour. Philos Trans R Soc B Biol Sci 367:2426–2443.

Lesch KP, Bengel D, Heils A, Sabol SZ, Greenberg BD, Petri S, Benjamin J, Müller CR, Hamer DH, Murphy DL. 1996. Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. Science 274:1527–1531.

Lewis MH, Gariepy JL, Gendreau P, Nichols DE, Mailman RB. 1994. Social reactivity and D1 dopamine receptors: Studies in mice selectively bred for high and low levels of aggression. Neuropsychopharmacology 10:115–122.

Loney BR, Butler MA, Lima EN, Counts CA, Eckel LA. 2006. The relation between salivary cortisol, callous-unemotional traits, and conduct problems in an adolescent non-referred sample. J Child Psychol Psychiatr 47:30–36.

Lundin KB, Giwercman A, Dizeyy N, Giwercman YL. 2007. Functional in vitro characterisation of the androgen receptor GGN polymorphism. Mol Cell Endocrinol 264:184–187.

Luppino D, Moul C, Hawes DJ, Brennan J, Dadds MR. 2014. Association between a polymorphism of the vasopressin 1B receptor gene and aggression in children. Psychiatr Genet 24:185–190.

Malik AI, Zai CC, Abu Z, Nowrouzi B, Beitchman JH. 2012. The role of oxytocin and oxytocin receptor gene variants in childhood-onset aggression. Genes Brain Behav 11:345–351.

Malki K, Pain O, Du Rietz E, Tosto MG, Paya-Cano J, Sandnabba KN, Boer de S, Schalkwyk LC, Sluyter F. 2014. Genes and gene networks implicated in aggression related behaviour. Neurogenetics 15:255–266.

Manuck SB, Flory JD, Ferrell RE, Dent KM, Mann JJ, Muldoon MF. 1999. Aggression and anger-related traits associated with a polymorphism of the tryptophan hydroxylase gene. Biol Psychiatry 45:603–614.

Manuck SB, Flory JD, Ferrell RE, Mann JJ, Muldoon MF. 2000. A regulatory polymorphism of the monoamine oxidase-A gene may be associated with variability in aggression, impulsivity, and central nervous system serotonergic responsiveness. Psychiatr Res 95:9–23.

Marino MD, Bourdèl-Parks BN, Cameron Liles W, Weisheiner D. 2005. Genetic reduction of noradrenergic function alters social memory and reduces aggression in mice. Behav Brain Res 161:197–203.

Márquez C, Poirier GL, Cordero MI, Larsen MH, Groner A, Marquis J, Magistretti PJ, Trono D, Sandi C. 2013. Peripubert stress leads to abnormal aggression, altered amygdala and orbitofrontal reactivity and increased prefrontal MAOA gene expression. Transl Psychiatry 3: e216.

Marsee MA, Barry CT, Childs KK, Frick PJ, Kinon ER, Muñoz LC, Aucoin KJ, Fassnacht GM, Kunimatsu MM, Lau KS. 2011. Assessing the forms and functions of aggression using self-report: Factor structure and invariance of the Peer Conflict Scale in youths. Psychol Assess 23:792–804.

Marsee MA, Frick PJ, Barry CT, Kinon ER, Muñoz Centifanti LC, Aucoin KJ. 2014. Profiles of the forms and functions of self-reported aggression in three adolescent samples. Dev Psychopathol 26:705–720.

Mathias CW, Stanford MS, Marsh DM, Frick PJ, Moeller FG, Swann AC, Dougherty DM. 2007. Characterizing aggressive behavior with the impulsive/premeditated aggression scale among adolescents with conduct disorder. Psychiatry Res 151:231–242.

McDermott R, Tingley D, Cowden J, Frazzetto G, Johnson DD. 2009. Monoamine oxidase A gene (MAOA) predicts behavioral aggression following provocation. Proc Natl Acad Sci USA 106:2118–2123.

Meaney MJ, Szfy M. 2005. Environmental programming of stress responses through DNA methylation: Life at the interface between a dynamic environment and a fixed genome. Dialogues Clin Neurosci 7:103–123.

Michopoulos V, Checchi M, Sharpe D, Wilson ME. 2011. Estradiol effects on behavior and serum oxytocin are modified by social status and polymorphisms in the serotonin transporter gene in female rhesus monkeys. Horm Behav 59:528–535.

