Neuroscience and Biobehavioral Reviews xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

Genetic influences on conduct disorder

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ARTICLE INFO

Article history:
Received 15 February 2016
Received in revised form 22 May 2016
Accepted 22 June 2016
Available online xxx

Keywords:
Conduct disorder
Heritability
Gene identification
G × E
rGE
Epigenetics
Pleiotropy
Externalizing
Aggression
Genome-wide association study
Quasi-causal designs

ABSTRACT

Conduct disorder (CD) is a moderately heritable psychiatric disorder of childhood and adolescence characterized by aggression toward people and animals, destruction of property, deceitfulness or theft, and serious violation of rules. Genome-wide scans using linkage and association methods have identified a number of suggestive genomic regions that are pending replication. A small number of candidate genes (e.g., *GABRA2*, *MAOA*, *SLC6A4*, *AVPR1A*) are associated with CD related phenotypes across independent studies; however, failures to replicate also exist. Studies of gene-environment interplay show that CD genetic predispositions also contribute to selection into higher-risk environments, and that environmental factors can alter the importance of CD genetic factors and differentially methylate CD candidate genes. The field's understanding of CD etiology will benefit from larger, adequately powered studies in gene identification efforts; the incorporation of polygenic approaches in gene-environment interplay studies; attention to the mechanisms of risk from genes to brain to behavior; and the use of genetically informative data to test quasi-causal hypotheses about purported risk factors.

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http://dx.doi.org/10.1016/j.neubiorev.2016.06.034
0149-7634/

1. Introduction

Conduct disorder is a psychiatric disorder of childhood and adolescence characterized by aggression toward people and animals, destruction of property, deceitfulness or theft, and serious violation of rules. The worldwide prevalence of conduct disorder is 3.2% (Canino et al., 2010) and was responsible for more than 5.75 million years of healthy life lost according to the Global Burden of Disease Study 2010 (Erskine et al., 2014). The impact of the disorder reaches far beyond the personal and financial costs incurred by affected children/adolescents and their families. For example, in the United States, the estimated public cost in terms of mental health, general health, education, and juvenile justice services for a child diagnosed with conduct disorder exceeds 70,000 USD over a 7-year period (Foster and Jones, 2005).

Understanding the etiology of conduct disorder is central to the goal of developing effective prevention and intervention efforts aimed at reducing its global burden. Familial factors have long been implicated in conduct disorder (Costello and Angold, 2001). The field of behavioral genetics has attempted to formalize these initial observations by disentangling the degree to which those familial influences can be ascribed to genetic or environmental factors. Our goal here is to provide an overview of this area of research. We begin with a summary of the latent genetic studies of conduct disorder and conduct disorder clinical criteria, which permit an estimation of the degree to which genetic and environmental influences contribute to variation in outcomes. Next, we review efforts to identify specific, measured genes associated with conduct disorder, ranging from candidate gene approaches to genome-wide scans of conduct disorder and related behaviors. We then turn to the study of gene-environment interplay for conduct disorder. Understanding how environmental risk and protective factors interface with genetic predispositions to predict conduct disorder is a particularly active, albeit controversial, area of research. Lastly, we close with a discussion of four key ways to move this area of research forward in the future.

There have been many genetically informed studies of conduct disorder and related/component behaviors such as aggression, externalizing behavior, psychopathy, and callous-unemotional traits. Accordingly, our review is selective rather than exhaustive. To the extent possible, we focus on genetically informed studies that are consistent with the Diagnostic and Statistical Manual Revised Third Version and Fourth Version (DSM-III-R and DSM-IV) (American Psychiatric Association, 1987, 1994) definition of conduct disorder as "a repetitive and persistent pattern of behavior in which the basic rights of others or major age-appropriate societal norms or rules are violated." Conduct disorder diagnoses are typically given to individuals under 18 years of age; accordingly, we focus on studies of conduct disorder in individuals < 18 years. We note, however, that research on the molecular genetics of conduct disorder is still in its infancy, and there are very few studies of conduct disorder according to the strict DSM criteria. Thus, in our review of gene identification efforts for conduct disorder we opted to include larger scale meta-analytic findings of phenotypes closely related to conduct disorder, including aggression and antisocial behavior.

2. Heritability of conduct disorder: twin studies

Most behavioral outcomes have some degree of genetic influence (Polderman et al., 2015), and conduct disorder is no exception. Conduct and related externalizing disorders (e.g., substance use and abuse) are among the most active areas of behavioral genetic research. In view of this, there are already several excellent reviews of the heritability of conduct disorder and broadband antisocial behavior (Burt, 2009; INSERM Collective Expertise Centre, 2005; Polderman et al., 2015; Rhee and Waldman, 2002). We provide highlights from this literature, where samples of twins are often used to estimate heritability. Twin studies permit the partitioning of latent genetic and environmental influences via comparison of the phenotypic correlations of monozygotic (MZ) and dizygotic (DZ) twin pairs. Additive genetic, shared environmental, and non-shared environmental influences can be estimated owing to the fact that both types of twins are exposed to the same rearing environment, but that MZ twins share all of their genetic variation, while DZ twins share half of their genetic variation, on average. Shared environmental influences refer to experiences or events that both twins experience that make them more similar (e.g., growing up in the same neighborhood). Non-shared environmental influences refer to experiences or events that one individual experiences, but not his/her co-twin (e.g., having different friends). When the MZ correlation for a variable is larger than the DZ correlation, this suggests that there are genetic influences. When the DZ correlation for a variable is approximately half of the MZ correlation or lower, this suggests that there are no shared environmental influences. Finally, when the DZ correlation for a variable is more than half of the MZ correlation, this suggests the presence of shared environmental influences.

