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Genetics of Aggressive Behavior: An Overview

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The Research Domain Criteria (RDoC) address three types of aggression: frustrative non-reward, defensive aggression and offensive/proactive aggression. This review sought to present the evidence for genetic underpinnings of aggression and to determine to what degree prior studies have examined phenotypes that fit into the RDoC framework. Although the constructs of defensive and offensive aggression have been widely used in the animal genetics literature, the human literature is mostly agnostic with regard to all the RDoC constructs. We know from twin studies that about half the variance in behavior may be explained by genetic risk factors. This is true for both dimensional, trait-like, measures of aggression and categorical definitions of psychopathology. The non-shared environment seems to have a moderate influence with the effects of shared environment being unclear. Human molecular genetic studies of aggression are in an early stage. The most promising candidates are in the dopaminergic and serotonergic systems along with hormonal regulators. Genome-wide association studies have not yet achieved genome-wide significance, but current samples are too small to detect variants having the small effects one would expect for a complex disorder. The strongest molecular evidence for a genetic basis for aggression comes from animal models comparing aggressive and non-aggressive strains or documenting the effects of gene knockouts. Although we have learned much from these prior studies, future studies should improve the measurement of aggression by using a systematic method of measurement such as that proposed by the RDoC initiative.

Key words: aggression; genetics; twin; GWAS; candidate genes; mutations

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INTRODUCTION

During the early stages of human evolution, aggression was probably an adaptive trait, as it is for many animals in the wild today. It seems logical that during this period of time people who had the variants of genes that promoted aggression were more likely to survive than other people. These variants have persisted in the human genome and partly explain why some people exhibit aggressive behaviors.

Although the word "irascibilem" comes from the Latin "irascibilem", meaning "to attack," in current language aggression means much more. In the genetics literature aggression has been

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operationalized in many ways. As a categorical disorder it has been studied as conduct disorder (CD), oppositional defiant disorder (ODD) and antisocial personality disorder (APD). These categories are convenient for diagnosticians because other work suggests aggression to be a quantitative trait that is better operationalized on dimensions of externalizing behavior, rule breaking, psychopathy and violence.

A dimensional view of aggression is consistent with the approach taken by the NIMH Research Domain Criteria (RDoC) Initiative [Sanislow et al., 2010]. RDoC seeks to focus researchers on the fundamental mechanisms underlying psychopathology. In doing so, it has been creating a dimensional taxonomy of behavior that, hopefully, corresponds better to underlying mechanisms than does a system of discrete diagnoses.

In the RDoC nomenclature, aggression is categorized into three areas: frustrative non-reward, defensive aggression and offensive (or proactive) aggression. Frustrative non-reward refers to behaviors that correspond to the withdrawal or prevention of reward. This derives from human and animal studies showing that aggression occurs after repeated, failed attempts to obtain rewards even after sustained efforts. Defensive aggression refers to behaviors caused by the perception of an immediate threat, which have the goal of eliminating the threat. Offensive (or proactive) aggressive behaviors are instrumental behaviors aimed at achieving a positive goal, often in the face of competition or in the context of social hierarchies.

The long-term goal of RDoC is to map RDoC phenotypes to underlying mechanisms. In this review, we sought to present the evidence for genetic underpinnings of aggression and to determine to what degree prior studies have examined phenotypes that fit neatly, or at all, into the RDoC framework. We focus the review on three types of genetic studies: twin studies, human association studies of aggression and animal model studies.

TWIN STUDIES OF AGGRESSION

This section outlines recent findings from twin studies on aggression and related psychopathology, i.e. ODD, CD and APD. Studies using the classical twin design estimate heritability by comparing the covariation between monozygotic (MZ; identical) and dizygotic (DZ; fraternal) twins [Plomin et al., 1994; Boomsma et al., 2002]. MZ twins are assumed to share 100% of their genetic material while DZ twins share 50% of their genetic material, and both types of twins share a common environment [Posthuma et al., 2003]. Under an ACE model [Neale and Cardon, 1992], the correlation (r) between phenotypes of MZ twin pairs encompasses additive genetic factors (a^2 or h^2; heritability) plus common environmental factors (c^2), that is $rMZ = h^2 + c^2$. For DZ twin pairs who share 50% of their segregating genetic material, $rDZ = 0.5^*h^2 + c^2$. This gives the following formula to calculate the fraction of phenotypic variance accounted for by genetic factors: $h^2 = 2(rMZ - rDZ)$. The influence of the common environment c^2 can be derived as follows: $rMZ - h^2$ (*or* $2^*rDZ - rMZ$). Genetic influences can also be non-additive (d^2), but these effects cannot be estimated simultaneously with c^2 if only using data from twin pairs who are raised together. Accordingly, variance within twin pairs that is not explained by genetic factors or the common environment, is attributed to influence of the non-shared environment, $e^2 = 1–rMZ$, which also includes measurement error [Holzinger, 1929; Falconer, 1960]. It is important to note here that the non-shared (unique) environment includes all experiences that contribute to differences between children in the same family, i.e. a common event (for example parents' divorce) can affect siblings differently.

Twin studies have investigated aggression from different perspectives, e.g. as a personality trait [Miles and Carey, 1997], as antisocial behavior [Rhee and Waldman, 2002] or as a symptom of childhood and adolescent psychopathology. Previous reviews of twin studies and adoption studies on aggression have estimated heritability up to 0.50, with an additional large role for non-shared environmental influences and a small influence of the shared environment [Viding et al., 2008; Tuvblad and Baker, 2011]. Genetic effects seem to predominantly account for phenotypic correlations between different forms of aggression, such as reactive (defensive) and proactive (offensive) aggression, although few studies have examined this [Rhee and Waldman, 2011]. To update these prior reviews, we conducted a systematic search for studies in the period January 2009 until February 2015. PubMed and PsycINFO were searched for peer-reviewed papers to identify studies of twins with characteristics of externalizing behavior and psychopathy, regardless of age. We used the following search strategy: aggress* OR antisocial behav* OR aggressive trait* OR behavior problem* OR behaviour problem* OR problem behavi* OR CD OR conduct disorder* OR conduct problem* OR crime OR criminal* OR delinquen* OR disruptive behav* OR ODD OR oppositional defiant disorder* OR antisocial personality OR psychopathy OR sociopathy AND heritabilit*.

A total of 254 records were retrieved. Neither books nor unpublished articles were retrieved from the references. Titles and abstracts were read by at least two of the authors (MJB and KV); article selection is summarized in Figure 1. Articles were retained if they: 1) included constructs related to aggression, i.e. aggressive traits, externalizing/impulsive-antisocial behavior and violent criminality/offences/delinquency or diagnostic categories ODD/CD/APD 2) reported univariate heritability estimates 3) had been published in peer–reviewed journals from January 2009 onwards. Reference lists from the identified articles were manually searched for relevant publications. Articles were excluded if they were not written in English, were a case-report, were review articles, reported only multivariate analyses, or were not specifically focused on aggression, e.g. publications about substance abuse, victimization, or sexual risk behavior.

From the literature search, which generated 254 hits, 80 articles were identified of which 40 articles were eligible for review according to the above guidelines. All included studies were published as articles in scientific journals. Online publication dates ranged from January 2009 to November 2014. The following information was extracted from the articles: sample size, age range (or mean if unavailable), clinical diagnostic criteria used, instruments used to measure the construct of aggression and key findings. A portion of the studies used interviews or reports to assess diagnoses of ODD, CD or APD based on the Diagnostic and Statistical Manual of Mental Disorders (DSM; APA, 2001) while other studies employed questionnaires and rating scales to assess aggressive symptoms on a

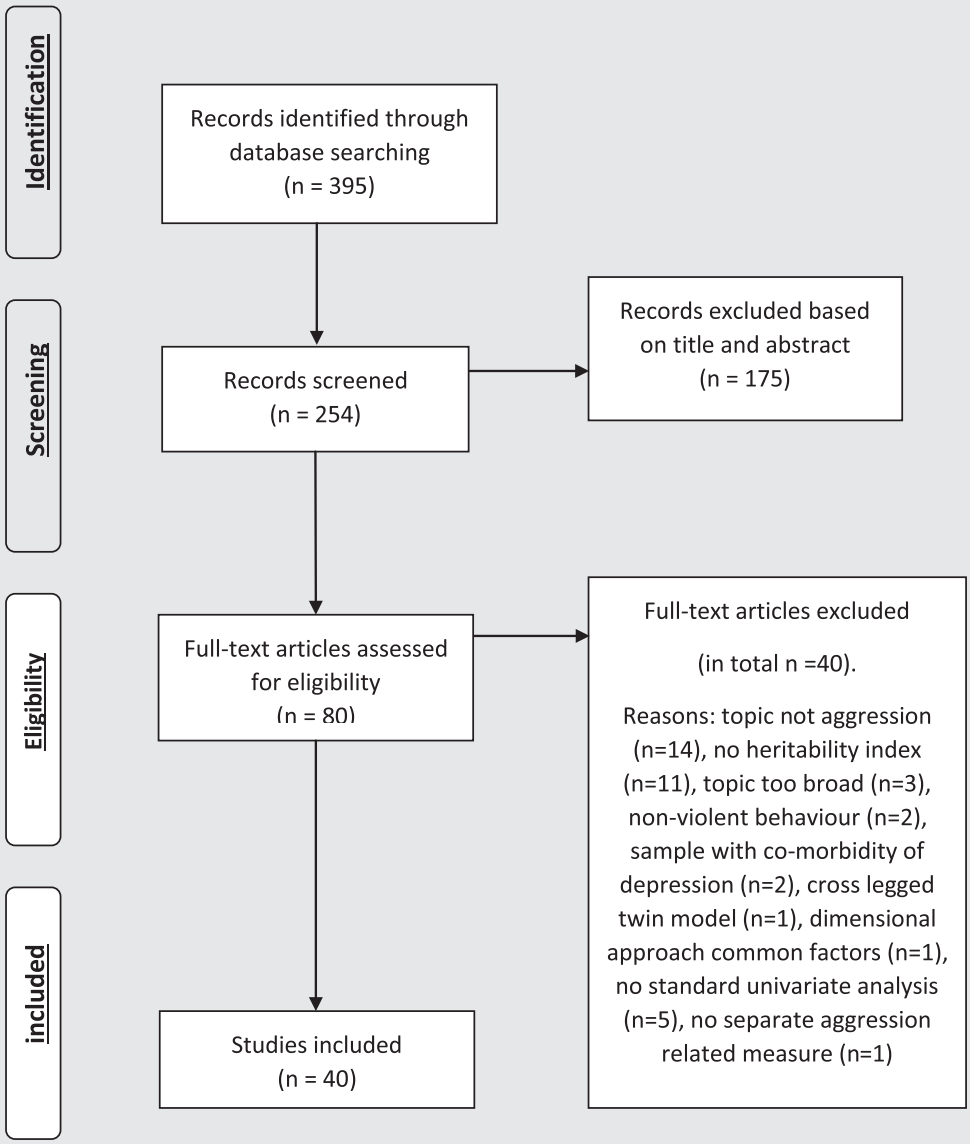

FIG. 1. Selection of publications for twin studies review.

continuum. All characteristics and details of the included studies are summarized in Table I. We discuss the findings below, starting with research on aggression as a dimensional measure followed by research on diagnostic categories. Within these subsections, results are ordered (where possible) on the basis of age.

Twin Studies of Aggression as a Dimension of Behavior

Aggression in children and adolescents. Researchers have explored the etiology of aggressive behavior in children as young as two years of age [Gagne et al., 2011]. The authors reported that more than half of the variance of externalizing behavior problems could be explained by genetic factors, and around one quarter by shared environmental influences. A genetic correlation between externalizing behavior and inhibitory control was also observed, pointing to deficient inhibitory control as a risk factor for aggressive traits. At age 4, somewhat lower heritability estimates for externalizing behavior have been found (0.39, 95% CI = 0.25–0.54; Tucker-Drob and Harden, 2013). The influence of the non-shared environment was of equal size as the genetic influences. Interestingly, the amount of variance accounted for by shared environmental factors changed with age depending on preschool enrollment. For 5-year-old children that attended preschool, there was no contribution of shared environment while heritability estimates increased. For children who did not attend preschool, the influence of the shared environment was more than 50% and the influence of additive genetic factors decreased. Another study in 4-year-olds from the same cohort found a gene- environment interaction [Boutwell et al., 2012]. In the context of maternal

TABLE I. Twin Studies on Aggression, ODD/CD and AAB/APD

Study	Twin registry	N	Age	Measure	a^2	c^2	e^2	Other findings
Dimensional measures of aggression in children								
Gagne et al. [2011]	Boston university twin project	291	2	CBCL externalizing scale	0.54	0.27	0.19	Genetic correlation with inhibitory control
Tucker-Drob and Harden [2013]	Early childhood longitudinal study birth cohort	~600	4 + 5	Parent-ratings externalizing problems	0.39	0.23	0.37	GxE interaction at age 5 with preschool attendance
Boutwell et al. [2012]	Early childhood longitudinal study birth cohort	~1600	4	Parent-ratings externalizing problems	~0.60	~0.08	~0.32	GxE interaction with maternal disengagement
Fujisawa et al. [2012]	Tokyo twin cohort project & cross sectional survey	1677	~6	SDQ conduct problems	0.46	–	0.54	Covariance with negative parenting Moderation by hyperactivity/ inattention problems
Lamb et al. [2012]	Netherlands twin registry	~3000	7 + 10 + 12	TRF externalizing scale	0.82	–	0.18	Lower a^2 for girls and for ratings by different teachers Similar effects at age 10 and 12
Barker et al. [2009]	Twins early development study	872	9	SDQ + APSD aggression teacher rating	0.69	0.04	0.27	Lower a^2 and higher e^2 for ratings by different teachers
Trzaskowski et al. [2013]	Twins early development study	2500	12	SDQ conduct problems parent- and self-report	0.55	0.22	0.23	Lower a^2 and higher e^2 for ratings by different teachers No genetic influence in GCTA
Fontaine et al. [2010]	Twins early development study	9462	7 + 9 + 12	SDQ + APSD	0.78	0.01	0.21	Boys with stable high CU over time
				CU traits teacher rating				Lower h^2 and higher c^2 for girls
Viding et al. [2013]	Twins early development study	2886	7 + 9 + 12	SDQ + APSD	0.64	–	0.36	No genetic influence in GCTA
Ficks et al. [2014]	Twins born in Georgia	885	417	CU traits teacher rating APSD	0.49	0.19	0.32	No sex differences for CU traits
				CU traits parent rating				Higher e^2 for impulsivity in boys
Robbers et al. [2012]	Netherlands twin registry	4592	3 + 12	CBCL externalizing	0.60	0.18	0.22	Lower a^2 for girls and higher a^2 for children from divorced families

TABLE I. (*Continued*)