Mick E, McGough J, Deutsch CK, Frazier JA, Kennedy D, Goldberg RJ, Reif A. 2014. Genome-wide association study of proneness to anger. PLoS ONE 9:e87257.

Miczek KA, de Almeida RMM, Kravitz EA, Rissman EF, de Boer SF, Raine A, Miczek KA, de Almeida RM, Kravitz EA, Rissman EF, de Boer SF, Raine A. 2007. Neurobiology of escalated aggression and violence. J Neurosci 27:11803–11806.

Mongillo DL, Kosyachkova EA, Nguyen TM, Holmes MM. 2014. Differential effects of chronic fluoxetine on the behavior of dominant and subordinate naked mole-rats. Behav Brain Res 258:119–126.
Monuteaux MC, Biederman J, Doyle AE, Mick E, Faroane SV. 2009. Genetic risk for conduct disorder symptom subtypes in an ADHD sample: specificity to aggressive symptoms. J Am Acad Child Adolesc Psychiatry 48:757–764.

Muglia L, Jacobson L, Dikkes P, Majzoub JA. 1995. Corticotropin-releasing hormone deficiency reveals major fetal but not adult glucocorticoid need. Nature 373:427–432.

Naumenko VS, Kondaurova EM, Bazovkina DV, Trybko AS, Il’chibaeva TV, Popova NK. 2014. On the role of 5-HT(1A) receptor gene in behavioral effect of brain-derived neurotrophic factor. J Neurosci Res 92:1035–1043.

Navarro JF, de Castro V, Martín-Lopez M. 2008. JN16259685, a selective mGlu1 antagonist, suppresses isolation-induced aggression in male mice. Eur J Pharmacol 586:217–220.

Navarro JF, Postigo D, Martin M, Burón E. 2006. Antiaggressive effects of MPEP, a selective antagonist of mGlu5 receptors, in agonistic interactions between male mice. Eur J Pharmacol 551:67–70.

Nebigil CG, Etienne N, Schaerlinger B, Hickel P, Launay JM, Maroteaux L, Launay J, Popova NK. 2009. C1473G polymorphism in mouse tph2 gene is linked to tryptophan hydroxylase-2 activity in the brain, intermale aggression, and depressive-like behavior in the forced swim test. J Neurosci Res 87:1168–1174.

Ouellet-Morin I, Wong C Y C, Danese A, Pariante CM, Papadopoulos AS, Mill J, Arseneault L, Wong C CY. 2013. Increased serotonin transporter gene (SERT) DNA methylation is associated with bullying victimization and blunted cortisol response to stress in childhood: A longitudinal study of discordant monozygotic twins. Psychol Med 43:1813–1823.

Pacey LK, Doss L, Cifelli C, van der Kooy D, Hexemer SP, Hampson DR. 2011. Genetic deletion of regulator of G-protein signaling 4 (RGS4) rescues a subset of fragile X related phenotypes in the FMR1 knockout mouse. Mol Cell Neurosci 46:563–572.

Pappa I, St Pourcain B, Benke K, Cavadino A, Hakulinen C, Nivard MG, Nolte IM, Tiessler CM, Bakermans-Kranenburg MJ, Davies GE, Evans DM, Geoffroy M, Grallert H, Groen-Blokhuiss MM, Hudziak JJ, Kemp JP, Keltikangas-Järvinen L, Mcmahon G, Mivea-Seitz VR, Motazed E, Power C, Raitakari OT, Ring SM, Rivadeneira F, Rodriguez A, Scheet PA, Seppalä I, Snieder H, Standl M, Thiering E, Timpson NJ, Veena R, Velders FP, Whitehouse AJ, Smith GD, Heinrich J, Hypponen E, Lehtimäki T, Middeldorp CM, Oldehinkel AJ, Pennell CE, Boomsma DI, Tiemeier H. 2015. A genome-wide approach to children’s aggressive behavior: The EAGLE consortium. Am J Med Genet Part B Neuropsychiatr Genet [Epub ahead of print]. PubmedID 26087016.