In a quantitative review of twin studies from the past fifty years, Polderman et al. (2015) report that ~50% of the variance in conduct disorder (broadly measured with over 200 phenotypes in 147,974 monozygotic twin pairs and 192,651 dizygotic twin pairs) is attributable to additive genetic influences. Interestingly, and in contrast to other disorders on the externalizing spectrum (Krueger et al., 2002), the results from this meta-analysis also suggest that shared environmental factors account for a significant (14%) proportion of the variance in conduct disorder (Polderman et al., 2015). To focus more narrowly on conduct disorder, we also present heritability estimates obtained from large-scale (n > 1000) population and community-based twin studies that have used reliable and valid measures of conduct disorder symptomatology or diagnoses according to DSM-III-R or DSM-IV criteria. Analyses in community and population-based samples are more likely to provide unbiased estimates of heritability compared to clinically ascertained samples, where affected individuals are over-represented. Conduct disorder is relatively common, and thus there is sufficient variation to provide reliable estimates of its heritability in population and community-based samples.

Table 1 summarizes the standardized variance component estimates for genetic, shared environmental, and non-shared environmental influences (i.e., h^2, c^2, and e^2, respectively) on conduct disorder. These studies are quite consistent in showing that genetic influences account for a modest to moderate amount of the variance in conduct disorder. In one large study of 5600 individuals from male-male and female-female twin pairs who were ascertained from a population-based registry, there was also evidence that common environmental factors accounted for a significant (32%) proportion of the variance in conduct disorder (Kendler et al., 2003) mirroring the results of the Polderman et al. (2015) meta-analysis of broad conduct disorder phenotypes.

Oftentimes twin studies are conducted using data collected at a single assessment in order to estimate the degree to which genetic and environmental influences account for variation in a behavior or trait. However, it should be noted that heritability estimates are not static, and can change over time. This is especially important to consider for a behavior like conduct disorder, for which there is some evidence for differences across development (Loeber et al., 2000; Moffitt, 1993). This raises two potential questions from a genetic perspective: First, does the degree to which genetic influences account for variance in conduct disorder change across time; and second, are the genes that contribute to conduct disorder earlier in

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Table 1
Summary of the standardized variance component estimates for genetic, shared environmental, and non-shared environmental influences (i.e., h^2, c^2, and e^2, respectively) on conduct disorder phenotypes in community and population-based twin samples.

Study	Country	N	Phenotype	h^2	c^2	e^2
Eaves et al. (1997)	USA	1412 individuals	Interview (CAPA) and questionnaire measures of DSM-III-R conduct disorder symptom counts as reported by mothers, fathers, children, and teachers	M range = 24–74	M range = 0–38	M range = 25–64
				F range = 5–72	F range = 0–44	F range = 23–77
Kendler et al. (2003)	USA	~5600 individuals	DSM-III-R Conduct Disorder	0.18	0.32	0.50
Gelhorn et al. (2005)	USA	2200 individuals	DSM-IV Conduct Disorder symptom counts from the DISC	0.53	0.00	0.47
Anckarsater et al. (2011)	Sweden	17,220 individuals	Conduct Disorder from the A-TAC Inventory (parent report)	0.60	0.03	0.37
Meier et al. (2011)	Australia	6383 individuals	DSM-IV Conduct Disorder from the SSAGA	M = 0.22	M = 0.23	M = 0.55
				F = 0.19	F = 0.20	F = 0.61

Note: Separate male (M) and female (F) estimates are presented for studies that reported heritability as a function of sex, only.

childhood/early adolescence the same as those that contribute to conduct disorder later in adolescence?

Using retrospective data collected on 2580 complete twin pairs from the population-based Virginia Adult Twin Study of Psychiatric and Substance Use Disorders sample, Jacobson et al. (2002) found that the heritability of DSM-III-R conduct disorder symptomatology increases between childhood (<15 years) and adolescence (15–17 years) for both males (h^2 = 0.06 and 0.41, respectively) and females (h^2 = 0.29 and 0.50, respectively). Furthermore, they found overlapping and unique genetic influences on conduct disorder symptomatology in childhood and adolescence. These findings provide evidence that the genetic influences on conduct disorder increase over time, and that this increase in heritability is in part due to genetic innovation, or new genes coming "online" to influence conduct disorder across development.

There is mixed evidence regarding qualitative and quantitative sex differences in the heritability of conduct disorder. Quantitative sex differences refer to differences in the degree to which genetic influences account for variance in a phenotype in males and females, and qualitative sex differences refer to the degree to which the genetic influences on a phenotype overlap for males and females (Neale et al., 2006). Some have reported no significant quantitative sex differences (Gelhorn et al., 2005); however, others have reported significant qualitative or quantitative sex differences. In a population-based US twin sample, Jacobson et al. (2002) found evidence of quantitative sex differences, such that genetic influences for conduct disorder were more pronounced for females compared to males in childhood but not adolescence. However, they did not find evidence for qualitative sex differences. The absence of qualitative sex differences suggests that the genes that influence conduct disorder in males are the same genes that influence conduct disorder in females. In contrast, in a population-based Australian twin sample, Meier et al. (2011) found that a model that allowed the genetic influences on conduct disorder to vary between males and females fit better than a model that constrained the sources of genetic variance to be equal, suggesting evidence of qualitative sex differences. However, they did not find any evidence for quantitative sex differences. Accordingly, questions remain regarding whether and how genetic influences on conduct disorder may differ between males and females.