Study	Twin registry	N	Age	Measure	a^2	c^2	e^2	Other findings
Nikolas et al. [2013]	Michigan state university twin registry	600	6–10	CBCL externalizing	0.46	0.20	0.34	Covariation with children's perception of inter-parental conflict
Burt & Klump [2012]	Michigan state university twin registry	312	6–10	CBCL aggressive scale	0.56	$d^2 = 0.13$	0.32	Nuclear twin family model
Bertoletti et al. [2014]	Italian twin registry	100	6–14	CBCL	0.52	–	0.48	Genetic correlation ($r = -0.33$) with P300 ERP amplitude
Spatola et al. [2010]	Italian twin registry	796	8–11 + 12–17	DOS conduct problems CBCL	0.57	–	0.43	Larger h^2 for 12–17 year olds
				DOS Conduct Problems				Different computational methods
Dimensional measures of aggression in adolescents								
Niv et al. [2013]	University of Southern California twin study	602	9–10 + 14–15	CBCL aggressive scale	0.41	0.40	0.19	Latent factor antisocial behavior
				CBCL rule-breaking scale				Novel genetic influences at 14–15
Niv et al. [2015]	University of Southern California twin study	383	14 – 15	CBCL aggressive scale	0.65	–	0.35	Genetic correlation ($r = 0.22$) with Frontal Alpha Power at age 9–10
Tuvblad et al. [2011]	Swedish twin registry	2600	8–20	CBCL at age 8–9 self-report delinquency	0.67	0.26	0.07	Latent factor antisocial behavior
			(4 ages)					Age-specific c^2 at 13–14 years old
Wichers et al. [2013]	Swedish twin registry	1480	8–20	CBCL and YSR	0.88	0.04	0.08	Novel e^2 at 13–14 years old
			(4 ages)	ABCL and ASR				Novel a^2 at age 13–14 and 16–17
Kendler et al. [2013]	Swedisch twin registry	442	16–17	CBCL externalizing criminal behavior	0.38	0.10	0.52	Self-report measures correlate with criminal behavior due to a^2 and c^2
Burt & Klump [2009]	Michigan state university twin registry	252	10–15	CBCL aggressive scale	0.49	0.22	0.29	Stability across age for aggression
				CBCL rule-breaking scale				Increased genetic influences on rule-breaking
Burt & Neiderhiser [2009]	Nonshared environment in adolescent development	192	10–18	Parent- and self-report aggression, delinquency	0.60	–	0.40	Twin/sibling design
								Stability over age for aggression
								Increase in h^2 on delinquency

TABLE I. (*Continued*)

Study	Twin registry	N	Age	Measure	a^2	c^2	e^2	Other findings
Tuvblad et al. [2009a]	University of Southern California twin study	607	9–10 + 11–14	RPQ parent-report	0.43	0.15	0.42	Novel e^2 and a^2 at age 11–14 Also for proactive aggression
Vaske et al. [2012]	Add health	784	12–20 + 18–26	Self-reported delinquency and criminal behavior	0.40	–	0.60	Smaller a^2 in young adults Correlation with violent victimization due to a^2 and e^2
Dimensional measures of aggression in adults								
Frisell et al. [2012]	Swedish total population	36877	18+	Conviction violent crime	0.49	0.15	x	GLMM without e^2 estimation Similar in sibling model
	Register			Dichotomous variable				Smaller a^2 and c^2 for adoptees
Yeh et al. [2010]	PennTwins Cohort	1470	26–42	Life history of aggression questionairre	0.54	–	0.64	General aggression factor Smaller a^2 for Physical aggression
Brook et al. [2010]	Vietnam era twin registry	272	41–58	MPQ dimension impulsive-antisocial	0.32	–	0.68	Genetic correlation with fearless-dominant dimension
Veselka et al. [2011]	Canada and US residents	456	17–92	Self-report psychopathy scale	0.34	0.22	0.44	Correlation with supernumerary personality inventory traits
ODD/CD								
Tuvblad et al. [2009a]	University of Southern California twin study	605	9–10	DISC CD and ODD interview child and parent	0.39	0.32	0.28	Slightly larger h^2 in girls Latent factor for CD, ODD, ADHD
Anckarsäter et al. [2011]	Child and adolescent twin study in Sweden	8610	9/12	Conduct module parental phone interview	0.60	0.03	0.37	No c^2 for mental problems, except for conduct problems in girls
Bornovalova et al. [2010]	Minnesota twin family study	1069	11	DICA CD and ODD	0.51	0.30	0.19	Larger h^2 and no c^2 for ODD
				Interview child and parent				Latent factor for CD, ODD, ADHD
				Also parental symptoms				Heritable liability for externalizing

TABLE I. (*Continued*)

Study	Twin registry	N	Age	Measure	a^2	c^2	e^2	Other findings
Singh and Waldman [2010]	Georgia twin registry	838	4–17	Parent-report CD, ODD	0.52	$d^2 = 0.27$	0.21	AE model for ODD
				DSM-based questionnaires				Link with negative emotionality
Waldman et al. [2011]	Tenessee twin study	1981	6–18	Parent-report CD	0.70	0.04	0.26	Smaller h^2 for self-ratings
				DSM-based questionnaires and interview child				Link with negative emotionality, daring and prosociality
Lahey et al. [2011]	Tenessee twin study	1571	6–18	DISC-based CD and ODD	0.76	–	0.24	Multivariate shows a^2 differentiation by global e^2 in ODD and CD
				Interview child and parent				
Young et al. [2009]	Colorado longitudinal twin study	293	12 + 17	DISC CD, CBCL and TRF externalizing	0.70	0.11	0.19	Smaller h^2 at age 17
								Link with behavioral disinhibition
Schulz-Heik et al. [2010]	Add Health	753	12–20	DSM-based self-report	0.41	$t^2 = 0.17$	0.42	Twin environment = t^2
				Conduct problems				Twin/sibling design Small correlation maltreatment
AAB/APD								
Hicks et al. [2009]	Minnesota twin family study	1315	17	DSM AAB	0.76	–	0.24	GxE interaction effects with academic achievement and engagement, anti-social peers, pro-social peers, mother-child relationship problems, stressful life events
Hicks et al. [2013]	Minnesota twin family study and sibling interaction and behavior study	1999	26	CD	0.35	0.26	0.39	Similar for AAB
				AAB				High a^2 and moderate c^2, e^2 in general externalizing liability
Meier et al. [2011]	Australian twin registry	6383	Adults	DSM CD ASB interview	0.32	–	0.68	Similar for females Stability greater for males

TABLE I. (*Continued*)

Study	Twin registry	N	Age	Measure	a^2	c^2	e^2	Other findings
Torgersen et al. [2012]	Norwegian institute of public health twin panel	~2800	Adults	APSD - cluster B	0.69	–	0.31	Latent factor
				Self-report interview				Method specificity resulting in no a^2 for interview only

Variance explained: a^2, heritability estimate; c^2, influence of shared environment; e^2, influence of nonshared environment; d^2, non-additive genetic influences. Diagnosis: CD, Conduct disorder; ODD, Oppositional defiant disorder; ADHD, Attention deficit hyperactivity disorder; APD, Antisocial personality disorder; ASB, Antisocial behavior; AAB, Adult antisocial behavior. Measure: ABCL, Adult behavior checklist; APSD, Antisocial process screening device; ASR, Adult self report; CBCL, Child behavior checklist; DICA, Diagnostic interview for children and adolescents; DSM, Diagnostic statistical manual of mental disorders; DISC, Diagnostic interview schedule for children; DOS, DSM-oriented scale; MPQ, Multidimensional personality questionnaire; RPQ, Reactive proactive aggression questionnaire; SDQ, Strengths and difficulties questionnaire; TRF, Teacher report form; YSR, Youth Self Report. Other: CU, Callous-unemotional; ERP, Event-related potential; GCTA, Genome-wide complex trait analysis; GLMM, Generalized linear mixed model; GxE, Gene-environment; N, Number of twin pairs; ~, Approximately; x, Not included.

disengagement, genetic risk factors had a strong effect on externalizing behavior problems. Genetic risk did not play a role in behavior problems when maternal disengagement was low, i.e. when children were securely attached. Remarkably, other researchers showed that genetic effects explained the correlation between negative parenting and conduct problems around age 6, but only for low levels of negative parenting [Fujisawa et al., 2012]. For high levels of negative parenting, there was a larger non-shared environmental correlation between negative parenting and conduct problems. To summarize, the reviewed twin studies in children between age 2 and 6 have focused on externalizing and conduct problems in a broad sense. Heritability estimates ranged from 0.39 to 0.60 with variation contingent upon the school and home environment.

From about the time when children start primary school, aggression can be operationalized more specifically. Self-report, parent-report or teacher ratings have been used to assess externalizing and aggressive behavior, with different measures leading to slightly different findings. Both the Twins Early Development Study (TEDS) from the UK and the Netherlands Twin Register (NTR) included twin pair ratings by the same teacher as well as by different teachers. Same teacher ratings provided larger heritability estimates (0.69, 95% CI = 0.57–0.76 – 0.82, 95% CI = 0.79–0.85) than different teacher ratings (0.40, 95% CI = 0.20–0.52 – 0.47, 95% CI = 0.38–0.55; Barker et al., 2009; Lamb et al., 2012). Also, heritability estimates of conduct problems based on parent-report were higher compared to estimates from self-report [Trzaskowski et al., 2013]. Several studies focused on callous-unemotional (CU) traits, which are considered a genetic risk for antisocial behavior [Viding and McCrory, 2012; Blair, 2013]. Distinct developmental trajectories have been found in 7 to 12 year olds, with the largest heritability for boys who have stable high CU traits (0.78, 95% CI = 0.42–0.88; Fontaine et al., 2010). Composite scores across ages confirmed high heritability of CU traits, while heritability estimates were close to zero in a Genome-Wide Complex Trait Analysis [GCTA; Viding et al., 2013]. Contrary to Fontaine et al. [2010], Ficks et al. [2014] observed no sex differences in genetic and environmental influences on CU traits, although nonshared environmental influences on impulsivity were larger in boys. For parent ratings of conduct problems, the Child Behavior Checklist [CBCL; Achenbach and Rescorla, 2001] is often employed. Scores are taken from the DSM-Oriented Scale (DOS) for conduct problems [Spatola et al., 2010; Bertoletti et al., 2014] or the externalizing scale of the CBCL encompassing the aggression and rule-breaking subscales [Burt and Klump, 2012; Robbers et al., 2012; Nikolas et al., 2013]. Meta-analyses have shown a distinction between aggression and rule-breaking, with the former primarily influenced by genetics and the latter by the shared environment [Burt, 2009, 2013]. In summary for children between 6 to 14 years old, the heritability of parental reports of aggression-related phenotypes ranged from 0.46 to 0.60. The estimates for non-shared environmental influences were between 0.18 and 0.48.

Some twin studies collected longitudinal data to examine stability and change in the etiology of behavior over time. In the Risk Factors for Antisocial Behavior twin study, children age 9–10 were followed into adolescence. Separate genetic and non-shared environmental influences were found on aggression versus rule-

breaking during childhood, in addition to joint influences on a latent common factor of antisocial behavior [Niv et al., 2013]. At age 14–15, novel genetic influences on the latent factor of general antisocial behavior were observed. In the same project, a link between adolescent aggression and brain functioning at age 9–10 was demonstrated [Niv et al., 2015]. The power of alpha waves, brain oscillations of 8–13 Hz measurable by electroencephalography (EEG), is a biomarker of low arousal. This intermediate phenotype was explored based on theories stating that low arousal evokes externalizing behavior to reach a higher, optimal level of arousal. Indeed, alpha power recorded over the frontal cortex at age 9–10 predicted aggression at age 14–15. The correlation could be explained by genetic factors and was shown in males but not females, and for aggressive behavior but not for rule-breaking.

In Swedish twins, followed from age 8 to 20, a latent factor representing persistent antisocial behavior was found as well as novel shared environmental influences on aggression and delinquency at age 13–14 [Tuvblad et al., 2011]. Within the same twin registry, self-reports of antisocial behavior and related traits at age 16–17 reflected shared environmental risk for criminality [Kendler et al., 2013]. Analyzing parent-reports in addition to self-reports revealed genetic continuity but also novel genetic influences at age 13–14 and 16–17, plus novel unique environmental influences for early adolescents [Wichers et al., 2013]. Data from the Add Health project suggested that for young adults (age 18 to 26), genetic influences on criminal behavior were smaller than those on self-reported delinquency in adolescence [Vaske et al., 2012]. An analysis combining CBCL data from 1022 Swedish twin pairs aged 7–9 years and 501 British twin pairs aged 8–16 years concluded that the etiologies of aggressive and nonaggressive antisocial behavior differ for males and females [Eley et al., 1999].

Interestingly, a meta-analysis reported an age-related increase in heritability estimates of externalizing behaviors [Bergen et al., 2007]. It has been suggested that this increase may be specific to rule-breaking and delinquency, while the magnitude of genetic and environmental influences on aggression only is stable across adolescence [Burt and Klump, 2009; Burt and Neiderhiser, 2009]. However, Tuvblad and colleagues probed reactive (impulsive; defensive) and proactive (instrumental; offensive) aggression and found larger heritability estimates in early adolescence than in childhood for both subtypes of aggression [Tuvblad et al., 2009a]. Altogether, aggression is heritable across development (range 0.38–0.88) but the magnitude of genetic and environmental influences varies according to age and assessment method.

Aggression in adults. A few extant twin studies focused specifically on aggressive traits in adults, some of which have used retrospective measures. With conviction of violent crime as a dichotomous variable, heritability estimates were comparable to previous heritability findings of self-reported anti-social behavior [Frisell et al., 2012]. Estimates for this outcome in the classic twin design were similar in a sibling model but for adoptees, genetic and shared environmental influences appeared smaller. Using the Lifetime History of Aggression Questionnaire [LHA; Coccara et al., 1997], two factors were distinguished [Yeh et al., 2010]; general aggression (temper tantrums, verbal and indirect aggression) plus physical aggression (fighting and physical assault). Genetic influences were larger for general aggression while non-shared environmental influences were larger for physical aggression, pointing to the importance of subtyping aggressive behavior. Two studies in adult twins have used questionnaires to measure the construct of psychopathy. Brook and colleagues administered the Multidimensional Personality Questionnaire [MPQ; Tellegen, 1982] to middle-aged males. On the impulsive-antisocial dimension, heritability was 0.32 (95% CI = 0.18–0.45), and a strong influence of the non-shared environment was reported with no effect of the shared environment [Brook et al., 2010]. Non-shared environmental factors also explained the correlation between the impulsive-antisocial dimension and the fearless-dominant dimension of psychopathy. On the Self-Report Psychopathy scale [SRP; Hare, 1985], heritability was 0.34 (95% CI = 0.10–0.69) and genetic plus non-shared environmental factors explained the phenotypic correlation of psychopathy with risk-taking, among other variables [Veselka et al., 2011].

Overall, in adult twin studies based on a dimensional approach to aggression, as in studies with children, various definitions and measures have been used. It is therefore difficult to compare results and to make a link with the RDoC classification [Sanislow et al., 2010]. In the next section, we will describe research that focused on diagnostic categories related to DSM criteria [APA, 2000].