Pavlov KA, Chistiakov DA, Chekhonin VP. 2012. Genetic determinants of aggression and impulsivity in humans. J Appl Genetics 53:61–82.

Perez-Rodriguez M, Weinstein S, New AS, Bevilacqua L, Yuan Q, Zhou H, Hodgkinson C, Goodman M, Koenigsburg HW, Goldman D, Siever LJ, Perez-Rodriguez MM. 2010. Tryptophan-hydroxylase 2 haplotype association with borderline personality disorder and aggression in a sample of patients with personality disorders and healthy controls. J Psychiatr Res 44:1075–1081.

Perroud N, Jaussent I, Guillaume S, Bellivier F, Baud P, Jollant F, Leboyer M, Lewis CM, Malafosse A, Courtet P. 2010. COMT but not serotonin-related genes modulates the influence of childhood abuse on anger traits. Genes Brain Behav 9:193–202.

Pietropaolo S, Guillemintot A, Martin B, D’Amato FR, Crucio WE. 2011. Genetic-background modulation of core and variable autistcic symptons in Fmr1 knock-out mice. PLoS ONE 6:e17073.

Pivonello R, Feron D, Lombardi G, Colao A, Lamberts SW, Hoffland LJ. 2007. Novel insights in dopamine receptor physiology. Eur J Endocrinol 156(Suppl 1):S13–S21.

Popma A, Doreleijers TA, Jansen LM, Van Goozen SH, van Engeland H, Vermeiren R. 2007. The diurnal cortisol cycle in delinquent male adolescents and normal controls. Neuropsychopharmacology 32:1622–1628.

Praschak-Rieder N, Kennedy J, Wilson AA, Hussey D, Boovariwala A, Willeit M, Ginovart N, Tharmalingam S, Maselli M, Houle S, Meyer JH. 2007. Novel 5-HTTLPR allele associates with higher serotonin transporter binding in putamen: a [(11)C] DASB positron emission tomography study. Biol Psychiatry 62:327–331.

Preuss UW, Koller G, Bondy B, Bahmann M, Soyka M. 2001. Impulsive traits and 5-HT2A receptor promoter polymorphism in alcohol dependent persons: possible association but no influence of personality disorders. Neuropsychobiology 43:186–191.

Prichard ZM, Jorm AF, Mackinnon A, Eastell S. 2007. Association analysis of 15 polymorphisms within 10 candidate genes for antisocial behaviourial traits. Psychiatr Genet 17:299–303.
Pritchard AL, Harris J, Pritchard CW, Coates J, Haque S, Holder R, Bentham P, Lendon CL. 2008. Role of 5HT 2A and 5HT 2C polymorphisms in behavioural and psychological symptoms of Alzheimer’s disease. Neurobiol Aging 29:341–347.

Provençal N, Binder EB. 2015. The neurobiological effects of stress as contributors to psychiatric disorders: Focus on epigenetics. Curr Opin Neurobiol 30:31–37.

Provençal N, Suderman MJ, Caramaschi D, Wang D, Hallett M, Vitaro F, Tremblay RE, Syzf M, Clelland JD. 2013a. Differential DNA methylation regions in cytokine and transcription factor genomic loci associate with childhood physical aggression. PLoS ONE 8:e71691.

Provençal N, Suderman MJ, Guillemot C, Vitaro F, Côté SM, Hallett M, Tremblay RE, Syzf M, Clelland JD. 2014. Association of childhood chronic physical aggression with a DNA methylation signature in adult human T cells. PLoS ONE 9:e89839.

Provençal N, Suderman MJ, Vitaro F, Syzf M, Tremblay RE, Clelland JD. 2013b. Childhood chronic physical aggression associates with adult cytokine levels in plasma. PLoS ONE 8:e69481.

Raabe FJ, Spengler D. 2013. Epigenetic risk factors in PTSD and depression. Front Psychiatry 4:80.

Raijender S, Pandu G, Sharma JD, Gandhi KPC, Singh L, Thangaraj K. 2008. Reduced CAG repeats length in androgen receptor gene is associated with violent criminal behavior. Int J Legal Med 122:367–372.

Ramírez J. 2000. Animal models in the research of human aggression. Aggress Violent Behav 5:281–290.