It is worth noting that the heritability estimates of conduct disorder reviewed here are at the aggregate symptom level. At the phenotypic level, researchers have distinguished between aggressive and non-aggressive subtypes of conduct disorder (Loeber et al., 2000), raising the question of the degree to which these subtypes are heritable and have distinct or overlapping genetic etiology. According to a meta-analysis of clinical and non-clinical measures of antisocial behavior, the heritability of aggressive behavior (h^2 = 0.65) is higher than the heritability of non-aggressive rule-breaking antisocial behavior (h^2 = 0.48) (Burt, 2009). With respect to DSM-oriented studies of conduct disorder, in a community sample of 1100 adolescent twin pairs, both the aggressive and non-aggressive domains were moderately heritable (49% and 55%, respectively) (Gelhorn et al., 2005). The phenotypic correlation between these domains was moderate (r = 0.32), and genetic influences accounted for a large proportion (61%) of the phenotypic correlation between aggressive and non-aggressive DSM-IV criteria (Gelhorn et al., 2006). However, criterion-level heritability analyses indicated that specific DSM-IV conduct disorder criteria (e.g., truancy) showed little to no heritability but rather high levels of shared environmental influence (Gelhorn et al., 2005). Exploratory twin models similarly show that there are distinct etiological influences on conduct disorder criteria. For example, a series of multivariate twin models of DSM-III-R conduct disorder criteria in a sample of male-male twin pairs found evidence for two genetic factors, one shared environmental factor, and one nonshared environmental factor (Kendler et al., 2013). The first genetic factor included items related to rule-breaking (truancy, running away, and telling lies), and the second genetic factor included items related to overt aggression (hurting people and fighting). Thus, both hypothesis-driven and data-driven approaches suggest that conduct disorder has a complex genetic architecture, meaning that there are multiple sources of genetic influence on the various behaviors that are encompassed in conduct disorder diagnoses.

Thus far, we have presented the results of univariate biometric analyses of conduct disorder. However, it is well known that conduct disorder is often correlated with other types of disinhibitory behavior, including substance use. For example, conduct disorder diagnoses in early adolescence are associated with increased odds of DSM-IV nicotine dependence, alcohol abuse/dependence, and cannabis abuse/dependence diagnoses by age 18 (OR = 4.75–5.43) (Elkins et al., 2007). Multivariate behavioral genetic studies, which permit examination of the degree to which genetic and environmental influences contribute to covariance among multiple phenotypes, suggest that genetic factors account for the majority of the covariance among externalizing disorders (Kendler et al., 2003; Krueger et al., 2002; Slutske et al., 1998; Young et al., 2000). In one example of this from the population-based Minnesota Twin Family Study, conduct disorder, adult antisocial behavior, alcohol dependence, drug dependence, and low levels of constraint loaded onto a single, highly heritable (h^2 = 0.81) additive genetic factor (Krueger et al., 2002). Of note, there were no unique genetic influences on conduct disorder. Rather, the additive genetic influences on conduct disorder were completely overlapping with the higher-level externalizing genetic factor. Multivariate analyses of externalizing psychopathology in other population-based samples similarly

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find evidence that these disorders share a single, highly heritable genetic factor (Kendler et al., 2003; Young et al., 2000). Thus, the genetic influences on conduct disorder broadly predispose individuals to a range of disinhibitory behaviors, rather than conduct disorder in particular.

Three general conclusions can be gleaned from this overview of the twin literature on conduct disorder. First, familial influences account for much of the variance in conduct disorder. At the aggregate level, there are moderate levels of genetic and shared environmental influence on conduct disorder symptomatology and diagnoses; however, for individual clinical DSM-IV criteria there is variation in the relative influence of genetic and environmental factors. Second, the heritability of conduct disorder increases over time, and is attributable, in part, to new genetic influences that emerge across development. Third, conduct disorder shares genetic influences with other forms of disinhibitory behavior, and does not have unique genetic influences. These general principles from latent genetic studies of conduct disorder have implications for efforts to identify its measured genetic variants.

3. Gene identification efforts for conduct disorder

Latent genetic studies conducted in multiple samples have produced a number of findings that begin to add to our understanding of the genetic architecture of conduct disorder. In what follows, we trace efforts to identify the specific genes associated with conduct disorder. Conduct disorder is a complex trait, meaning that many genes and genetic variants contribute to the phenotype. We group these efforts into approaches that are largely hypothesis free (e.g., linkage and high-throughput association analyses) and those that are more hypothesis driven (e.g., candidate gene approaches). Although we provide a historical overview of many of the methods used to identify genes associated with conduct disorder, we put a particular emphasis on approaches that are consistent with the current state of the science for identifying genetic variants for complex traits.

3.1. Hypothesis-free approaches

Hypothesis-free approaches to gene identification scan the entire genome for regions or variants for possible association with a trait or behavior of interest. This approach is hypothesis-free in that all regions of the genome are examined, without any a priori hypotheses about where relevant genes may reside. Systematic scans of the genome using both linkage and association-based methods have been used in attempts to identify genetic regions and variants associated with conduct disorder.