Aggressive Psychopathology

Oppositional defiant disorder (ODD) and conduct disorder (CD) in children and adolescents. Several studies of twin children and adolescents (N = 12, age range: 4–23 years) have focused on aggression expressed in childhood and adolescent psychopathology (e.g. CD or ODD). All these studies were characterized by a wide age range, encompassing both childhood and adolescence. For example, Singh and Waldman [2010] focused on an age range from 4 to 17 years in a sample characterized by symptoms of ODD and CD rated by the parent [Singh and Waldman, 2010]. Based on a univariate standard ACDE model (95% CI's not provided), both disorders showed a different model of best fit, in which heritability was roughly the same. An AE model was the best fit for ODD, in which two thirds of variance was accounted for by genetic effects. While an ADE model was a best fit for CD: nearly half of the variance was explained by additive genetic factors, followed by non-additive genetic and non-shared environment effects. In the Tennessee Twin Study, high heritabilities were reported for CD 0.70 (95% CI = 0.44–1.00; Waldman et al., 2011) and confirmed by Lahey et al. [2011]. In addition, for ODD symptoms heritability was 0.69 (95% CI's not provided; Lahey et al., 2011). However, self-reports showed a reduction in variance explained by genetic influences 0.39 (95% CI = 0.16–0.72) and a small to moderate role for the common 0.14 (95% CI = 0.004–0.47) and non-shared environment 0.47 (95% CI = 0.38–0.57) effects [Waldman et al., 2011]. In contrast, Lahey et al. [2011] reported strong genetic influences and moderate non-shared environmental influences for both CD and ODD based on combined adult caretaker- and youth-reports. In addition, a multivariate model based on a global factor for internalizing and externalizing disorders showed moderate genetic and non-shared environmental effects of the externalizing factor in both CD and ODD. The non-shared environment effect was moderate in ODD and small in CD.

As these few studies mentioned above show, there are mixed results for CD and ODD; some studies favor an ACE/ADE model and others an AE model. Another example of an ACE model is a study (N = 605 twin pairs) of Tuvblad et al. [2009a,b]. Both CD and ODD symptoms were assessed with the DISC-IV structured interview. The authors found unique genetic and environmental influences for each set of symptoms, which suggests unique influences of the two disorders. Moreover, the relative effects of genetic, shared, and non-shared environmental factors were similar between CD and ODD. Furthermore, it has been suggested that both the genetic (95% CI_f = 0.17–0.74, 95% CI_m = 0.12–0.70) and non-shared environmental (95% CI_f = 0.23–0.39, 95% CI_m = 0.22–0.37) influences on CD are slighter higher in girls (f) than boys (m) and slighter lower for shared environment (95% CI_f = 0.00–0.50, 95% CI_m = 0.03–0.56). Furthermore, common influences have been reported based on a latent externalizing behavior factor, indicating high genetic and moderate non-shared environmental influences. Anckarster et al. [2011] reported that both CD and ODD are more influenced by genetic (95% CI_f = 0.13–0.36, 95% CI_m = 0.61–0.67) factors in boys (m) than in girls (f). In contrast, the influence of shared environment was negligible (95% CI_f = 0.17–0.35, 95% CI_m = 0.00–0.02), the one exception being conduct problems in girls.

Bornovalova et al. [2010] studied a large sample of twin pairs (aged 11 years) in which an ACE model was the best fit. A higher heritability of 0.73 (95% CI = 0.59–0.79) and non-shared environmental influences of 0.24 (95% CI = 0.21–0.26) was found for ODD compared with CD, in which heritability was 0.51 (95% CI = 0.39–0.63) and common environment was 0.30 (95% CI = 0.18–0.41). In addition, common environment was significant for CD only. In the longitudinal study of Young et al. [2009], twin pairs were assessed at 12 and 17 years of age on both childhood and adolescent psychopathology and aggressive traits (CBCL and TRF- externalizing behavior). They reported smaller genetic 0.49 (95% CI = 0.25–0.76) and non-shared environmental 0.25 (95% CI = 0.20–0.32) influences at age 17 compared with age 12 (a^2 = 0.70, 95% CI = 0.46–0.85; e^2 = 0.19, 95% CI = 0.15–0.24). This AE model was linked to structural stability of behavioral and response disinhibition across adolescence, and this relationship was primarily genetic in origin.

To conclude this section on developmental psychopathology in childhood and adolescence, one large study in adolescents reported an AE model with moderate genetic effects in conduct problems [Schulz-Heik et al., 2010].

Aggressive psychopathology in older adolescents and adults. Among the studies of CD or ODD, two also reported on Adult Antisocial Behavior (AAB) [Hicks et al., 2009, 2013]. For AAB, Hicks et al. [2009] reported strong genetic influences (95% CI = 0.65–0.79) and moderate non-shared environment influences (95% CI = 0.21–0.26). Across six environmental risk factors (low academic achievement and engagement, antisocial peers, lack of prosocial peers, mother-child relationship problems, father-child relationship problems, stressful life events), genetic variance in externalizing disorders increased in the context of greater environmental adversity. This indicates that as environmental stress increases genetic differences among young adults become more important in the etiology of externalizing disorders. Three studies focused on adults with CD and AAB [Meier et al., 2011; Hicks et al., 2013] and cluster B personality antisocial personality disorder [Torgersen et al., 2012]. Hicks et al. [2013] focused on both biological twins and non-biological siblings. They reported for both CD and AAB moderate genetic (95% CI = 0.35–0.52), shared (95% CI = 0.11–0.25) and non-shared environmental influences (95% CI–0.34–0.42). Meier et al. [2011] reported approximately two thirds of the variance explained by non-shared environmental influences (95% CI = 0.63–0.74), followed by genetic effects (95% CI = 0.26–0.37) in CD regardless of gender. No gender differences were reported for AAB for which the non-shared environment explained two thirds of the variance followed by genetic influences. However, males showed greater stability in antisocial behavior from childhood to adulthood. As for the study on cluster B personality [Torgersen et al., 2012], one-third of the variance was explained by genetic influences and two thirds by non- shared environment based on interview measures of personality disorders. These findings were method specific, since the magnitude of the genetic component varied by type of interview compared to self-reported questionnaires. Thus, differences in twin studies on AAB and APD may be due to gender or to differences in measurement methods.

Overall, the non-shared environmental effects are less strong compared to genetic effects. Furthermore, a risk of bias arises in the cited studies, given that the power to detect shared environmental influences is often low in biometric analyses of twin data and these studies assume that the environmental effects are free of influence by genetic effects [Burt, 2013]. Therefore, results should be interpreted with caution.

Summary: Twin Studies of Aggressive Behavior and Psychopathology

Recent publications about twin data on aggression-related problems suggest that around 50% of the variance in aggressive behavior may be explained by genetic influences. The non-shared environment seems to have a moderate influence. With regard to the shared environment, findings are mixed: About half of the reviewed studies report no influence while other studies indicate estimates between 0.15 and 0.35. The former is in line with a previous review that showed the presence of only non-shared environmental and genetic influences of 0.50 each [Tuvblad and Baker, 2011]. Although a meta-analysis demonstrated increased heritability estimates for externalizing with age [Bergen et al., 2007], this pattern was not evident in the current review. However, most of the included articles examined children and adolescents, and only a few articles focused specifically on adults. An effect of gender has occasionally been observed [Tuvblad et al., 2009b; 2011; Meier et al., 2011; Lamb et al., 2012; Robbers et al., 2012] but, for most studies, similar models for boys and girls were suitable. Hence, heritability estimates may be comparable between males and females despite the finding that aggression occurs more often in males, particularly direct, overt aggression as opposed to relational aggression [Ligthart et al., 2005]. Of note, genetic influences on aggressive behavior might

depend on the environment, as gene-environment interaction appears to play an important role.

The operationalization of the construct aggression differed widely across the reviewed articles. Some researchers investigated aggression as a trait in the general population while others focused on DSM-based psychopathology, i.e. ODD, CD and AAB/APD. Both the dimensional and the categorical approaches yielded heritability estimates ranging from approximately 0.30 to 0.80. Several studies found a latent factor of externalizing/antisocial behavior with unique genetic or environmental influences on specific forms of aggression [Bornovalova et al., 2010; Yeh et al., 2010; Lahey et al., 2011; Tuvblad et al., 2011; Niv et al., 2013]. Thus, a limitation of the current state of the field is that researchers do not use common definitions with regard to aggression, which makes it difficult to compare studies. Future studies may improve the measurement of aggression by using dimensional constructs from the RdoC framework, i.e. defensive aggression, offensive aggression and frustrative non-reward (http://www.nimh.nih.gov/research-priorities/rdoc/negative-valence-systems-workshop-proceedings.shtml). These constructs are defined and will be continuously refined based on multiple units of analysis, such as genes, brain circuits and behavior, to better integrate clinical findings with neuroscience [Sanislow et al., 2010; Cuthbert and Insel, 2013]. Discovering genes that are related to various aggression dimensions is one step towards advanced understanding of psychopathology.

HUMAN ASSOCIATION STUDIES OF AGGRESSION

Based on previous searches performed by Vassos et al. [2014] and Gunter et al. [2010] we searched articles on PubMed using the terms "(aggression OR aggressivity OR aggressive OR anger OR hostility OR irritability OR violence OR convict* OR crimin* OR offend* OR externalizing OR conduct OR antisocial OR impulsive aggression OR psychopathy OR ODD OR oppositional defiant OR callous unemotional) AND (genetics OR gene OR polymorphism OR genotype OR allele OR genome OR haplotype)" to update their searches from December 2009 until February 2015, with an output of 7,202 articles. Subsequently, we filtered works written in English language, performed in humans, including sample characteristics and performing genetic association studies that had been published as articles in scientific journals. We selected 268 potential articles within this range of dates and some additional 263 articles from a previous review [Gunter et al., 2010] and a meta-analysis [Vassos et al., 2014]. From these 531 articles we selected those studies that included traits related to aggression (aggressiveness, anger, externalizing behavior, impulsive aggression, criminality, violence or delinquency), or diagnostic categories of ODD, CD, antisocial behavior or ASPD, callous unemotional or psychopathy. Also, we excluded studies assessing aggressive or antisocial traits in drug use or dependence cohorts, or samples of other psychiatric disorders (e.g. schizophrenia, bipolar disorder, major depression). A total of 277 articles were finally considered for this review. Our selection process is described in Figure 2.

Most association studies exploring the genetic susceptibility to aggression have focused on candidate genes (candidate gene association studies, CGAS), especially those related to serotonergic and dopaminergic neurotransmission. Additionally, a few genome-wide association studies (GWAS) have been performed and will also be reviewed. These studies have used either trait measures of aggression (Table II) or measures of aggression psychopathology (Tables III and IV). Candidate gene association studies have often rendered conflicting results, since in several cases associations were identified with different alleles of the same variation or could not be replicated in the same phenotype. In addition, many of the CGAS were performed in small samples that often lead to false positive or false negative findings due to lack of statistical power. Finally, GWAS of aggression phenotypes have not identified genome-wide significant associations so far. In consequence, results obtained in previous association studies, either CGAS or GWAS, must be taken with caution.

Candidate Genes Studied Across the Lifespan

The *MAOA* and *5HTT* genes have been studied quite extensively in aggressive traits in children, adolescents and adults (Table II), and also in diagnostic categories of aggression in children (Table III) and adults (Table IV). *MAOA* encodes the enzyme monoamine oxidase A, responsible for the catabolism of dopamine, serotonin and other neurotransmitters. An upstream polymorphism consisting of a variable number of tandem repeats (uVNTR) located in the promoter region of the gene, with an effect on transcription, has been extensively studied. In children, several studies identified the uVNTR variants determining low gene expression levels associated with aggression, anger, externalizing behavior and delinquency, especially in high risk environments (maltreatment or low maternal sensitivity) [Weder et al., 2009; Edwards et al., 2010; Pickles et al., 2013]. In adolescents and young adults, low activity variants were found associated with increased aggressive reactions, violent delinquency and even the use of weapons, stabbing and shooting [Guo et al., 2008; Kuepper et al., 2013; Beaver et al., 2010a,b, 2014). In adults, many studies have associated the low activity variants with aggression, impulsivity, hostility and violent criminal and delinquent behaviors [Manuck et al., 2000, 2002; Eisenberger et al., 2007; Frazzetto et al., 2007; Reif et al., 2007; Gallardo-Pujol et al., 2013; Armstrong et al., 2014; Gorodetsky et al., 2014; Tiihonen et al., 2014]. Only a few studies have failed to replicate these results or have identified high activity variants as risk alleles for these phenotypes [Huizinga et al., 2006; Yang et al., 2007; van der Vegt et al., 2009; Perroud et al., 2010; Verhoeven et al., 2012]. Thus, the bulk of the evidence indicates that low activity alleles of the *MAOA*-uVNTR are probably associated with aggressive traits. Interestingly, the *MAOA* gene has not been associated with CD or ODD in children. Indeed, it has only been associated with CD in the presence of an adverse childhood environment [Caspi et al., 2002; Foley et al., 2004; Haberstick et al., 2005; Kim-Cohen et al., 2006; Young et al., 2006; Prom-Wormley et al., 2009; Qian et al., 2009; Wakschlag et al., 2010; Kieling et al., 2013]. Many studies assessing *MAOA* in adults identified associations with antisocial behavior, conduct problems and psychopathy in the presence of adverse childhood environment, most of them identifying the shorter variant of the uVNTR as the risk allele [Lu et al., 2003; Widom and Brzustowicz, 2006; Prichard et al., 2007; Fowler et al., 2009; Williams et al., 2009; Beach et al., 2010; Derringer et al.,

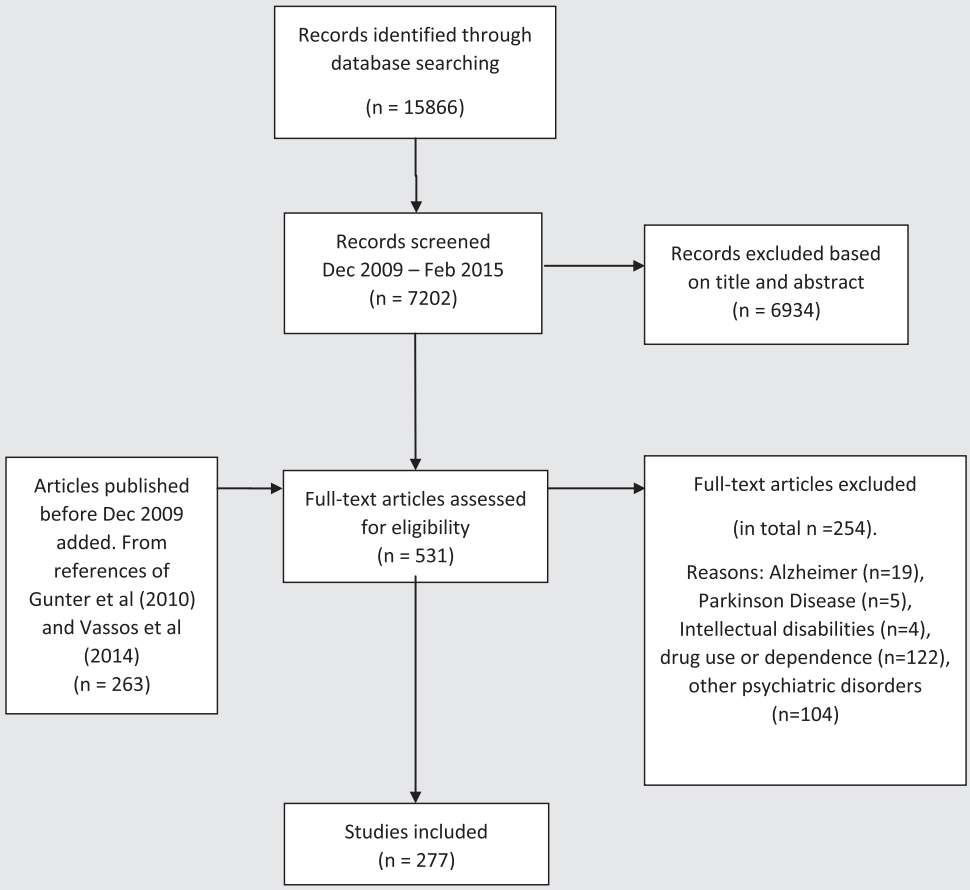

FIG. 2. Selection of publications for association studies review.