Ramírez JM, Andreu JM. 2006. Aggression, and some related psychological traits of suicidal behavior. Int J Legal Med 122:367–372.

Rama˜n JM, Andreu JM. 2006. Aggression, and some related psychological traits of suicidal behavior. Int J Legal Med 122:367–372.

Ramey J. 2000. Human T cells. PLoS ONE 9:e89839.

Ramirez J. 2000. Aggression Violent Behav 5:281–290.

Ramirez JM, Andreu JM. 2006. Aggression, and some related psychological constructs (anger, hostility, and impulsivity); some comments from a research project. Neurosci Biobehav Rev 30:276–291.

Reefj, Diamantopoulos S, van Meurs J, Verhulst FC, van der Ende J. 2013a. Association of childhood chronic physical aggression with a DNA methylation signature in adult human T cells. PLoS ONE 9:e89839.

Reefj, Diamantopoulos S, van Meurs J, Verhulst FC, van der Ende J. 2013b. Childhood chronic physical aggression associates with adult cytokine levels in plasma. PLoS ONE 8:e69481.

Raabe FJ, Spengler D. 2013. Epigenetic risk factors in PTSD and depression. Front Psychiatry 4:80.

Rajender S, Pandu G, Sharma JD, Gandhi KPC, Singh L, Thangaraj K. 2008. Reduced CAG repeats length in androgen receptor gene is associated with violent criminal behavior. Int J Legal Med 122:367–372.

Ramirez J. 2000. Animal models in the research of human aggression. Aggress Violent Behav 5:281–290.

Ramirez JM, Andreu JM. 2006. Aggression, and some related psychological constructs (anger, hostility, and impulsivity); some comments from a research project. Neurosci Biobehav Rev 30:276–291.

Reefj, Diamantopoulos S, van Meurs J, Verhulst FC, van der Ende J. 2013a. Association of childhood chronic physical aggression with a DNA methylation signature in adult human T cells. PLoS ONE 9:e89839.

Reefj, Diamantopoulos S, van Meurs J, Verhulst FC, van der Ende J. 2013b. Childhood chronic physical aggression associates with adult cytokine levels in plasma. PLoS ONE 8:e69481.

Raabe FJ, Spengler D. 2013. Epigenetic risk factors in PTSD and depression. Front Psychiatry 4:80.

Rajender S, Pandu G, Sharma JD, Gandhi KPC, Singh L, Thangaraj K. 2008. Reduced CAG repeats length in androgen receptor gene is associated with violent criminal behavior. Int J Legal Med 122:367–372.

Ramirez J. 2000. Animal models in the research of human aggression. Aggress Violent Behav 5:281–290.

Ramirez JM, Andreu JM. 2006. Aggression, and some related psychological constructs (anger, hostility, and impulsivity); some comments from a research project. Neurosci Biobehav Rev 30:276–291.

Reefj, Diamantopoulos S, van Meurs J, Verhulst FC, van der Ende J. 2013a. Association of childhood chronic physical aggression with a DNA methylation signature in adult human T cells. PLoS ONE 9:e89839.

Reefj, Diamantopoulos S, van Meurs J, Verhulst FC, van der Ende J. 2013b. Childhood chronic physical aggression associates with adult cytokine levels in plasma. PLoS ONE 8:e69481.

Raabe FJ, Spengler D. 2013. Epigenetic risk factors in PTSD and depression. Front Psychiatry 4:80.

Rajender S, Pandu G, Sharma JD, Gandhi KPC, Singh L, Thangaraj K. 2008. Reduced CAG repeats length in androgen receptor gene is associated with violent criminal behavior. Int J Legal Med 122:367–372.

Ramirez J. 2000. Animal models in the research of human aggression. Aggress Violent Behav 5:281–290.

Ramirez JM, Andreu JM. 2006. Aggression, and some related psychological constructs (anger, hostility, and impulsivity); some comments from a research project. Neurosci Biobehav Rev 30:276–291.

Reefj, Diamantopoulos S, van Meurs J, Verhulst FC, van der Ende J. 2013a. Association of childhood chronic physical aggression with a DNA methylation signature in adult human T cells. PLoS ONE 9:e89839.