3.1.1. Linkage

In linkage analysis, patterns of inheritance for genetic markers across the genome are examined in families. Statistical genetic probabilities about allele sharing and the concept of "identical by descent" (IBD) are the basis for this analysis. For example, when siblings inherit the same marker allele from the same parent, that allele is said to be IBD. When a marker is near a gene that influences a phenotype of interest, then siblings who are more similar to one another on that phenotype are expected to share more IBD marker alleles. Likewise, siblings who are less like one another on that phenotype are expected to share fewer IBD marker alleles. A "linkage peak" is an indication that a particular section of a chromosome co-segregates with the trait within families. The degree to which this co-segregation deviates from chance is quantified using a logarithm base 10 of odds (lod) score. Typically, lod scores of 2.2, 3.6, and 5.4 are considered the cutoffs for evidence of suggestive, significant, and highly significant linkage for genetically complex (i.e., multifactorial) behaviors and traits (Lander and Kruglyak, 1995).

The first linkage analysis of conduct disorder diagnoses came from the Collaborative Study on the Genetics of Alcoholism (COGA; Begleiter et al., 1995; Dick et al., 2004). In total, 2282 participants from 262 families densely affected with alcoholism were genotyped on 336 markers that were 10.5 cM apart, on average. Nonparametric linkage analysis identified regions of interest (defined in this study as lod $\geq$1.5) on chromosomes 2, 3, 12, and 19. The region identified on chromosome 2 was also identified in linkage studies of alcohol dependence and suicidality in the same sample (Foroud et al., 2000; Hesselbrock et al., 2004) and suicidality in other samples (Willour et al., 2007; Zubenko et al., 2004), which is notable in view of the genetic correlation between conduct disorder and other disorders characterized by disinhibition (Kendler et al., 2003; Krueger et al., 2002; Slutske et al., 1998; Young et al., 2000).

Other linkage analyses of conduct disorder include analyses of DSM-III-R (American Psychiatric Association, 1987) and DSM-IV (American Psychiatric Association, 1994) conduct disorder criterion counts in a clinically ascertained sample of adolescent probands affected with substance abuse and delinquency and their siblings (249 proband-sibling pairs from 191 families genotyped on 374 markers; Stallings et al., 2005), and a linkage analysis of 733 sibling pairs in the Irish Affected Sib Pair Study of Alcohol Dependence (IASPSAD; genotyped on 1020 markers; Kendler et al., 2006). In the clinically ascertained sample of adolescents, evidence of linkage (lod > 1.26) was found for regions on chromosomes 9, 3, and 17. In the IASPSAD, the strongest evidence for linkage (defined as lod >2.0) was found for regions on chromosomes 1 and 14, with additional evidence for linkage on chromosome 2 (lod = 1.12) near the genomic region identified in the COGA study (Dick et al., 2004). Finally, in another linkage study of conduct disorder in a sample of 616 individuals from 18 families densely segregating highly comorbid ADHD and CD were genotyped on approximately 400 markers that were 9 cM apart, on average. Linkage analysis identified regions of interest (defined as non-parametric linkage scores >2.0) on chromosomes 4, 12, 14, and 17 (Jain et al., 2007).

Linkage studies were the earliest method for scanning the genome to narrow the search for genes involved in complex outcomes. As the findings reviewed above indicate, few regions reach conventional thresholds for suggestive or significant linkage, and there is little consistency among the regions identified across samples, with the exception of the region on chromosome 2 identified in COGA with suggestive evidence of replication in IASPSAD. The limited success of linkage studies for conduct disorder likely reflects multiple factors. Most notably, linkage methods are well suited for finding genes of large effect size and have thus had the greatest success in identifying genes for monogenic disorders rather than genes for complex disorders, which typically involve many genes of more modest effect (Bush and Haines, 2010). In view of the modest effect sizes expected for genes implicated in conduct disorder, these early linkage analyses were likely underpowered.

3.1.2. Association

In association analyses, genetic variants are examined for whether a particular version or versions increase risk for a phenotype. There are many different types of genetic variation, including single nucleotide variation and structural variation (e.g., insertions, inversions, deletions, duplications, and copy-number variants). Single nucleotide polymorphisms (SNPs), which are single-nucleotide substitutions of one base (adenine, thymine, guanine, or cytosine) for another, are the most common type of genetic variation. Hypothesis-free association analyses can be used to fine-map an area of interest identified through linkage to more precisely locate the source of a genetic signal. In an example of this from the COGA sample, chromosome 2—for which there was earlier evidence of linkage to alcohol dependence (Foroud et al., 2000),

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conduct disorder (Dick et al., 2004), and suicidality (Hesselbrock et al., 2004)—was fine-mapped for association using a combined phenotype of alcohol dependence with conduct disorder or suicidality (Dick et al., 2010). In total, 23 genes on chromosome 2 were associated with this combined phenotype.

At present, high-throughput genome-wide association study (GWAS) methods are the most common hypothesis-free approach to genetic association. Like linkage, GWAS provides systematic coverage of the genome, without a priori hypotheses about where causal variants are likely to be located. The basic question in an association study is whether individual differences in a phenotype correspond to allele differences in a SNP. In a GWAS, hundreds of thousands to millions of SNPs are tested for association in this way. To date, gene identification efforts for complex traits have been notoriously difficult, and it is becoming increasingly clear that large sample sizes are required.