2010; Fergusson et al., 2011, 2012; Philibert et al., 2011; Reti et al., 2011; McGrath et al., 2012; Sadeh et al., 2013; Byrd and Manuck, 2014; Ficks and Waldman, 2014; Haberstick et al., 2014].

Studies of the *MAOA*-uVNTR and aggression have usually been restricted to males; since this is an X-linked gene. Because information on the inactivation of the locus is not available, association results are difficult to interpret in females. Other *MAOA* variants, such as the single nucleotide polymorphisms (SNPs) rs5906957, rs909525, rs6323, and rs2064070, have been associated with physical aggression in boys or anger in male adults [Antypa et al., 2013; Pingault et al., 2013]. Also, another VNTR (10 bp) in this gene was found associated with ASPD [Philibert et al., 2011].

The *SLC6A4 or 5HTT* gene, which encodes the serotonin transporter, has been associated with several aggressive phenotypes. A functional polymorphism in the promoter, called 5HTTLPR for *5HTT*-Linked Polymorphic Region, has been associated in children and adolescents with aggression, violence, delinquency and externalizing behavior, although with contradictory results regarding the identity of the risk variant and the associated genotypes [Zalsman et al., 2001; Cadoret et al., 2003; Gerra et al., 2005; Beitchman et al., 2006; Haberstick et al., 2006; Hohmann et al., 2009; Zimmermann et al., 2009; Aslund et al., 2013]. In contrast, many studies of adults have found the short variant (S) of 5HTTLPR to drive lower transcription levels of the gene and to be associated with aggression, anger, hostility, neuroticism, violence and criminality [Greenberg et al., 2000; Liao et al., 2004; Retz et al., 2004; Verona et al., 2006; Reif et al., 2007; Gonda et al., 2009; Sysoeva et al., 2009; Conway et al., 2012; Gyurak et al., 2013; Lopez-Castroman et al., 2014].

The shorter variant of 5HTTLPR has been associated with conduct problems and CD [Sakai et al., 2006, 2007, 2010; Brody et al., 2011]. The 5HTTLPR has been associated with psychopathy and antisocial behavior, although with conflicting results [Fowler et al., 2009; Garcia et al., 2010; Sadeh et al., 2013; Ficks and Waldman, 2014].

SNP rs25531 modifies the transcription of 5HTTLPR: The long 5HTTLPR allele with a G (Lg) at rs25531 drives low transcription levels, similar to the short allele (S), whereas the La allele at rs25531determines higher transcription levels. This could explain contradictory association results. Beitchman et al., [2006] considered this SNP when analyzing 5HTTLPR genotypes, identifying association between lower transcription genotypes (S/S, S/Lg and Lg/Lg) and childhood aggression [Beitchman et al., 2006].

TABLE II. Genes Associated With Aggression Trait Measures

Gene symbol	Gene name	Phenotype	Study	References
Children and adolescents				
AVP	Arginine vasopressin	Aggression	CGAS	Malik et al. [2014]
AVPR1A	Arginine vasopressin receptor 1A	Aggression	CGAS	Malik et al. [2014]
AVPR1B	Arginine vasopressin receptor 1A	Aggression	CGAS	Zai et al. [2012b]; Luppino et al. [2014]
BDNF	Brain-derived neurotrophic factor	Aggressive behavior	CGAS	Kretschmer et al. [2014]; Musci et al. [2014]
CHRM2	Cholinergic receptor, muscarinic 2	Externalizing behavior	CGAS	Dick et al. [2011]; Latendresse et al. [2011]
CYP19	Cytochrome P450, family 19	Externalizing behavior	CGAS	Miodovnik et al. [2012]
DRD2	Dopamine receptor D4	Aggressive behavior and violent delinquency	CGAS	Guo et al., [2007]; Zai et al., [2012a]
DRD4	Dopamine receptor D4	Aggression, externalizing behavior and delinquency	CGAS	Nobile et al. [2007]; Hohmann et al. [2009]; Dmitrieva et al. [2011]; Buchmann et al. [2014]; Farbiash et al. [2014]; Schlomer et al. [2015]
MAOA	Monoamine oxidase A	Aggression, anger, externalizing behavior, delinquency and use of weapons	CGAS	Beaver et al. [2014]; Edwards et al. [2010]; Guo et al. [2008]; Pickles et al. [2013]; Pingault et al. [2013]; van der Vegt et al. [2009]; Weder et al. [2009]
ESR1	Estrogen receptor 1	Anger	CGAS	Vermeersch et al. [2013]
LRRC7	Leucine rich repeat containing 7	Aggressive behavior	GWAS	Mick et al. [2011]
OXTR	Oxytocin receptor	Aggression	CGAS	Malik et al. [2012, 2014]
SLC6A4 (5HTT)	Solute carrier family 6 (neurotransmitter transporter), member 4 (serotonin transporter)	Aggression, violence, delinquency and externalizing behavior	CGAS	Aslund et al. [2013]; Beitchman et al. [2006]; Cadoret et al. [2003]; Gerra et al. [2005]; Haberstick et al. [2006]; Hohmann et al. [2009]; Zalsman et al. [2001]; Zimmermann et al. [2009]
SLC6A3 (DAT1)	Solute carrier family 6 (neurotransmitter transporter), member 3 (dopamine transporter)	Externalizing behavior, pathological violence, serious delinquency and criminal conduct	CGAS	Beaver et al. [2008]; Chen et al. [2005]; Guo et al. [2007]; Young et al. [2002]
SLIT2	Slit homolog 2 (Drosophila)	Anger	CGAS	Sokolowski et al. [2010]
STIP1	Stress-induced phosphoprotein 1	Aggressive behavior	GWAS	Mick et al. [2011]
Adults				
AR	Androgen receptor	Violent criminal behavior, aggression, impusivity and neuroticism	CGAS	Aluja et al. [2011]; Cheng et al. [2006]; Jonsson et al. [2001]; Rajender et al. [2008]; Westberg et al. [2009]
ABCG1	ATP-binding cassette, sub-family G (WHITE), member 1	Aggression and anger	CGAS	Gietl et al. [2007]
AKAP5	A kinase (PRKA) anchor protein 5	Anger	CGAS	Richter et al. [2011]
ANK3	Ankyrin 3, node of Ranvier (ankyrin G)	Externalizing behavior	CGAS	Logue et al. [2013]
CDH13	Cadherin 13	Violent behavior	CGAS	Tiihonen et al. [2014]
CHRM2	Cholinergic receptor, muscarinic 2	Externalizing behavior	CGAS	Dick et al. [2008]
COMT	Catechol-O-methyltransferase	Aggression, externalizing and anger	CGAS	Kulikova et al. [2008]; Perroud et al. [2010]; Shehzad et al. [2012]
CRHR1	Corticotropin releasing hormone receptor 1	Aggressive behavior	CGAS	Chen et al. [2014]
CYP2D6	Cytochrome P450, family 2, subfamily D, polypeptide 6	Aggression	CGAS	Gonzalez et al. [2008]

(*Continued*)

TABLE II. (*Continued*)

Gene symbol	Gene name	Phenotype	Study	References
DARPP32	Protein phosphatase 1, regulatory (inhibitor) subunit 1B	Anger	CGAS	Reuter et al. [2009]
DBH	Dopamine beta-hydroxylase (dopamine beta-monooxygenase)	Aggressive hostility, impulsivity and neuroticism	CGAS	Hess et al. [2009]
FYN	FYN proto-oncogene, Src family tyrosine kinase	Anger	GWAS	Mick et al. [2014]
HTR1B	5-hydroxytryptamine (serotonin) receptor 1B, G protein-coupled	Aggressive behavior, anger and hostility	CGAS	Conner et al. [2010]; Hakulinen et al. [2013]; Zouk et al. [2007]
HTR2A	5-hydroxytryptamine (serotonin) receptor 2A, G protein-coupled	Aggression, anger, hostility and criminality	CGAS	Banlaki et al. [2015]; Berggard et al. [2003]; Dijkstra et al. [2013]; Giegling et al. [2006]; Keltikangas-Jarvinen et al. [2008]
MAOA	Monoamine oxidase A	Aggression, impulsivity, hostility, use of weapons and violent criminal and delinquent behaviors	CGAS	Antypa et al. [2013]; Armstrong et al. [2014]; Beaver et al. [2010a,b]; Eisenberger et al. [2007]; Frazzetto et al. [2007]; Gallardo-Pujol et al. [2013]; Gorodetsky et al. [2014]; Kuepper et al. [2013]; Manuck et al. [2000]; Manuck et al. [2002]; Reif et al. [2007]; Tiihonen et al. [2014]; Verhoeven et al. [2012]
NOS1	Nitric oxide synthase 1 (neuronal)	Impulsive aggressivity and aggression	CGAS	Reif et al. [2009]; Retz et al. [2010]; Rujescu et al. [2008]
NOS3	Nitric oxide synthase 3 (endothelial cell)	Aggressive behavior	CGAS	Rujescu et al. [2008]
SLC6A4 (5HTT)	Solute carrier family 6 (neurotransmitter transporter), member 4 (serotonin transporter)	Aggression, anger, hostility, neuroticism, violence and criminality	CGAS	Conway et al. [2012]; Gonda et al. [2009]; Greenberg et al. [2000]; Gyurak et al. [2013]; Liao et al. [2004]; Lopez-Castroman et al. [2014]; Reif et al. [2007]; Retz et al. [2004]; Sysoeva et al. [2009]; Verona et al. [2006]
TBX19	T-box 19	Angry hostility	CGAS	Wasserman et al. [2007]
TH	Tyrosine hydroxylase	Angry hostility and neuroticism	CGAS	Persson et al. [2000]
TPH1	Tryptophan hydroxylase 1	Aggression, aggressive behavior, anger and violence	CGAS	Evans et al. [2000]; Hennig et al. [2005]; Manuck et al. [1999]; Reuter and Hennig [2005]; Rotondo et al. [1999]; Rujescu et al. [2002]; Yang et al. [2010]
TPH2	Tryptophan hydroxylase 2	Anger	CGAS	Ke et al. [2006]; Mann et al. [2008]; Yang et al. [2010]; Yoon et al. [2012]

CGAS, Candidate gene association study; GWAS, Genome-wide association study.

Several meta-analyses have evaluated the contribution of the *MAOA*-uVNTR and 5HTTLPR to aggressive behavior. Vassos et al. [2014] assessed these two variants, among others, in a total of 31 genes, and did not observe any significant contribution to the phenotype for any of the variants assessed. Heterogeneity (I^2) for the uVNTR and LPR was higher than 50% ($P < 0.01$). In contrast, the meta-analysis of Ficks and Waldman [2014] identified an association between aggressive behaviors and the low activity alleles of the *MAOA*-uVNTR (OR = 1.14; $P = 1.37e\text{-}06$) and the short allele of the 5HTTLPR (OR = 1.52; $P = 7.59e\text{-}11$). Also, Byrd and Manuck [2014] found the low activity alleles of the *MAOA*-uVNTR to be associated with aggressive behaviors in the presence of childhood maltreatment ($P = 8e\text{-}07$).

Candidate Genes Studied in Children and Adolescents

Association studies assessing aggressive traits in children and adolescents have also considered other candidate genes (Table II). Thus, a 48-bp VNTR polymorphism in intron 3 of *DRD4*, encoding the dopamine receptor D4, has been studied. Carriers of the 7-repeat (7R) allele showed higher levels of aggression, externalizing behavior and delinquency [Nobile et al., 2007; Hohmann et al., 2009; Dmitrieva et al., 2011; Buchmann et al., 2014; Farbiash et al., 2014; Schlomer et al., 2015]. Interestingly, an epistatic effect of this allele and the S allele of 5HTTLPR has been reported for aggressive and delinquent behavior [Hohmann et al., 2009]. Also, polymorphic

TABLE III. Genes Associated With Aggression Psychopathology Measures in Children and Adolescents

Gene symbol	Gene name	Phenotype	Study	References
RBFOX1 (A2BP1)	RNA binding protein, fox-1 homolog (C. elegans) 1	Conduct problems and CD	GWAS	Anney et al. [2008]; Sonuga-Barke et al. [2008]
ADH1C	Alcohol dehydrogenase 1C (class I), gamma polypeptide	CD	GWAS	Sonuga-Barke et al. [2008]
BDNF	Brain-derived neurotrophic factor	ODD and CU	CGAS	Willoughby et al. [2013]
MYRFL (C12orf28)	Myelin regulatory factor-like	Conduct problems	GWAS	Anney et al. [2008]
COMT	Catechol-O-methyltransferase	CD	CGAS	Caspi et al. [2008]; DeYoung et al. [2010]; Qian et al. [2009]
DRD4	Dopamine receptor D4	CD, ODD and CU	CGAS	Kirley et al. [2004]; Nikitopoulos et al. [2014]; Zohsel et al. [2014]
KIAA2012 (FLJ39061)	KIAA2012	Conduct problems	GWAS	Anney et al. [2008]
HTR1B	5-hydroxytryptamine (serotonin) receptor 1B, G protein-coupled	CD and CU	CGAS GWAS	Moul et al. [2013]; Viding et al. [2010]
HTR2A	5-hydroxytryptamine (serotonin) receptor 2A, G protein-coupled	CU	CGAS	Moul et al. [2013]
KIRREL	Kin of IRRE like (Drosophila)	Conduct problems	GWAS	Anney et al. [2008]
RPS24P4 (LOC729257)	Ribosomal protein S24 pseudogene 4	Conduct problems	GWAS	Anney et al. [2008]
MAOA	Monoamine oxidase A	CD and ODD with adverse childhood environment	CGAS	Caspi et al. [2002]; Foley et al. [2004]; Haberstick et al. [2005]; Kieling et al. [2013]; Kim-Cohen et al. [2006]; Prom-Wormley et al. [2009]; Qian et al. [2009]; Wakschlag et al. [2010]; Young et al. [2006]
MFHAS1	Malignant fibrous histiocytoma amplified sequence 1	CD	GWAS	Sonuga-Barke et al. [2008]
OXTR	Oxytocin receptor	CD and CU	CGAS	Beitchman et al. [2012]; Dadds et al. [2014]; Malik et al. [2012]; Sakai et al. [2012]; Smearman et al. [2015]
PAWR	PRKC, apoptosis, WT1, regulator	Conduct problems	GWAS	Anney et al. [2008]
PKD1L2	Polycystic kidney disease 1-like 2 (gene/pseudogene)	Conduct problems	GWAS	Anney et al. [2008]
PKD1L3	Polycystic kidney disease 1-like 3	Conduct problems	GWAS	Anney et al. [2008]
RGL1	Ral guanine nucleotide dissociation stimulator-like 1	Conduct problems	GWAS	Anney et al. [2008]
RIT1	Ras-like without CAAX 1	CD	GWAS	Sonuga-Barke et al. [2008]
ROBO2	Roundabout, axon guidance receptor, homolog 2 (Drosophila)	CU	GWAS	Viding et al. [2010]
SLC6A1 (GAT1)	Solute carrier family 6 (neurotransmitter transporter), member 1 (GABA transporter)	CD	GWAS	Sonuga-Barke et al. [2008]
SLC6A4 (5HTT)	Solute carrier family 6 (neurotransmitter transporter), member 4 (serotonin transporter)	CD and conduct problems	CGAS	Brody et al. [2011]; Sakai et al. [2006, 2007, 2010]
SLC6A3 (DAT1)	Solute carrier family 6 (neurotransmitter transporter), member 3 (dopamine transporter)	ODD and conduct problems	CGAS	Burt and Mikolajewski [2008]; Lee et al. [2007]

CGAS, Candidate gene association study; GWAS, Genome-wide association study; CD, Conduct disorder; ODD, Oppositional defiant disorder; CU, Callous-unemotional

variants within the dopamine transporter gene (*SLC6A3* or *DAT*) and the dopamine receptor 2 gene (*DRD2*) have also been associated with aggressive behavior, externalizing behavior, violence, criminal conduct and violent delinquency in children and adolescents [Young et al., 2002; Chen et al., 2005; Guo et al., 2007; Beaver et al., 2008; Zai et al., 2012a].