Reefj, Diamantopoulos S, van Meurs J, Verhulst FC, van der Ende J. 2013b. Childhood chronic physical aggression associates with adult cytokine levels in plasma. PLoS ONE 8:e69481.
Vekovischeva OY, Aitta-Aho T, Echenko O, Mössner R, Zeng Y, Brocke B, Lesch K, Mössner R, Lesch K. 2003. Allelic variation in 5-HT1A receptor expression is associated with anxiety- and depression-related personality traits. J Neural Transm 110:1445–1453.

Sweet RA, Nimgaonkar VL, Kamboh MI, Lopez OL, Zhang F, DeKosky ST. 1998. Dopamine receptor genetic variation, psychosis, and aggression in Alzheimer disease. Arch Neurol 55:1335–1340.

Takahashi A, Micek KA. 2014. Neurogenetics of aggressive behavior: Studies in rodents. Curr Top Behav Neurosci 17:3–44.

Takahashi A, Shiroishi T, Koidi T. 2014. Genetic mapping of escalated aggression in wild-derived mouse strain MSM/Ms: Association with serotonin-related genes. Front Neurosci 8:156.

Temchek CE, Serbin LA, Martin-Storey A, Stack DM, Hastings P, Ledingham J, Schwartzman AE. 2011. Childhood aggression, withdrawal and likeability, and the use of health care later: A longitudinal study. CMAJ 183:2095–2101.

Thornton LC, Frick PJ, Crapanzano AM, Terranova AM. 2013. The incremental utility of callous-unemotional traits and conduct problems in predicting aggression and bullying in a community sample of boys and girls. Psychol Assess 25:366–378.

Tiihonen J, Rautiainen M, Ollila HM, Repo-Tiihonen E, Virkkunen M, Tiihonen J, Honkanen A, Sprengel R, Korpi ER. 2004. Reduced aggression in AMPA-R1 deficient mice. Ann NY Acad Sci 1018:255–265.

Veenema AH, Neumann ID. 2007. Neurobiological mechanisms of aggression and stress coping: A comparative study in mouse and rat selection lines. Brain Behav Evol 70:274–285.

Venihami M, Majzoub J. 2002. Lessons from CRH knockout mice. Neuropeptides 36:96–102.

Victoria EFA, Booj J, Krujit A, Cerit H, Antypa N, Does W. 2012. The effects of MAOA genotype, childhood trauma, and sex on trait and state-dependent aggression. Brain Behav 2:806–813.

Vermeersch H, T’Sjoen G, Kaufman JM, Vincke j, van Houtte M. 2010. Testosterone, androgen receptor gene CAG repeat length, mood and behaviour in adolescent males. Eur J Endocrinol 163:319–328.

Vishnivetskaya GB, Skrinskyaya JA, Seif I, Popova NK. 2007. Effect of MAOA deficiency on different kinds of aggression and social investigation in mice. Aggr Behav 33:1–6.

Volavka J, Bilder R, Nolan K. 2004. Catecholamines and aggression: The role of COMT and MAO polymorphisms. Ann NY Acad Sci 1036:393–398.

Vukovic V, Kolassa I, Fastenrath M, Gschwind L, Spalek K, Milnik A, Heck A, Vogler C, Wilker S, Demougin P, Peter F, Atucha E, Stetak A, Roodzaenda B, Elbert T, Papasotropoulos A, de Quervain DJ. 2014. Epigenetic modification of the glucocorticoid receptor gene is linked to traumatic memory and post-traumatic stress disorder risk in genocide survivors. J Neurosci 34:10274–10284.

Wagner S, Baskaya O, Dahmen N, Lieb K, Tadić A. 2010. Modulatory role of the brain-derived neurotrophic factor Val66Met polymorphism on the effects of serious life events on impulsive aggression in borderline personality disorder. Genes Brain Behav 9:97–102.

Walters GD, Ruscio J. 2013. Trajectories of youthful antisocial behavior: Categories or continua? J Abnorm Child Psychol 41:653–666.

Walton KE, Ormel J, Krueger RF. 2011. The dimensional nature of externalizing behaviors in adolescence: Evidence from a direct comparison of categorical, dimensional, and hybrid models. J Abnorm Child Psychol 39:553–561.