There have been two GWAS of conduct disorder that have identified suggestive association signals. In an early example of this, a family-based association test of clinical and subclinical conduct problems in 958 ADHD affected proband-parent trios found evidence for association meeting a suggestive significance level of $P <= 1 \times 10^{-5}$ in nine genes, including *A2BP1, c12orf28, FLJ39061, KIRREL3, LOC729257, PAWR, PKD1L2, PKD1L3,* and *RGL1* (Anney et al., 2008). In the Study of Addiction: Genes and Environment (SAGE) sample, a GWAS study of retrospectively reported DSM-IV conduct disorder criterion counts in 3963 individuals identified four SNPs (on chromosomes 4, 11, and 13) that met a genome-wide significance level of $P < 5 \times 10^{-8}$ (Dick et al., 2011). A subsequent attempt to replicate these four SNPs with a non-diagnostic antisocial behavior phenotype in a community sample of 4816 individuals did not reach nominal significance ($P < 0.05$) (Tielbeek et al., 2012). In a related analysis, the Early Genetics and Lifecourse Epidemiology (EAGLE) consortium conducted a GWAS meta-analysis of aggressive behavior in 18,988 children and adolescents and found suggestive evidence ($P = 5.30 \times 10^{-8}$) for SNP rs11126630, located on chromosome 2 between genes *LRRTM4* and *SNAR-H* (Pappa et al., 2015).

The studies reviewed thus far have focused on genetic variation in common SNPs, where the frequency of the minor allele is typically greater than 1%. Other forms of genetic variation may also contribute to the heritability of conduct disorder. In particular, there has been a growing interest in variants that are likely to be highly deleterious (and thus rare, with a minor allele frequency of less than 1%) located in the exome, which is the protein-coding portion of the genome. There are now cost effective methods to conduct systematic tests of association for rare variant exonic SNPs. Although there has not yet been a rare variant association study of conduct disorder diagnoses or symptom counts, there has been a study of a closely related behavioral disinhibition phenotype, which included antisocial and dissocial behaviors. In a sample of 7181 individuals, approximately 100,000 rare (minor allele frequency <0.05) non-synonymous exonic SNPs were examined for association with the behavioral disinhibition phenotype (Vrieze et al., 2014). In aggregate, these SNPs accounted for 14% of the variance in behavioral disinhibition ($p = 0.05$). However, no significant associations emerged from SNP and gene-based burden tests of association.

3.2. Hypothesis-driven approaches

In addition to data-driven linkage and association approaches, investigators have also applied a top-down approach to first specify the likely location of genes or variants of interest, and then carry these forward to examine their association with conduct disorder. In the following sections, we describe two of these approaches.

3.2.1. Candidate genes identified from studies of genetically correlated behaviors

Twin studies have shown that conduct disorder shares genetic influences with other externalizing disorders, including alcohol and other substance use disorders (Kendler et al., 2003; Krueger et al., 2002; Slutske et al., 1998; Young et al., 2000). This suggests that there are likely to be some genes that have pleiotropic effects, meaning that one gene may be associated with multiple externalizing disorders. Researchers have capitalized on this shared genetic architecture in analyses that examine whether genes identified for other externalizing disorders also influence conduct disorder.

Perhaps the clearest example of this comes from analyses of *GABRA2*. *GABRA2* codes for the receptor for the central nervous system inhibitory neurotransmitter $GABA_A$ alpha-2 subunit. $GABA_A$ receptors are involved in the mesolimbic dopamine system (Enoch, 2008), suggesting that *GABRA2* is likely involved in a range of reward-related disinhibited behaviors that broadly reflect the inability to control one's impulses. *GABRA2* was initially associated with adult alcohol dependence in multiple independent samples (Covault et al., 2004; Edenberg et al., 2004; Enoch et al., 2009; Zintzaras, 2012), and has also shown association with drug dependence (Agrawal et al., 2006). Analyses of 860 children and adolescents ascertained as part of the COGA study found association for *GABRA2* SNP rs279871 with childhood conduct disorder symptoms (Dick et al., 2006). It was also associated with trajectories of behavior problems in the independent Child Development Sample (Dick et al., 2009). Another *GABRA2* SNP (rs9291283) was also associated with conduct disorder symptoms in participants from the Genetics of Antisocial Drug Dependence sample (Melroy et al., 2014). Of note, rs279871 and rs9291283 are in linkage equilibrium ($r^2 = 0.04$) according to the CEU 1000 Genomes Phase I CEU reference panel. Thus, there may be more than one association signal for conduct disorder in *GABRA2*.

Although these findings provide proof of principle for the approach of carrying forward genes identified in GWAS of other externalizing disorders to test for association with conduct disorder, it should be noted that other attempts to replicate the association between *GABRA2* and conduct disorder have produced inconsistent or null results. In a case-control sample of adolescents, *GABRA2* SNP rs279871 was nominally associated with conduct disorder ($n = 428$, $p = 0.02$) (Sakai et al., 2010); however, the effect was in the opposite direction reported by Dick et al. (2006) and Sakai et al. (2010). Furthermore, a broader family-based association test that included siblings and parents of adolescent patients and controls ($n = 1582$) found no evidence for association between rs279871 and conduct disorder ($p = 0.48$) (Sakai et al., 2010). Finally, a series of six *GABRA2* SNPs genotyped in COGA adolescent ($n = 933$) and young adult ($n = 1191$) offspring were not associated with conduct disorder clinical criteria, but several SNPs were associated with subclinical Achenbach externalizing behavior (Dick et al., 2013).