The genes for vasopressin and for the oxytocin and vasopressin receptors (*AVP*, *OXTR*, *AVPR1A* and *AVPR1B*) have been associated with aggression in children [Malik et al., 2012, 2014; Zai et al., 2012b; Luppino et al., 2014]. Oxytocin and vasopressin encode neurohypophysial hormones with primary roles in sexual reproduction and in water retention, respectively, but they have also

TABLE IV. Genes Associated With Aggression Psychopathology Measures in Adults

Gene symbol	Gene name	Phenotype	Study	References
AR	Androgen receptor	Antisocial behavior	CGAS	Prichard et al. [2007]
BDNF	Brain-derived neurotrophic factor	psychopathy	CGAS	Kourmouli et al. [2013]
DYRK1A	Dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A	Antisocial behavior	GWAS	Tielbeek et al. [2012]
ESR1	Estrogen receptor 1	Antisocial behavior, neuroticism and psychoticism	CGAS	Prichard et al. [2007]; Westberg et al. [2003]
HTR2A	5-hydroxytryptamine (serotonin) receptor 2A, G protein-coupled	Antisocial behavior	CGAS	Burt and Mikolajewski [2008]
MAOA	Monoamine oxidase A	Antisocial behavior, conduct problems and psychopathy	CGAS	Beach et al. [2010]; Byrd and Manuck [2014]; Derringer et al. [2010]; Fergusson et al. [2012]; Fergusson et al. [2011]; Fowler et al. [2009]; McGrath et al. [2012]; Philibert et al. [2011]; Reti et al. [2011]; Sadeh et al. [2013]; Williams et al. [2009]
NR4A2	Nuclear receptor subfamily 4, group A, member 2	Antisocial behavior	CGAS	Prichard et al. [2007]
SLC6A4 (5HTT)	Solute carrier family 6 (neurotransmitter transporter), member 4 (serotonin transporter)	Psychopathy and antisocial behavior	CGAS	Ficks and Waldman [2014]; Fowler et al. [2009]; Garcia et al. [2010]; Sadeh et al. [2013]
SNAP25	Synaptosomal-associated protein, 25kDa	Antisocial personality disorder	CGAS	Basoglu et al. [2011]
TFAP2B	Transcription factor AP-2 beta (activating enhancer binding protein 2 beta)	Antisocial behavior	CGAS	Prichard et al. [2007]

CGAS, candidate gene association study; GWAS, genome-wide association study.

been related with different behavioral traits. Associations with other less studied genes were identified in children and adolescent samples, such as *BDNF* with aggressive behavior [Kretschmer et al., 2014; Musci et al., 2014], *CHRM2* and *CYP19* with externalizing behavior [Dick et al., 2011; Latendresse et al., 2011; Miodovnik et al., 2012] or *SLIT2* and *ESR1* with anger [Sokolowski et al., 2010; Vermeersch et al., 2013].

Candidate gene association studies evaluating CD and ODD in children and adolescents have also considered other genes related to serotonergic and dopaminergic neurotransmission (Table III). The *COMT* Val/Val genotype of the p.Val158Met polymorphism was found associated with CD [Caspi et al., 2008; Qian et al., 2009; DeYoung et al., 2010]. *COMT* encodes the enzyme cathecol-o-methyltransferase, involved in the degradation of dopamine, epinephrine and norepinephrine. Also, the *DRD4*-7R allele was found associated with ODD, CD and callous unemotional (CU) traits [Kirley et al., 2004; Nikitopoulos et al., 2014; Zohsel et al., 2014]. *DAT* has been associated with ODD and conduct problems [Lee et al., 2007; Burt and Mikolajewski, 2008]. The genes for the serotonergic receptors *HTR1B* and *HTR2A* have been associated with CD and CU [Jensen et al., 2009; Moul et al., 2013]. Several variants within the *OXTR* gene have been associated with CD and CU [Beitchman et al., 2012; Malik et al., 2012; Sakai et al., 2012; Dadds et al., 2014; Smearman et al., 2015]. Also, associations have been described for *BDNF* with ODD and CU [Willoughby et al., 2013].

Candidate Genes Studied in Adults

Association studies with aggression traits in adults are summarized in Table II. The Val/Val genotype of the p.Val158Met (rs4680G>A) polymorphism in the *COMT* gene has been associated with aggression, externalizing behavior and anger. It has also been found to moderate the influence of childhood sexual abuse in these traits [Kulikova et al., 2008; Perroud et al., 2010; Shehzad et al., 2012]. However, other studies did not replicate these results [Flory et al., 2007; Kang et al., 2008; Albaugh et al., 2010]. Several associations have been reported for the serotonin receptor genes *HTR1B* and *HTR2A* in adult samples. [Berggard et al., 2003; Giegling et al., 2006; Zouk et al., 2007; Keltikangas-Jarvinen et al., 2008; Conner et al., 2010; Dijkstra et al., 2013; Hakulinen et al., 2013; Banlaki et al., 2015], but no significant associations were identified for *HTR1A* or *HTR2C* [Serretti et al., 2007; Keltikangas-Jarvinen et al., 2008; Perroud et al., 2010]. No consistent results were obtained for *TPH1* and *TPH2* genes in the susceptibility to aggressive behaviors [Manuck et al., 1999; Rotondo et al., 1999; Evans et al., 2000; Rujescu et al., 2002; Hennig et al., 2005; Reuter and Hennig, 2005; Mann et al., 2008; Yang et al., 2010; Yoon et al., 2012]. Associations with the nitric oxide synthase genes *NOS1* and *NOS3* have been reported for aggressive behaviors [Rujescu et al., 2008; Reif et al., 2009; Retz et al., 2010]. An androgen receptor (*AR*) haplotype has been associated with aggression, impulsivity, violent criminal behavior and neuroticism, mostly in adult males [Jonsson et al.,

2001; Cheng et al., 2006; Rajender et al., 2008; Westberg et al., 2009; Aluja et al., 2011]. Other less studied genes in adult samples are: *ABCG1, AKAP5, ANK3, CDH13, CHRM2, CRHR1, CYP2D6, DARPP32, DBH, TBX19,* and *TH*. These have been associated with aggressive behaviors in one or a few studies [Persson et al., 2000; Gietl et al., 2007; Wasserman et al., 2007; Dick et al., 2008; Gonzalez et al., 2008; Hess et al., 2009; Reuter et al., 2009; Richter et al., 2011; Logue et al., 2013; Chen et al., 2014; Tiihonen et al., 2014].

Only a few association studies have been performed for antisocial behavior and psychopathy (Table IV). Studies in which antisocial behavior was assessed in alcoholic individuals or as an outcome of drug use are not considered here. Other less studied genes showed association with antisocial behavior, conduct problems or psychopathy in adults are the ones encoding the androgen receptor (*AR*) and the estrogen receptor 1 (*ESR1*), and also *BDNF, HTR2A, NR4A2, SNAP25* and *TFAP2B* [Westberg et al., 2003; Prichard et al., 2007; Burt and Mikolajewski, 2008; Basoglu et al., 2011; Kourmouli et al., 2013].

Genome-Wide Association Studies (GWAS)

GWAS studies of aggression have highlighted genes involved in synaptic plasticity, which had previously not been assessed by any candidate gene association study (Tables II–IV). None of the association signals reached genome-wide significance, but suggestive associations at $P \leq$ 1e-05 will be discussed. Two GWAS have been performed on aggressive traits (Table II). Mick et al. identified several genes that were nominally associated with aggressive behavior scores in children, such as *LRRC7* and *STIP1*. These genes are involved in neuronal excitability and astrocyte differentiation, respectively [Mick et al., 2011]. Another GWAS was performed in adults and identified 11 nominal association signals with anger ($P \leq$ 1e-05). The most significant association was found with the *FYN* gene, involved in calcium influx and release in the postsynaptic density and also in long-term potentiation [Mick et al., 2014]. The long-term potentiation pathway could play a role in aggressive behaviors both in children and in adults, since *FYN*, *LRRC7* and *STIP1*, as well as other nominally associated genes in the children GWAS, such as *BDNF*, *NTRK2,* and *CAMK2A*, are mediators in this pathway [Mick et al., 2011, 2014]. Another study assessed hostility in adolescents and in adult males and identified several SNPs that showed nominal associations with anger, some of them in the *PURG* and *SHISA6* genes. However, little is known about the function of these genes [Merjonen et al., 2011].

GWAS studies in children have been performed for CD and CU traits (Table III). Anney *et al.* performed a family-based genome-wide study and identified nine genes that were associated with conduct problems: *A2BP1, c12orf28, FLJ39061, KIRREL3, LOC729257, PAWR, PKD1L2, PKD1L3, a*nd *RGL1* [Anney et al., 2008]. *A2BP1* and *KIRREL3* encode proteins involved in neuron development and synaptic plasticity, respectively, and *PAWR* participates in the regulation of dopamine receptor D2 signaling. However, little is known about the function of the other genes in the brain. Another GWAS studied the interaction between genes and environmental risk factors (GxE). It found nominal associations between CD and mother's warmth interacting with several variants in five genes: *RIT1, ADH1C, SLC6A1, A2BP1*, and *MFHAS1* [Sonuga-Barke et al., 2008]. *SLC6A1* codes for a GABA transporter, and the proteins encoded by *RIT1* and *A2BP1* are involved in neuronal development and regeneration. Interestingly, the latter also shows suggestive associations with CD the GWAS discussed above [Anney et al., 2008]. Hamshere et al. performed a meta-analysis of ADHD GWAS data and observed that polygenic risk for ADHD was higher in ADHD with CD, and that was mainly associated with aggression [Hamshere et al., 2013].

Regarding CU, Viding et al. performed a two-stage GWAS, identifying several suggestive associations. Some SNPs that were associated with psychopathic traits in the discovery sample (all of them showing 01e-05 $< P <$ 0.05) and that were nominally replicated were located in neurodevelopmental genes, such as *ROBO2* [Viding et al., 2010]. One of the genes within the top-30 list is close to the serotonin receptor *HTR1B*, which had previously been found associated with CU traits, CD, childhood aggressive behavior, impulsive aggression, anger and hostility [Zouk et al., 2007; Jensen et al., 2009; Conner et al., 2010; Hakulinen et al., 2013; Moul et al., 2013].

Finally, a GWAS that assessed antisocial behavior in adults (Table IV) identified association with *DYRK1A*, which encodes a kinase with a role in synaptic plasticity and brain development [Tielbeek et al., 2012].

Summary: Genetic Association Studies of Aggression

Both CGAS and GWAS approaches have identified potential susceptibility genes for aggressive behaviors. Candidate gene studies have focused mainly in dopaminergic and serotonergic genes and have identified several associations in these (*MAOA, 5HTT, HTR1B, HTR2A, DAT, DRD2, DRD4*, etc.) and other systems (e.g., hormone-related genes like *ESR1, AR, AVP* or *OXTR*). However, most of these associations showed contradictory results or were identified in underpowered samples. Thus these results should be interpreted with caution. On the other hand, genome-wide studies, although not reaching genome-wide significance, have highlighted genes involved in neurodevelopmental processes and synaptic plasticity, not previously considered in candidate gene studies. This may indicate that aggressive behavior does not only involve neurotransmitters or hormonal functions, but also molecules involved in establishing neuronal circuits, neuron-to-neuron connectivity and brain plasticity.

The lack of genome-wide significant findings in the GWAS and the variable results obtained from many of the GCAS is likely due to the small sample sizes of these studies and also to clinical and etiological heterogeneity of the patient groups studied. When assessing aggression-related phenotypes it may be relevant to separate the different phenotypes into more homogeneous groups (e.g., reactive versus proactive aggression) rather than considering them as a whole, since variability in the causes of each type of aggressive behavior may dilute genetic susceptibility effects. In this review we have considered only those data obtained from studies in which aggressive behaviors could not be attributed to other psychiatric conditions, such as drug dependence, bipolar disorder or schizophrenia. For instance, a recent meta-analysis of violent or

aggressive behaviors considered 277 associations in 31 genes and did not find any significant result, although GxE interactions were not considered. However, this meta-analysis included data from studies with very different phenotypic traits, psychiatric and neurological disorders, and probably that may have prevented from identifying significant associations [Vassos et al., 2014]. On the other hand, other meta-analyses identified associated the *MAOA*-uVNTR and 5HTTLPR polymorphisms [Byrd and Manuck, 2014; Ficks and Waldman, 2014].

ANIMAL MODEL STUDIES OF AGGRESSION

Aggression is an evolutionarily conserved behavior that has been studied in many non-human species. This section of the review focuses on four species of animal models that have helped tremendously to shape the basis of our current understanding of neurobiological and molecular mechanisms underlying aggression: avian models, zebrafish, rodents and drosophila models. We particularly emphasize the utilities and potential of these animal model organisms for future genetic studies of aggression.