Wang P, Niv S, Tuublud C, Raine A, Baker LA. 2013. The genetic and environmental overlap between aggressive and non-aggressive antisocial behavior in children and adolescents using the self-report delinquency interview (SR-DI). J Crim Justice 41:277–284.

Weder N, Yang BZ, Douglas-Palumberi H, Massey J, Krystal JH, Gelernter J, Kaufman J. 2009. MAOA genotype, maltreatment, and aggressive behavior: The changing impact of genotype at varying levels of trauma. Biol Psychiatry 65:417–424.

Wersinger SR, Ginns EI, O’Carroll A, Lolait SJ, Young WS. 2002. Vasopressin V1b receptor knockout reduces aggressive behavior in male mice. Mol Psychiatry 7:975–984.

Wilson M, Daly M. 1985. Competitiveness, risk taking, and violence: The young male syndrome. Ethol Sociobiol 6:59–73.

Yeh MT, Coccaro EF, Jacobson KC. 2010. Multivariate behavior genetic analyses of aggressive behavior subtypes. Behav Genet 40:603–617.

Young SE, Smolen A, Corley RP, Krauter KS, DeFries JC, Crowley TJ, Hewitt JK. 2002. Dopamine transporter polymorphism associated with externalizing behavior problems in children. Am J Med Genet 114:144–149.

Young WS, Shepard E, DeVries AC, Zimmer A, DeFries JC, Lalonde J, M. Emil, Amico J, Nelson RJ, Hemmingshausen L, Wagner J. 1998. Targeted reduction of oxytocin expression provides insights into its physiological roles. Adv Exp Med Biol 449:231–240.
Yu Y, Shi J. 2009. Relationship between levels of testosterone and cortisol in saliva and aggressive behaviors of adolescents. Biomed Environ Sci 22:44–49.

Zabetian CP, Anderson GM, Buxbaum SG, Elston RC, Ichinose H, Nagatsu T, Kim KS, Kim CH, Malison RT, Gelernter J, Cubells JF. 2001. A quantitative-trait analysis of human plasma-dopamine beta-hydroxylase activity: Evidence for a major functional polymorphism at the DBH locus. Am J Hum Genet 68:515–522.

Zabetian CP, Buxbaum SG, Elston RC, Köhnke MD, Anderson GM, Gelernter J, Cubells JF. 2003. The structure of linkage disequilibrium at the DBH locus strongly influences the magnitude of association between diallelic markers and plasma dopamine beta-hydroxylase activity. Am J Hum Genet 72:1389–1400.

Zai CC, Ehtesham S, Choi E, Nowrouzi B, de Luca V, Stankovich L, Freeman K, King N, Kennedy N, Beitchman JL, Beitchman JH. 2012a. Dopaminergic system genes in childhood aggression: Possible role for DRD2. World J Biol Psychiatry 13:65–74.

Zai CC, Muir KE, Nowrouzi B, Shaikh SA, Choi E, Berall L, Trépanier M, Beitchman JH, Kennedy JL. 2012b. Possible genetic association between vasopressin receptor 1B and child aggression. Psychiatry Research 200:784–788.

Zhao X, Sun L, Jia H, Meng Q, Wu S, Li N, He S. 2009. Isolation rearing induces social and emotional function abnormalities and alters glutamate and neurodevelopment-related gene expression in rats. Prog Neuropsychopharmacol Biol Psychiatry 33:1173–1177.

Zhou Z, Roy A, Lipsky R, Kuchipudi K, Zhu G, Taubman J, Enoch M, Virkkunen M, Goldman D. 2005. Haplotype-based linkage of tryptophan hydroxylase 2 to suicide attempt, major depression, and cerebrospinal fluid 5-hydroxyindoleacetic acid in 4 populations. Arch Gen Psychiatry 62:1109–1118.

Zill P, Büttner A, Eisenmenger W, Möller H, Ackenheil M, Bondy B. 2007. Analysis of tryptophan hydroxylase I and II mRNA expression in the human brain: A post-mortem study. J Psychiatr Res 41:168–173.

Zouk H, McGirr A, Lebel V, Benkelfat C, Rouleau G, Turecki G. 2007. The effect of genetic variation of the serotonin 1B receptor gene on impulsive aggressive behavior and suicide. Am J Med Genet Part B 144B:996–1002.