3.2.2. Candidate genes in plausibly relevant biological systems

To date, the most common measured genetic design for conduct disorder has been to examine a single variant in a handful of "usual suspect" candidate genes that have a purported biological function, typically related to serotonin and dopaminergic pathways or the stress response. There are numerous examples of this approach for conduct disorder related outcomes, as recently reviewed in Veroude et al. (2015). Although this approach is popular, it is problematic for a few reasons. First, history has shown that researchers have not been very good at identifying plausible candidate genes that confer risk for behavioral outcomes, and very few well-replicated associations have emerged from these hypothesized genes of interest (Bosker et al., 2011; Collins et al., 2012). Exceptions to this include variants in the alcohol dehydrogenase (*ADH*) gene cluster and alcohol outcomes (Gelernter

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et al., 2013; Thomasson et al., 1991) and nicotinic receptor genes (*CHRNA5-CHRNA3-CHRNB4*) for smoking outcomes (Broms et al., 2012; Tobacco and Genetics Consortium, 2010). Unlike alcohol and smoking behaviors, where there are concrete biological links to metabolism of the substance that may predispose some individuals to be more likely to develop alcohol or nicotine dependence, conduct disorder has highly probabilistic, but not absolute, links to particular neurobiological systems. Several candidate genes for conduct disorder have been proposed and examined (Veroude et al., 2015). Owing to the growing concern over the replicability of candidate gene approaches for genetically complex traits and behaviors (Dick et al., 2015; Duncan and Keller, 2011), here we chose to highlight three candidate genes (*MAOA, SLC6A4*, and *AVPR1A*) for which there is recent meta-analytic evidence for association with phenotypes related to conduct disorder (antisocial behavior and aggression).

The serotonergic system has been implicated in the neurobiology of aggression and antisocial behavior (Ficks and Waldman, 2014; van Goozen et al., 2007), and thus genes implicated in the metabolism and availability of serotonin have emerged as plausible candidates for association. Two polymorphisms in serotonergic system genes, the monoamine oxidase-A promoter variable number of tandem repeats (*MAOA-uVNTR* in the *MAOA* gene) and serotonin transporter-linked polymorphic region (*5-HTTLPR* in the *SLC6A4* gene), are among the most commonly studied candidates for behavioral outcomes (Gunter et al., 2010). A meta-analysis found significant association between the *MAOA-uVNTR* low activity allele and aggressive or antisocial behavior (OR = 1.08) as well as association between the *5-HTTLPR* short allele and aggressive or antisocial behavior (OR = 1.41) (Ficks and Waldman, 2014).

Genes implicated in the neurobiology of social behavior or aggression have also been hypothesized as plausible candidates for conduct disorder related phenotypes. One example is the Arginine Vasopressin Receptor 1A (*AVPR1A*) gene, which codes for arginine vasopressin receptor 1A (AVPR1A) receptors in the brain and is associated with social behavior (Ebstein et al., 2010; Walum et al., 2012). Of the 21 candidate genes across the serotonin, dopaminergic, adrenergic, and stress response systems that were tested as part the EAGLE Consortium's GWAS meta-analysis of childhood aggression (Pappa et al., 2015), only *AVPR1A* had a gene-based $P < 0.05$ ($P = 1.61 \times 10^{-3}$). Although this approach is intuitively appealing, selecting the relevant genes for social behavior phenotypes is challenging. In a systematic effort to identify relevant genes, Zhang-James and Faraone (2015) used the Online Mendelian Inheritance in Man (OMIM) catalog to identify 86 genes that harbor known rare variants associated with human disorders that have aggressive features. Although these genes await replication, this illustrates a novel use of validated rare, functional variants to guide gene identification efforts for conduct disorder.

3.3. Summary of gene identification efforts for conduct disorder

Gene identification efforts for conduct disorder are in their infancy. Although the linkage and association studies have identified a number of suggestive signals, the inconsistencies across the studies are noticeable. This reflects the inherent difficulties in identifying replicable genes and genetic variants associated with complex psychiatric and behavioral outcomes. There are many potential reasons for this difficulty, including small effect sizes, rigorous corrections for multiple testing of thousands and millions of genetic variants, and genetic heterogeneity. Furthermore, the sample sizes for the conduct disorder GWAS summarized here are relatively small compared to other areas of psychiatric and complex traits genetics, which impacts the power to detect small effects. The large sample sizes needed for gene identification efforts for psychiatric traits is illustrated most clearly in the area of schizophrenia research, where the most recent mega-analysis of 36,989 schizophrenia cases and 113,075 controls identified association with 108 loci (Schizophrenia Working Group of the Psychiatric Genomics, 2014).

Although hypothesis-free approaches have not yet yielded replicable associations for conduct disorder, there has been at least modest success in using hypothesis-driven approaches to identify association for conduct disorder related phenotypes. We cite these candidate gene associations here in view of the meta-analytic evidence supporting their association; however, even these should be interpreted cautiously, as only one (*AVPR1A*) was also detected in GWAS. However, it is worth noting that the landscape of psychiatric genetics is changing rapidly, and candidate gene approaches are generally not considered to reflect the state-of-the-science due to issues of replicability as well as new evidence from other areas of psychiatric genetics that the genes and gene networks likely to be relevant for behavioral outcomes may not be immediately obvious, such as the association between immune-related genes and schizophrenia that emerged through large scale GWAS (Schizophrenia Working Group of the Psychiatric Genomics, 2014).

4. Gene-environment interplay for conduct disorder

Thus far we have focused on the efforts to partition the variance in conduct disorder into genetic and environmental influences, as well as the methods for specifying which genetic variants, genes, and gene regions are likely to be associated. Of course, genetic predispositions for complex behavioral outcomes like conduct disorder are probabilistic rather than deterministic. In view of this, understanding how genetic predispositions and environmental factors come together is critically important, and has been a major research focus in the area of conduct disorder.