Avian Models of Aggression

As one of the earliest species used to study the biological basis of aggression, songbirds, demonstrate rich social behaviors such as territoriality, flock hierarchies and male dominance, as well as breeding and parenting behaviors. Most studies focused on offensive behavior associated with territoriality. Defensive behaviors have been studied using intruders or subordinate birds. Study of songbirds behavior and their hormonal and neuronal correlates have shaped our basic understanding of aggressive behavior including, for example, the roles of plasma testosterones and hypothalamo-pituitary-gonadal (HPG) axis (see reviews [Adkins-Regan, 2005; Maney and Goodson, 2011]), and the serotonin and dopamine systems. In contrast to the large amount of behavioral, neurochemical and endocrine studies of songbirds over the last several decades, dissecting the genetic underpinnings of aggression has been scarce.

A naturally occurred segregation of high vs. low aggression with a plumage polymorphism in white-throated sparrow offers a unique opportunity for identifying causal genetic factors responsible for aggressive songbird phenotypes [Thorneycroft, 1966; Ficken et al., 1978]. Half of white-throated sparrows are heterozygous carriers of a rearranged chromosome 2 ($ZAL2^m$); they have a white stripe in the crown and show high aggressive and poor parenting behaviors. Another half are homozygous for wild-type chromosomes (ZAL2); they are less aggressive, show normal parenting and have a tan stripe in the crown. Heterozygotes almost always mate with wild-type birds, which maintains the population structure. Horton et al reported a behavioral characterization of a homozygote female, demonstrating extremely aggressive and dominating behavior and supporting the causal role of rearranged chromosome 2 in increased aggression [Horton et al., 2013]. However, it has taken nearly 30 years after the discovery of this phenotype to describe causal genes and variants in the affected regions [Davis et al., 2011; Huynh et al., 2011]. Among them a prime candidate gene is estrogen receptor 1(ESR1), in which promoter polymorphisms linked with the rearranged chromosome were shown to regulate brain region-specific expression of ESR1 which was correlated with aggressive behavior [Horton et al., 2014].

Rodent Models of Aggression

Rodents, including mouse, rat, hamster and prairie vole, are well-studied models for aggressive behavior due to controlled breeding, and their rich repertoire of species-specific social behaviors. Similar to many birds, rodents are also territorial. Adult male mice or rats will establish a territory when given sufficient living space and attack unfamiliar males intruding in their home cage. The intruders will show defensive behaviors in response to the offensive attacks by the resident. In this classic resident-intruder test setting, both offensive aggression (resident) and defensive behavior (intruder) can be studied [Mineur and Crusio, 2002]. Usually, the latency to initiate the first attack from the resident from the first sniff of the opponent is indicative of the aggressiveness of the resident.

Variations of the resident-intruder test are often used to evaluate the factors influencing aggressive behavior. For example, social isolation (individual housing from days to weeks) can increase offensive aggression of male mice towards group-housed strangers [DaVanzo et al., 1986]. However isolation can also induce timidity in a small but considerable percentage of mice, which show alert and defensive postures, and behaviors such as running away, non-agonistic social interactions rather than delivering attack bites [Krsiak, 1975; DaVanzo et al., 1986]. The difference in social isolation induced abnormal aggressive behavior in mice provides a model to study underlying genetic, hormonal and environmental factors. For example, cannabinoid CB1 receptor (CB1r) knockout mice showed lack of isolation-induced aggression, which was associated with higher expression of 5HT1Br, COMT and MAO-A in amygdala [Rodriguez-Arias et al., 2013]. Social isolation also disrupts immune function and enhances agonistic behavior in prairie voles [Scotti et al., 2015]. Social-isolated rats show hyper- aroused behavior during aggressive contacts, respond inappropriately to species-typical social cues and attack more aggressively by aiming at vulnerable body parts such as head, throat and belly. The enhanced abnormal aggressive behavior was associated with significantly increased activation of brain regions that are known to regulate inter-male aggression in rats [Toth et al., 2012].

For female mice or rats, a well-studied aggressive behavior is maternal aggression. Female mice show enhanced aggression during the first two weeks of the post-partum period. The lactating female will attack male and female intruders to protect her litter. The attack bites of dominant females are usually directed towards the head and snout of opponents [Miczek et al., 2001]. These offensive attacks are usually fast and rarely preceded by anogenital investigation or threats; although sniffing the intruder's genital area after an attack is also considered offensive aggressive behavior. Sometimes, highly aggressive females will attack this vulnerable part. Maternal aggressive behavior can also be defensive, for example piloerection and an upright posture in front of the intruder, boxing and holding down the intruder with her front

legs, etc [Bosch and Meddle, 2005]. Neural manipulation studies showed that disrupting offensive attacks may not affect defensive expressions and vice versa, suggesting that the two categories of maternal aggressive behavior are neurobiologically dissociable domains. However, some argued that all maternal aggression can be collectively categorized as defensive because the ultimate goal of such behavior was to defend and protect the litter [Lonstein and Gammie, 2002]. Lonstein et al. thoroughly reviewed the neural circuitry underlying the maternal aggression and the sensory, hormonal and neurochemical control of the behavior [Lonstein and Gammie, 2002]. A large number of studies have evaluated the roles of neuropeptides such as oxytocin, vasopressin and opioid, neurotransmitter systems such as dopamine, serotonin, GABA, as well as corticotrophin releasing hormone and nitric oxide in contributing to the presentation of maternal aggression in rodents (reviewed [Lonstein and Gammie, 2002].

Noxious and painful stimuli (for example electric shock) have been used to induce aggressive bites in rodents, even in non-aggressive strains. However, the validity of such approaches is questioned in regard to human aggression. The tube dominance test is another standardized laboratory test that is commonly used to measure aggression and social dominance in rodents [Lindzey et al., 1961]. The test employs a transparent tube that allows two animals (mice or rats) to enter from opposite ends face to face and to interact in the center. Dominant animals will force the opponent to completely retreat from the tube. The numbers of winning vs. losing interactions are indicative of the dominance status. Defensive burying refers to a stereotypical response in rodents to a noxious stimuli (such as an electric shock-probe), demonstrated by shoving bedding material to bury the threats. Behaviors observed in a standardized shock-probe/defensive bury test such as burying, freezing, rearing, grooming and exploration are often used to measure anxiety levels and different coping strategies that are correlated with aggression phenotypes.

Strain differences in rodents (particularly mice) have clearly shown that aggressive phenotypes are inherited. Several genetic tools have been developed for rodent models to study the molecular and biological mechanisms underlying aggressive behavior. The earliest one was artificial breeding. Using standardized behavioral testing paradigms, artificial selective breeding was carried out to produce contrasting inbred strains with high vs. low aggression scores. These inbred strains include the Finland Turku aggressive (TA) and non-aggressive (TNS) strains [Sandnabba, 1996], the North Carolina NC900 and NC100 strains [Caramaschi et al., 2007], and the Netherlands short attack latency (SAL) and long attack latency (LAL) mice [van Oortmerssen and Bakker, 1981]. Cross-fostering and the post-natal environment do not alter the development of aggression in these mouse lines, further supporting the genomic etiology of their aggression. The TA and TNS lines demonstrated Mendelian segregation and autosomal inheritance [Sandnabba, 1996]. The Y chromosome was found to play a role in the difference of attack latencies between the SAL and LAL lines [Sluyter et al., 1995; Sluyter et al., 1997]. Several naturally developed inbred lines with different levels of aggression were also recognized as useful models for studying the genetics of aggression. For example, the FVB/NtacfBR male shows more aggression toward females when compared with C57BL/6J males [Canastar and Maxson, 2003]; the NZB/B1NJ strain shows extremely high inter-male aggression, whereas A/J mice rarely show any aggressive behavior [Roubertoux and Guillot, 2005]. A useful summary of commonly used inbred mouse lines was provided by Crawley et al. who compared a wide variety of behavioral traits including aggression, anxiety and parental behaviors based on an extensive literature review [Crawley et al., 1997].

Like the studies of songbirds, studies of these inbred strains in the past three decades have helped our understanding of neural circuitry, hormonal and neurochemical correlates for different domains of aggressive behavior. See reviews [Miczek et al., 2001]. However, identification of causal genetic determinants has not been fruitful. A few attempts have been made to identify quantitative trait loci (QTLs) underlying differences in aggressive phenotypes between inbred lines. QTL analysis showed that aggressive attacks measured in different testing conditions, for example the inter-male aggression and isolation induced aggression, have overlapping, yet different genetic contributions [Roubertoux and Guillot, 2005]. This observation supports the distinction of different domain/categories of aggressive behavior and highlights the complexity of underlying genetic causality. However, we are still far away from pinpointing the causal genes within these QTL regions which often contain hundreds of genes. New analytic methodologies have recently been used to uncover such complex genetic causes of aggression. Malki et al. [2014] used a weighted gene co-expression network analysis (WGCNA) method to examine transcriptome-wide differences between the three inbred mouse lines with high vs. low aggression levels. They uncovered two important pathways involving NF-kB and MAPKs. The study also yielded 14 differentially expressed genes from the two significant pathways as plausible candidates and some of them, such as Adrbk2, had previously been implicated in aggressive behavior. Since gene expression is an unbiased approach, identifying previously implicated candidate genes confirms the biological relevance of those co-expression networks in mouse aggressive phenotypes. Although we still have not pinpointed the genetic determinants underlying the differences in aggression between those inbred models, we are one step closer towards understanding the complex genetic networks that are underlying the phenotypes.

Another useful genetic approach is single gene manipulation, i.e., transgenic and gene knockout or mutations, particularly in mice. A detailed review of earlier genetic knockout studies has been provided elsewhere [Takahashi and Miczek, 2014]. We performed an updated PubMed search using keywords of "Knockout AND (Mice OR Mouse) AND ((aggressive behavior) OR aggression)" and retrieved 265 articles on non-human animals. After filtering through title, abstract and full texts, we summarized 85 genes that altered one or more subtypes of aggressive behavior in knockout mice (or were silenced by siRNA, see Table V). Many of these genes regulate sensory, hormonal and neurochemical/neurotransmitter systems and neurodevelopmental processes. KO mice phenotype information can also easily searched through databases such as Mouse Phenome Database at The Jackson Laboratory and currently ~50 strains of mutant mice with abnormal aggressive behavior are available from the Jackson Laboratory inventory.

In this section, we give some classical examples and highlight the advantages and limitations of the single gene approach. For example, gene knockouts of 5-HT neuron-specific transcription factor Pet-1 or tryptophan hydroxylases 2 (TPH2) lead to enhanced offensive aggression in resident-intruder tests accompanied by reduced 5-HT content or 5-HT neural activities [Hendricks et al., 2003; Alenina and Kikic, 2009; Angoa-Perez et al., 2012; Mosienko et al., 2012]. Knockout of alpha-calcium-calmodulin–dependent kinase II (α-CaMKII) induced a decreased fear response and an increase in defensive aggression accompanied by reduced serotonin release in dorsal raphe neurons [Chen et al., 1994]. In contrast, knockout of the monoamine oxidase A (MAOA) gene increased brain 5-HT content. In humans, deficiency of MAOA causes Brunner syndrome characterized by impulsive aggressiveness [Brunner and Nelen, 1993]. MAOA knockout mice also display enhanced aggression toward intruder mice [Scott et al., 2008], but reduced defensive behavior in the presence of predator-related cues [Godar et al., 2011]. These examples show the complexity of the genetic mechanisms underlying different aggression domains and also highlight the limitations of the single gene approach.

Manipulation of a single gene produces a cascade of expression and biochemical changes during development, which interact with environmental factors and other genetic factors. For example MAOA knockout mice showed enhanced expression of NMDA receptor subunit 2A and 2B expression in the prefrontal cortex and their abnormal aggressive behavior can be selectively countered by administration of NMDAR antagonists [Bortolato and Godar, 2012]. This showed a critical role of NMDA receptor in the pathogenesis of escalated aggression among MAOA knockout mice. Consistent with this, an NR1 subunit deficient mouse line shows reduced social investigation and lack of species-typical aggressive behavior in a resident-intruder paradigm [Mohn et al., 1999; Duncan et al., 2004]. Therefore, interpretation of single gene knockout studies needs to be cautious and take into consideration downstream and compensatory changes in the context of the whole organism.

Two species of voles distinct in their social behaviors exist as a perfect model to study genes and aggression. Prairie and pine voles are highly social and monogamous, whereas meadow and montane voles are asocial and promiscuous [Insel and Shapiro, 1992; Young and Wang, 2004]. Prairie voles develop pair bonds between mates. Males display intense aggression toward female or male conspecific strangers in the resident-intruder paradigm but they maintain a high level of social affiliation with their familiar female partners [Aragona and Liu, 2006; Gobrogge et al., 2007]. Although similar in nonsocial behaviors, nonmonogamous vole species do not show partner preference or increased aggression towards stranger conspecifics [Insel et al., 1995]. Species comparisons show that polymorphisms in the arginine vasopressin (AVP) receptor gene, V1aR, were associated with distinct patterns of gene expression in the brain associated with differences in pair bonding and selective aggression of voles [Lim et al., 2004; Hammock et al., 2005; Ophir et al., 2008]. Genetic variations of V1aR and plasma levels of AVP were also associated with human social behaviors including aggression and partner relationships [Walum et al., 2008; Gouin et al., 2012; Luppino et al., 2014].

Drosophila Models of Aggression

Aggressive behavior in the fruit fly, Drosophila melanogaster, has been observed since 1915 when first reported by Sturtevant [Sturtevant, 1915]. Males spread their wings and engage in antagonistic encounters when competing for mating females. Both offensive and defensive behaviors have been observed. Drosophila's nervous system is simple but recapitulates a range of cellular and network properties relevant to humans. With modern genetic tools for drosophila, this model system has made significant contributions to our genetic understanding of aggressive behavior. Similar approaches that we described for rodent models, such as artificial selection, QTL mapping and single gene manipulation, have been used in drosophila research. A detailed summary of these studies and the genetic, pheromonal regulation, neurobiological and genetic regulation of aggressive behavior has been reviewed elsewhere [Dahanukar and Ray, 2011; Zwarts et al., 2012; Fernandez and Kravitz, 2013]. In this section we highlight several recent significant contributions.

Edwards et al. compared the transcriptomes of high vs. low aggression drosophila lines. They identified 1593 probe sets that were differentially regulated in these lines [Edwards et al., 2006]. Remarkably, out of 19 genes selected for behavioral validation using genomic manipulation in an isogenic background, 15 showed significant effects in altering aggressive behaviors after Bonferonni corrections. These genes are involved in diverse biological processes, including electron transport, catabolism, nervous system development and G-protein coupled receptor signaling. Seven were computationally predicted genes and none had been previously implicated in aggressive behavior. Dierick and Greenspan also examined the gene expression between the high aggression and neutral lines [Dierick and Greenspan, 2006]. Among the significantly, differentially expressed genes, a cytochrome gene, *Cyp6a20* that might be involved in pheromone degradation, was confirmed to directly regulate aggressive behavior by using a mutant line and an odor- binding protein. *Obp56a,* showed the most robust reduction in expression in the aggressive line [Dierick and Greenspan, 2006].