4.1. Gene-by-environment interaction (G × E)

In recent years, there has been a proliferation of interest in identifying the environments that alter the relationship between one's genetic predispositions and the likelihood that they will express conduct disorder (i.e., gene-by-environment interaction effects, or G × E). Thus, even an individual who has a high genetic loading for conduct problems may never go on to develop an actual disorder. Studies of twins have shown that the genetic influences on conduct disorder related phenotypes vary as a function of urban-rural residency (Legrand et al., 2008); peer deviance (Button et al., 2007); parent-child conflict (Burt and Klump, 2014); paternal drug dependence (Haber et al., 2010); and parental monitoring (Dick et al., 2007). These twin studies of G × E demonstrate that genetic variance for conduct disorder differs across levels of the environment. And across many of these latent G × E analyses, one theme that has emerged is that genetic variance for conduct disorder is higher in less restrictive environments (e.g., those characterized by higher peer deviance, less parental monitoring, or urban residency), which is consistent with the social opportunity mechanism of G × E described by Shanahan and Hofer (2005). The reverse also holds, such that genetic variance is minimized in more restrictive environments characterized by lower peer deviance, higher parental monitoring, or rural residency, which is consistent with the social control mechanism of G × E (Shanahan and Hofer, 2005). In the time since Purcell (2002) popularized biometric models for probing latent G × E effects, others have raised concerns about Type I error and proposed alternative parameterizations (Rathouz et al., 2008; van der Sluis et al., 2012). The robustness of G × E effects for conduct disorder related phenotypes to these alternative specifications has not been examined systematically.

Please cite this article in press as: Salvatore, J.E., Dick, D.M., Genetic influences on conduct disorder. Neurosci. Biobehav. Rev. (2016), http://dx.doi.org/10.1016/j.neubiorev.2016.06.034

There has also been a great deal of interest in delineating whether and how environmental factors moderate *measured* genetic predispositions for conduct disorder. In an early example of this, Caspi et al. (2002) showed that genetic variation in *MAOA* interacted with harsh physical discipline to predict antisocial behavior. Although there is much enthusiasm for this type of approach (Caspi and Moffitt, 2006), the study of candidate gene-by-environment interaction (cG × E) in psychiatry has also been met with skepticism and criticism out of concern for Type I error (Duncan and Keller, 2011), particularly in view of the difficulty in identifying genes and genetic variants associated with psychiatric outcomes such as conduct disorder (Dick et al., 2015). There are many studies of cG × E for conduct disorder (Veroude et al., 2015). However, given the controversy surrounding cG × E research and the concern for Type I error, we review here selected examples that have used a hypothesis-driven approach to select the environment, and that have built upon large-scale gene identification results to select the relevant genes/genetic variants.

Environments for which there are latent G × E effects offer promising avenues for follow-up with cG × E studies. In a few examples of this, findings coming out of the twin G × E literature were used to develop hypotheses about how the association between *GABRA2* genotype and externalizing behavior might change as a function of parental monitoring and peer deviance. The logic of this approach is that if a significant G × E effect is detected using twin methodology, it must indicate that the environmental factor changes the association between most genetic variants and the outcome (assuming the outcome is influenced by a large number of small genetic effects). Consistent with what would be expected given the latent G × E literature, adolescents with more copies of the major allele for SNPs in the risk-increasing *GABRA2* haplotype block were more likely to exhibit an elevated persistent trajectory of externalizing behavior if they also experienced less parental monitoring (Dick et al., 2009). Similarly, the association between *GABRA2* genotype and externalizing behavior was stronger under conditions of high peer deviance and weaker under conditions of low peer deviance (Villafuerte et al., 2014). These specific cG × E effects are in need of replication, and meta-analytic approaches that combine effect sizes across multiple studies would provide more conclusive evidence about interactions between parental monitoring, peer deviance, and *GABRA2* for conduct disorder related outcomes. Still, it is encouraging that the pattern is similar to what would be expected given previous latent G × E results as well as theory about how certain social contexts may constrain or amplify genetic differences.

More recently, many G × E studies for conduct disorder are framed within a differential susceptibility or vantage sensitivity framework. The differential susceptibility framework posits that particular genotypes may confer risk in a negative/risky environment, but may also be associated with especially good outcomes in a positive/protective environment (Belsky et al., 2009). Relatedly, the vantage sensitivity framework posits that particular genotypes may confer heightened responsivity to positive environments (Pluess and Belsky, 2013). A recent meta-analysis of twelve studies of externalizing behavior showed that carriers of putative susceptibility loci across a number of "usual suspect" genes were more responsive to a family-based intervention compared to non-carriers (Bakermans-Kranenburg and van Ijzendoorn, 2015). Further exploration of this area is warranted, particularly by expanding beyond a classic candidate gene approach. Considering our poor record of selecting genes with effects on complex behavioral outcomes, it may be overly optimistic to think we will be better at guessing genes involved in environmental sensitivity.

4.2. Gene-by-environment correlation (rGE)

Several of the environmental factors that have been examined in G × E studies for conduct disorder (e.g., parenting, deviant peer affiliations), as well as other known risk factors for poor behavioral and emotional health outcomes in general are also genetically influenced to some degree (Kendler and Baker, 2007; McAdams et al., 2013). This raises the possibility that one's genetic predisposition for conduct disorder may be correlated with environmental exposures for conduct disorder through the process of gene-by-environment correlation (rGE). There are multiple mechanisms that may result in a correlation between an individual's genotype and environment, including evocative gene-environment correlation (where an individual's heritable behavior elicits a particular environmental response); active gene-environment correlation (where an individual's genetic predispositions lead them to seek out particular environments), and passive gene-environment correlation (where the type of environment provided to a child is correlated by his/her inherited genotype because biological parents provide both genetic material and a rearing environment for their offspring) (Scarr and McCartney, 1983). With respect to conduct disorder, there is retrospective longitudinal evidence that males select into peer groups whose level of deviance are consistent with their own genetic predispositions for conduct disorder (Kendler et al., 2008). Thus, individuals who are at greater genetic risk for developing conduct disorder also select into environments that further increase their risk.