High-throughput and automated behavioral assays were developed to measure drosophila social behavior including aggression, enabling larger scale genetic correlations with the behavior [Hoyer et al., 2008; Dankert et al., 2009]. Forty inbred lines were quantified for aggressive behavior and genome-wide association screens for quantitative trait transcripts were performed on these lines [Edwards et al., 2006]. Two hundred sixty-six novel candidate genes associated with aggressive behavior were identified. Nine genes were confirmed to show altered aggression from behavioral evaluation of 12 selected candidate genes [Edwards et al., 2006]. Furthermore, a network based co-expression analysis revealed functional modules of correlated transcripts that were associated with variations of aggressive behavior. Table VI, lists the candidate genes for aggression implicated by drosophila studies. We also included the genes that were identified through the above describe expression analysis and were confirmed by behavior changes on the mutant lines. Of note, none of these genes have been implicated in human aggression.More recently, collective efforts were made to generate 192 genome-sequenced inbred lines derived from a single

TABLE V. Genes Implicated by Aggressive Phenotypes in Knockout Mice Studies

Gene names	Human homolog	Aggression phenotype/domain	Studied for aggression in humans
Hormonal regulators			
AVP receptor V1aR (Avpr1a)	AVPR1A	Social aggression was unaffected in KO mice [Wersinger et al., 2007]	Yes (Table II)
Vasopressin 1b receptor (Avpr1b)	AVPR1B	Avp1b gene knockout affected social memory, reduced inter-male aggression and maternal aggression [Scotti et al., 2015; Toth et al., 2012]	Yes (Table II)
Corticotropin-releasing factor receptor 1(Crfr1)	CRHR1	Gene deficiency reduces maternal aggression [Gammie et al., 2007]	Yes (Table II)
Corticotropin-releasing factor receptor type 2(Crfr2)	CRHR2	KO mice showed increased aggression [Coste et al., 2006] and reduced maternal aggression [Gammie et al., 2005]	No human studies
Corticotropin releasing hormone binding protein(Crhbp)	CRHBP	Gene Knockout specifically impaired maternal aggression [Gammie et al., 2008]	No human studies
Aromatase P450 (CYP19)	CYP19	KO male exhibited a complete loss of aggressive behavior [Toda et al., 2001]	Yes (Table II)
Estrogen receptor-α (ERα)	ESR1	Reduction of ERα expression in preoptic neurons significantly increased aggression toward both sexual partners and male intruder [Ribeiro et al., 2012]	Yes (TablesIIandIV)
Estrogen receptor-beta(Esr2)	ESR2	Gene disruption elevated aggression levels [Nomura et al., 2006]	No human studies
Growth hormone releasing hormone(Ghrh)	GHRH	Gene knockout reduces aggressiveness [Sagazio et al., 2011]	No human studies
Melanocortin-5 receptor (MC5R)	MC5R	MC5R deficiency disinhibits an aggression-suppressing pheromonal signal [Morgan et al., 2004]	No human studies
Steroidogenic factor 1 (SF1), or Nuclear Receptor Subfamily 5, Group A, Member 1(Nr5a1)	NR5A1	KO mice were significantly more aggressive [Grgurevic et al., 2008]	No human studies
Oxytocin (OT)	OT	KO mice showed reduced aggression and increased social investigation [Lazzari et al., 2013]; enhanced offensive aggression and infanticidal behavior were observed in KO mice [Ragnauth et al., 2005]	OT reduces reactive aggression in state anxious women [Campbell and Hausmann, 2013]
Oxytocin receptor (Oxtr)	OXTR	Male Oxtr−/− mice had elevated levels of aggression [Dhakar et al., 2012]	Yes (TablesIIandIV)
Granulin(Grn), progranulin(Pgrn)	PGRN	Pgrn-deficient mice showed enhanced aggressiveness to intruders [Kayasuga et al., 2007]	A missense mutation in PGRN gene was found in a patient of frontotemporal dementia with aggressiveness and abnormal sexual behavior [Rainero et al., 2011]
Melanin-concentrating hormone (MCH)	PMCH	Mch Ko mice showed abnormal olfactory behaviors and male showed increased aggression [Adams et al., 2011]	No human studies
Prostaglandin E receptor subtype EP1 (Ptger1)	PTGER1	KO mice showed impulsive aggression [Matsuoka et al., 2005]	No human studies
Steroid-5-alpha-reductase, alpha polypeptide 1(Srda1)	SRD5A1	KO mice is lack of testosterone induced aggression [Frye et al., 2002]	No human studies
Thyroid Stimulating Hormone Receptor(Tshr)	TSHR	TSHR KO mice show ADHD phenotype with increased aggression [Mouri et al., 2014]	No human studies
Urocortin 2(Ucn2)	UCN2	Male UCN2 null mice showed reduced aggressiveness [Breu et al., 2012]	No human studies.

(*Continued*)

TABLE V. (*Continued*)

Gene names	Human homolog	Aggression phenotype/domain	Studied for aggression in humans
Neurochemical and neurotransmitter systems			
Acetylcholinesterase (AChE)	ACHE	AChE KO mice were lack of aggressive behavior [Duysen et al., 2002]	No human studies
Adenosine receptor A1 (Adora1)	ADORA1	Mice lacking the adenosine A1 receptor are anxious and aggressive [Gimenez-Llort et al., 2002]	No human studies
Adenosine A2a receptor	ADORA2A	KO male showed enhanced aggression towards intruder [Ledent et al., 1997]	No human studies
Adrenoceptor alpha 2C(Adra2c)	ADRA2C	KO mice showed increased aggression [Scheinin et al., 2001]	No human studies
Cannabinoid CB1 receptors (Cnr1)	CNR1	KO mice housed in groups showed higher levels of offensive aggression, and lack of isolation induced enhance in aggression [Rodriguez-Arias et al., 2013]	No human studies
Dopamine beta-hydroxylase knockout (Dbh)	DBH	DBH KO mice showed absence of resident-intruder aggression [Marino et al., 2005]	Yes (Table II)
Dopamine D2 receptor (Drd2)	DRD2	DRD2 long isoform KO mice showed reduced aggression [Vukhac et al., 2001]	Yes (Table II)
Glutamic acid decarboxylase (GAD65)	GAD2	KO mice showed reduced intermale aggression [Stork et al., 2000]	No human studies
Glutamate receptor, ionotropic, AMPA 3(Gria3)	GRIA3	GluA3-deficient mice showed an increase in isolation-induced male aggression [Adamczyk et al., 2012]	No human studies
Glutamate delta-1 receptor(Grid1)	GRID1	KO mice showed robust aggression in the resident-intruder test [Yadav et al., 2012]	No human studies
5-hydroxytryptamine (serotonin) receptor 1B (Htr1b)	HTR1B	KO mice showed increased aggression towards intruder [Bouwknecht et al., 2001]	Yes (TablesIIandIII)
Monoamine oxidase A(Maoa)	MAOA	KO mice display enhanced aggression toward intruder mice [Scott et al., 2008], but showed reduction of defensive and fear-related behaviours [Godar et al., 2011]	Yes (Tables II–IV)
Membrane metallo-endopeptidase (Mme)	MME	KO mice showed enhanced aggression to intruder [Fischer et al., 2000]	No human studies
NPY1R neuropeptide Y receptor Y1 (Npy1r)	NPY1R	Receptor deletion resulted in increase in territorial aggression [Karl et al., 2004]	No human studies
Enkephalins(Enk), Proenkephalin (Penk)	PENK	ENK KO mice showed increased offensive aggression [Konig et al., 1996]	No human studies
Solute Carrier Family 6 (Neurotransmitter Transporter), Member 1(*Slc6a1)*	SLC6A1	GABA transporter 1 KO mice showed reduced aggression [Liu et al., 2007]	Yes (Table III)
Solute carrier family 6 (neurotransmitter transporter), member 3 (dopamine transporter)(Slc6a3, Dat1)	SLC6A3/DAT1	DAT1 KO mice exhibited increased aggression [Rodriguiz et al., 2004]	Yes (TablesIIandIII)
Solute carrier family 6 (5-HT transporter), member 4, *Slc6a4*	SLC6A4/5-HTT	5-HT transporter (5-HTT) knockout mice showed reduced maternal aggression [Heiming et al., 2013]	Yes (TablesII–IV)
Tryptophan hydroxylase 2 (Tph2)	TPH2	Mice lacking Tph2 (and brain 5HT) show intense compulsive and impulsive behaviors to include extreme aggression [Angoa-Perez et al., 2012]	Yes (TableII)
Nerve system development			
Brain-derived neurotrophic factor (Bdnf)	BDNF	KO mice exhibited elevated conspecific aggression and social dominance [Ito et al., 2011]	Yes (Tables II–IV)

(*Continued*)

TABLE V. (*Continued*)

Gene names	Human homolog	Aggression phenotype/domain	Studied for aggression in humans
Alpha-calcium/calmodulin-dependent protein kinase II (Camk2a)	CAMK2A	Camk2a overexpression increases offensive aggression [Hasegawa et al., 2009]	No human studies
Calcium channel, voltage-dependent, N type, alpha 1B(Cacna1b)	CACNA1B	Gene KO enhanced aggressive behavior to the intruder [Kim et al., 2009]	No human studies
Calcium channel, voltage-dependent, beta 3 subunit(Cacnb3)	CACNB3	Null mice showed increase aggression [Murakami et al., 2007]	No human studies
Cell adhesion molecule 1(Cadm1)	CADM1	KO mice showed excessive aggression and anxiety [Tanabe et al., 2013]	No human studies
CREB-regulated transcription coactivator 1 (Ctrc1)	CRTC1	Crtc1(−/−) mice exhibit impulsive aggressiveness and many other behavioral abnormalities [Breuillaud et al., 2012]	No human studies
ENGRAILED 2 (EN2)	EN2	KO mice displayed reduced aggression [Cheh et al., 2006]	No human studies
v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 4(Erbb4) and 2(Erbb2)	ERBB2 and ERBB4	ErbB2/B4-deficient mice show increased aggression [Barros et al., 2009]	No human studies
Protein FEV (Fev) or plasmacytoma-expressed transcript 1(Pet1)	FEV (or PET1)	Pet-1 plays a critical role in 5-HT neuron development and is required for normal anxiety-like and aggressive behavior [Hendricks et al., 2003]	No human studies
GDP Dissociation Inhibitor 1(Gdi1)	GDI1	Gdi1-deficient mice show lowered aggression [D'Adamo et al., 2002]	No human studies
Neuronal Immediate Early Gene, 1 (Homer1)	HOMER1	Heterozygous mice showed increased aggression [Jaubert et al., 2007]	No human studies
Densin-180, leucine rich repeat containing 7(LRRC7)	LRRC7	KO male showed enhanced aggression [Carlisle et al., 2011]	Yes (Table II)
Limbic system-associated membrane protein(Lsamp)	LSAMP	KO mice showed reduced aggressiveness and reduced dominance [Innos et al., 2011]	No human studies
Neural cell adhesion molecule (Ncam)	NCAM	NCAM deletion increased inter-male aggression and altered emotionality [Kohl et al., 2013]	No human studies
Methyl-CpG binding protein 2 (Mecp2)	MECP2	Mecp2 conditional knockout (CKO) mice were aggressive, hyperphagic, and obese [Fyffe et al., 2008].	A patient with Rett syndrome demonstrated episodes of uncontrolled aggression [Huppke et al., 2006]
Neuregulin-1 (Nrg1)	NRG1	Mutant animals demonstrated increased aggressive following [O'Tuathaigh et al., 2008]	No human studies
Neuronal nitric oxide synthase (nNOS, Nos1)	NOS1	nNOS knockout mice were significantly more aggressive than wild-type [Trainor et al., 2007]	Yes (Table II)
Tailless, nuclear receptor subfamily 2, group E, member 1 (Nr2e1)	NR2E1	Deletion of *Tailless* gene produded highly aggressive phenotype [Juarez et al., 2013]	NR2E1 showed forebrain-specific expression and may be associated with bipolar disorder, schizophrenia, or aggressive disorders [Kumar et al., 2008]
Neurexin 1α (Nrxn1α)	NRXN1	Knockout increased intermale aggression [Grayton et al., 2013]	Gene mutations were found in autism and intellectual disabilities [Yangngam et al., 2014]
Neuronal PAS domain protein 4 (Npas4)	NPAS4	Ko mice spend more time avoiding an unfamiliar male during a first encounter, showed higher social dominance than their WT littermates [Coutellier et al., 2012]	No human studies
p21-activated kinase(Pak4, Pak5, and Pak6)	PAK4, PAK5, and PAK6	All the knockout genotypes were found to be less aggressive [Furnari et al., 2013]	No human studies

(*Continued*)

TABLE V. (*Continued*)

Gene names	Human homolog	Aggression phenotype/domain	Studied for aggression in humans
ST8 Alpha-N-Acetyl-Neuraminide Alpha-2,8-Sialyltransferase 2 (St8sia2)	ST8SIA2	KO mice displayed both a decreased social motivation and an increased aggressive behavior [Calandreau et al., 2010]	No human studies
Olfactory and other sensory systems			
Alpha-1,3 galactosyltransferase gene (Ggta1)	A3GALT2	Increased aggression in KO mice [Sorensen et al., 2008]	No human studies
Type 3 adenylyl cyclase (AC3)	AC3	AC3 KO female is lack of maternal aggression [Wang and Storm, 2011]	No human studies
Acid-sensing ion channel 3 (Asic3)	ASIC3	Gene KO reduced aggressiveness [Wu et al., 2010]	No human studies
Beta2-microglobulin (B2m)	B2M	B2M deficient mice show specific defect in inter-male aggression [Loconto et al., 2003]	No human studies
Transient receptor potential cation channel, subfamily C, member 2 (Trpc2)	N/A	Trpc2 knockout mice is lack of male-male aggression [Miller, 2014]	N/A
Cyclic nucleotide-gated channel alpha2 (*Cnga2*)	CNGA2	Knockout mice failed mate or fight [Mandiyan et al., 2005]	No human studies
Mitogen-activated protein kinase 7 (Mapk7)	MAPK7	Conditional deletion of the Mapk7 gene in neural stem cells impairs several pheromone-mediated behaviors including aggression and mating in male mice [Zou et al., 2013]	No human studies
Guanine nucleotide binding protein (G protein), alpha activating activity polypeptide O(Gnao1)	GNAO1	G protein G(alpha) o is essential for vomeronasal function and aggressive behavior in mice [Chamero et al., 2011]	No human studies
Olfactory G-protein -subunit G8 (Gng8)	GNG8	Gene knockout reduced pheromone-mediated aggressiveness in both males and females, with other socio-sexual behaviours remaining unaltered [Montani et al., 2013]	No human studies
Kin of IRRE like 3 (Kirrel3)	KIRREL3	Kirrel3(−/−) mice display a loss of male-male aggression [Prince et al., 2013]	No human studies
Prepronociceptin	PNOC	Group housed KO mice showed enhanced aggression under competitive conditions [Ouagazzal et al., 2003]	No human studies
Pituitary adenylate cyclase-activating polypeptide (Pacap)	PACAP	Social isolation induced aggressive behavior in KO mice but not in WT mice [Ishihama et al., 2010]	No human studies
Pituitary adenylate cyclase-activating polypeptide (PACAP) type 1 receptor (PAC1)	PAC1	PAC1-deficient males displayed reduced aggression and increased mounting towards males [Nicot et al., 2004]	No human studies
Potassium intermediate/small conductance calcium-activated channel, subfamily N, member 3, (Kcnn3)	KCNN3	KO mice showed deficits in mating and aggressive behaviors [Kim et al., 2012]	No human studies
Potassium inwardly-rectifying channel, subfamily J, member 3 (Kcnj3)	KCNJ3	KO mice showed deficits in mating and aggressive behaviors [Kim et al., 2012]	No human studies
Vomeronasal type-1 receptor 1 (Vn1r1)	VN1R1	Mice with deletion of a cluster of V1r genes display abnormal inter-male and maternal aggression [Del Punta et al., 2002]	No human studies
Other unspecified genes			
Early growth response 3(Egr3)	EGR3	Gene KO increased offensive aggression towards the intruder [Gallitano-Mendel et al., 2008]	No human studies

(*Continued*)

TABLE V. (*Continued*)

Gene names	Human homolog	Aggression phenotype/domain	Studied for aggression in humans
Glycogen synthase kinase-3 alpha (Gsk3a)	GSK3A	Mutant mice showed reduced aggression [Kaidanovich-Beilin et al., 2009]	No human studies
TNF receptor type 1 and type 2 (Tnfrsf1a and Tnfrsf1b)	TNFRSF1A and TNFRSF1B	Combined deletion of two receptors resulted in a lack of aggressive behavior [Patel et al., 2010]	No human studies
Heat shock factor 1 (Hsf1)	HSF1	HSF1 deficiency increased aggression [Uchida et al., 2011]	No human studies
Maternally imprinted/paternally expressed gene, Peg3	PEG3	KO animal showed higher maternal aggression [Champagne et al., 2009]	No human studies
Prion protein (Prnp)	PRNP	Prnp knockout showed enhanced offensive aggression [Budefeld et al., 2014]	3'UTR polymorphism was associated with increased risk for delusions, anxiety, agitation/aggression [Flirski et al., 2012]

Raleigh population. The drosophila melanogaster Genetic Reference Panel (DGRP) was constructed to share these inbred lines and their genetic data [Mackay et al., 2012]. DGRP provides powerful resources for mapping genetype- phenotype relationships. Taking the advantage of the DGRP resources and standardized quantitative behavioral assays, a GWAS study for aggressive behavior was conducted. 74 common variants in 39 genes were reported as significant association candidates and one SNP in the intron of CG14869 (AdamTS-A) met the genome-wide significance threshold ($2.61 \times 10-8$) [Shorter et al., 2015]. Only one significant candidate gene association, 5-HT1A, had been previously implicated in aggression. Additionally, 22 genes harboring rare variants were significantly associated with aggressive behaviors and 10 passed Bonferroni corrections. None of these genes had been implicated in aggression previously [Shorter et al., 2015]. The same paper also described an extreme QTL GWA study of the advanced intercross populations (AIPs) derived from the most and least aggressive DGRP lines. This approach identified 746 SNPs in or near 355 genes with significant association, of which 22 passed Bonferroni corrections. The top genes included some in the serotonin, dopamine and glutamate pathways, consistent with the well-known roles of these genes in aggression. Due to the large number of genes with significant associations, these are not included in Table VI. See the original reference for the complete list of genes and variants [Shorter et al., 2015]. Surprisingly, this list of genes has almost no overlap with the GWA results from the original DGRP lines. Despite this non-overlap in genes and variants, two results were mapped and enriched onto a genetic interaction network inferred from an analysis of pairwise epistasis in the DGRP lines [Shorter et al., 2015]. This observation supports the multifactorial nature of the genetic underpinnings for aggression and suggests that different aggression genes may converge on the same interconnected networks or pathways.

Frustrative Non-Reward Reactions

Frustrative non-reward aggression has been less well studied in animal models. Discontinuation or omission of scheduled reinforcement can effectively induce escalated levels of aggressive behavior in fish [Vindas et al., 2012, 2014], birds [Azrin and Hutchinson, 1966; Cherek and Pickens, 1970], rodents [Stanford and Salmon, 1989; Miczek et al., 2001], pigs [Melotti et al., 2013], monkeys and humans [Barzman and Eliassen, 2014]. An operant procedure has been implemented in mice using sucrose as a reinforcer to examine extinction induced aggressive confrontation to intruder mice [Miczek et al., 2001]. Similar paradigms have been used to induce aggressive responses in other species. Studies have examined the roles of the nonadrenergic system [Stanford and Salmon, 1989], the 5-HT1B receptor [de Almeida and Miczek, 2002], neurosteroids and GABAA receptors [Miczek et al., 2003] in frustrative non-reward induced reactions in rodents and fish. Barzman et al found that the expression of TNF-related inflammatory cytokine genes was positively correlated with frustrative non-reward and aggressive behaviors in pediatric patients with bipolar disorder [Barzman and Eliassen, 2014]. However, no studies have examined the genes underlying frustrative nonreward aggression in animals.

TABLE VI. Drosophila Genes for Aggression

Genes	Human homolog	Methods in fly	Phenotype	Fly reference	Studied in human aggression
Neurochemical and neurotransmitter systems					
Tyramine-β-hydroxylase (TβH)	Dopamine beta-hydroxylate (DBH)	Mutant line	Null animal show reduced Intermale aggression and maternal aggression	[Hoyer et al., 2008]	Yes (Table II)
Tyrosine decarboxylase, neuronal (Tdc2)	N/A	Mutant line	Mutant fly showed reduced inter-male aggression	Hoyer et al. [2008]	N/A
Tryptophan hydroxylase (Trh)	Tryptophan hydroxylase 1 (TPH1)	Overexpression	Overexpression increased aggression, escalated aggression	Dierick and Greenspan [2007]; Alekseyenko et al. [2010]	Yes (Table II)
5-HT receptors (5-HT2a, 5-HT1A-like)	5-HT receptors (HTR2A, HTR1A)	Pharmacological manipulation	Activation of 5-HT2 receptors decreases overall aggression, activation of 5-HT1A-like receptors increases aggression. Different aspects of aggression was also affected by different receptor subtypes	Johnson et al. [2009]	Yes (TablesII,III)
Neuropeptide F (npf)	Neuropeptide Y (NPY)	Genetic silencing of the neuropeptide F (*npf*)-neurons	Lack of npf-neuron activity increased fly aggression	Dierick and Greenspan [2007]	Cerebrospinal fluid neuropeptide Y-level correlates with impulsive aggression in human subjects [Coccaro et al., 2012]
Dopa decarboxylase (Ddc),	Dopa decarboxylase (aromatic L-amino acid decarboxylase, DDC)	Genetic inactivation of Ddc-neurons	Inactivation of Ddc-neurons eliminated mid- and high-level aggression	Alekseyenko et al. [2010]	No human studies
Sensory (olfactory and vision) system					
Odorant receptor 67d (Or67d);	N/A	Pharmacological activation	Pheromone cVA promotes aggression among males via activating Or67d expressing olfactory receptor neurons	Wang and Anderson [2011]; Liu et al. [2011]	N/A
Odorant receptor 65a (Or65a)	N/A	Pharmacological activation	Pheromone cVA suppresses aggression via activating Or65a olfactory receptor neurons	Liu et al. [2011]	N/A
White, ATP-binding cassette (ABC) transporter	ATP-binding cassette sub-family G member 1 (ABCG1)	Mutation line	Mutant showed abnormal vision and impaired aggressive behavior such as Lunging behavior	Hoyer et al. [2008]	Yes (Table II)
Genes identified through expression analysis					
Cytochrome P450, 6a20 (Cyp6a20)	Thromboxane A synthase 1 (TBXAS1)	Gene expression and mutant line	Gene mutation or deficiency decreased aggression	Dierick and Greenspan [2006]; Robin, Daborn et al. [2007]	No human studies
Odor-binding protein (Obp56a)	N/A	Gene expression	Decreased gene expression in high aggressive lines	Dierick and Greenspan [2006]	N/A

TABLE VI. (*Continued*)

Genes	Human homolog	Methods in fly	Phenotype	Fly reference	Studied in human aggression
Muscleblind (mbl)	Muscleblind-like splicing regulator 3 (MBNL3)	Gene expression and Mutant lines	Mutant showed increased aggression score	Edwards et al. [2006]	No human studies
CG17154	N/A	Gene expression and Mutant lines	Mutant showed increased aggression score	Edwards et al. [2006]	N/A
CG5966	Pancreatic triacylglycerol lipase precursor(PNLIP)	Gene expression and Mutant lines	Mutant showed increased aggression score	Edwards et al. [2006]	No human studies
CG30015	N/A	Gene expression and Mutant lines	Mutant showed increased aggression score	Edwards et al. [2006]	N/A
Darkener of apricot (Doa)	CDC-like kinase 2 (CLK2)	Gene expression and Mutant lines	Mutant showed increased aggression score	Edwards et al. [2006]	No human studies
CG14478	N/A	Gene expression and Mutant lines	Mutant showed increased aggression score	Edwards et al. [2006]	N/A
CG12292, spichthyin (spict)	Non-imprinted in Prader-Willi/ Angelman syndrome 2 (NIPA2)	Gene expression and Mutant lines	Mutant showed decreased aggression score	Edwards et al. [2006]	No human studies
Tramtrack(ttk)	N/A	Gene expression and Mutant lines	Mutant showed decreased aggression score	Edwards et al. [2006]	N/A
CG1623, Hebe	N/A	Gene expression and Mutant lines	Mutant showed decreased aggression score	Edwards et al. [2006]	N/A
CG13512	N/A	Gene expression and Mutant lines	Mutant showed decreased aggression score	Edwards et al. [2006]	N/A
SP71	N/A	Gene expression and Mutant lines	Mutant showed decreased aggression score	Edwards et al. [2006]	N/A
Longitudinals lacking(lola)	Zinc finger protein with interaction domain (ZID)	Gene expression and Mutant lines	Mutant showed decreased aggression score	Edwards et al. [2006]	No human studies
Scribbler	Zinc finger protein 609 (ZNF609)	Gene expression and Mutant lines	Mutant showed decreased aggression score	Edwards et al. [2006]	No human studies
Male-specific RNA 87F	N/A	Gene expression and Mutant lines	Mutant showed decreased aggression score	Edwards et al. [2006]	N/A

TABLE VI. (*Continued*)

Genes	Human homolog	Methods in fly	Phenotype	Fly reference	Studied in human aggression
Kismet	Chromodomain helicase DNA binding protein 6,7,8,9 (CHD6, CHD7, CHD8,CHD9)	Gene expression and Mutant lines	Mutant showed decreased aggression score	Edwards et al. [2006]	No human studies
CG11448	Rab interacting lysosomal protein-like 1 (RILPL1)	Gene expression and Mutant lines	Mutant showed increased aggression score	Edwards et al. [2009]	No human studies
CG13760	N/A	Gene expression and Mutant lines	Mutant showed increased aggression score	Edwards et al. [2009]	N/A
CG2556	N/A	Gene expression and Mutant lines	Mutant showed increased aggression score	Edwards et al. [2009]	N/A
CG31038	N/A	Gene expression and Mutant lines	Mutant showed increased aggression score	Edwards et al. [2009]	N/A
CG32425	N/A	Gene expression and Mutant lines	Mutant showed increased aggression score	Edwards et al. [2009]	N/A
Late bloomer, Tetraspanin 42Ek (Tsp42Ek)	N/A	Gene expression and Mutant lines	Mutant showed increased aggression score	Edwards et al. [2009]	N/A
Skuld (skd)	Mediator complex subunit 13 (MED13)	Gene expression and Mutant lines	Mutant showed increased aggression score	Edwards et al. [2009]	No Human Studies
GTPase-activating protein 1 (Gap1)	RAS p21 protein activator 3 (RASA3)	Gene expression and Mutant lines	Mutant showed decrease aggression score	Edwards et al. [2009]	No Human Studies
Schizo	ADP-ribosylation factor guanine nucleotide exchange factor 2 (ARFGEF2)	Gene expression and Mutant lines	Mutant showed decrease aggression score	Edwards et al. [2009]	No Human Studies

Summary of Animal Models of Aggression

The face, construct and predictive validities for aggression models of various species have been extensively evaluated. Although evolutionarily conserved, many aggressive measurements in animal models are species-specific and should be cautiously translated to human behavior. Nevertheless, animal models have facilitated our understanding of the neurobiological and molecular underpinning of normal and pathological aggressive behaviors. Although many classical pathways such as hormonal and neurotransmitter pathways have been largely replicated and confirmed in various animal and human studies, recent advances in genetic tools and network based analysis have suggested novel genetic mechanisms. This is not surprising, since previous candidate gene centered studies had already suggested a multifactorial genetic contribution with small and pleiotropic effects and complex epistatic relationships. Future directions are 1) to focus on developing network based analytic approaches to identify of causal genes and networks and to clarify the relationship of genes and networks with aggressive behavior; and 2) to further delineate the species-specific and non-specific domains of aggressive behavior as well as escalated/abnormal aggression, and to clarify the overlapping yet distinct causal genes and networks underlying these separable domains, particularly overlooked domains such as frustrative non-reward.

SUMMARY AND CONCLUSIONS

In planning this review, we had set out to learn about the genetic underpinnings of the RDoC constructs associated with aggression: frustrative non- reward, defensive aggression and offensive (or proactive) aggression. Although the constructs of defensive and offensive aggression have been widely used in the animal genetics literature, the human literature is mostly agnostic with regard to all the RDoC constructs. That said, many aggression phenotypes have been studied in human genetic paradigms and the insights from these studies are likely relevant to the RDoC constructs.

We know from twin studies that about half the variance in behavior may be explained by genetic risk factors. This is true for both dimensional, trait- like, measures of aggression and categorical definitions of psychopathology. The non-shared environment seems to have a moderate influence with the effects of shared environment being unclear. Gene-environment interaction appears to play an important role but the details need to be worked out.

Human molecular genetic studies of aggression are in an early stage. The most promising candidates are in the dopaminergic and serotonergic systems along with hormonal regulators. Genome-wide association studies have not yet achieved genome-wide significance, but current samples are too small to detect variants having the small effects one would expect for a complex disorder. These studies have implicated genes involved in neurodevelopmental processes and synaptic plasticity, not previously considered in candidate gene studies. This may indicate that aggressive behavior does not only involve neurotransmitters or hormonal functions, but also molecules involved in establishing neuronal circuits, neuron-to-neuron connectivity and brain plasticity.

Future studies should improve the measurement of aggression by using a systematic method of measurement such as that proposed by the RDoC initiative, which differentiates defensive aggression, offensive aggression and frustrative non-reward [Sanislow et al., 2010]. Although the RDoC matrix provides some guidance about the measurement of frustrative non-reward in humans, it does not provide guidance for the measurement of offensive and defensive aggression, although relevant measures are well-developed in the animal literature. These measurement gaps suggest a role for the creation of reliable and valid measures of RDoC constructs for use in human aggression studies. Replication has been difficult for the field of psychiatric and behavioral genetics. Such problems will only be magnified for aggression if the field cannot come to a consensus about how aggression phenotypes should be measured.

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