4.3. Epigenetics

Epigenetics generally refers to modifications of the genome that do not involve a change in nucleotide sequence; rather, epigenetic changes involve chemical modifications to the DNA that impact the likelihood that a particular gene will be "turned on or off". These patterns of activation and inactivation across the genome have been suggested as biological mechanisms that may underlie some forms of gene-environment interplay (El-Sayed et al., 2013). Environmental factors can induce epigenetic changes. In the example likely to be most familiar to readers, maternal licking and grooming of rat pups induces changes in genes related to the stress response (Meaney and Szyf, 2005). In this sense, epigenetic changes can be thought of as one way that environmental experiences get "under the skin" to influence subsequent behavioral outcomes. Epigenetics complements studies of latent and measured G × E—which provide evidence of a statistical interaction—to provide a biologically plausible mechanism for G × E (Tremblay, 2008).

Methylation studies of conduct disorder-related outcomes to date have focused on cytokine genes and their regulators (Provencal et al., 2013), and the oxytocin receptor (*OXTR*) gene (Dadds et al., 2014), which show differential patterns of methylation as a function of physical aggression and callous-unemotional traits. In an effort to directly link environmental exposures with one of these methylation profiles, Cecil et al. (2014) found that prenatal risk factors such as maternal psychopathology, criminal behavior, and substance use predicted higher levels of methylation in/around the oxytocin receptor (*OXTR*) gene at birth in a subsample from the Avon Longitudinal Study of Parents and Children. In turn, methylation of *OXTR* was associated with higher levels of callous-unemotional traits in adolescence (Cecil et al., 2014), which define a subtype of conduct disorder (Blair et al., 2014; Frick and Ellis, 1999). The study of epigenetics for conduct disorder-related outcomes is an emerging area of research that is likely to expand, and these preliminary findings should be interpreted keeping in mind that many of the concerns related to testing cG × E (e.g., selection of the gene, selection of the environment, and Type I error) are also relevant when considering epigenetic changes. An additional con-

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cern is distinguishing among the possibilities that methylation of a particular gene is the cause, consequence, or correlate of disorder. Answering these questions will require converging evidence across longitudinal and quasi-causal designs.

5. Conclusion and future directions

In this review, we have provided a summary of the genetic influences on conduct disorder, including the genetic epidemiology of conduct disorder, attempts to identify specific predisposing genes, and efforts to understand gene-environment interplay. Twin studies of conduct disorder and antisocial behavior consistently show that at least some of the risk for these outcomes is attributable to genetic factors. Importantly, however, these genetic predispositions have only a probabilistic relation to subsequent conduct disorder, and environmental factors can be correlated with and moderate these genetic predispositions. Attempts to identify the measured genetic variants associated with conduct disorder using hypothesis-free and hypothesis-driven approaches have had limited success to date, although there is evidence for association between conduct disorder related phenotypes and *GABRA2, MAOA, SLC6A4*, and *AVPR1A* across independent samples. This limited success is not surprising in view of difficulty of gene identification efforts for psychiatric and complex traits more generally. However, it has raised concerns about the replicability of cG × E effects.

The landscape of complex trait genetics is changing rapidly, and we are optimistic that over the next few years there will be further gains in the field's understanding of the genes implicated in conduct disorder, as well as how environmental factors interface with this risk through G × E, rGE, and epigenetic processes. We offer a few suggestions on potential ways forward for this area of research. First, the Diagnostic and Statistical Manual was developed as a clinical tool, and accordingly, separates externalizing disorders into distinct clinical diagnoses. However, the results from multiple twin studies indicate that there is a common genetic etiology across externalizing spectrum disorders (Kendler et al., 2003; Krueger et al., 2002; Slutske et al., 1998; Young et al., 2000). This suggests that there remains a great deal of leverage to be gained through gene identification efforts that combine phenotypes across the externalizing spectrum, as illustrated in Dick et al. (2008). Relatedly, forthcoming results from the substance use workgroup of the Psychiatric Genomics Consortium's analyses of nicotine, cannabis, cocaine, opioid, alcohol, and other substances will likely produce several candidates worth following up for association with conduct disorder.

Second, in the absence of highly significant genetic associations for conduct disorder, and in view of the fact that it is a genetically complex trait, we encourage the use of polygenic scores in measured genetic studies of rGE and G × E (Wray et al., 2014). Polygenic approaches consider the weighted effects of SNPs across the genome, and thus characterize aggregate genetic risk in a way that is consistent with our understanding that many variants of small effect are likely to contribute to conduct disorder. A particular benefit of this approach is that it avoids the Type I error concerns associated with single variant/single gene cG × E approaches since the genetic effects are tested in aggregate. Typically, the results from large scale meta- or mega-analyses are used to create weighted linear combinations that reflect the degree to which an individual carries alleles that predispose him/her to conduct disorder. Thus, high polygenic scores indicate that an individual has a greater genetic predisposition to conduct disorder, and lower polygenic scores indicate that an individual has a lower genetic predisposition to conduct disorder. These scores can be carried forward into tests of rGE and G × E.

Third, the ability to summarize aggregate genetic risk in a meaningful way opens up more opportunities for developmental psychologists and neuroscientists to use the theories and tools of their fields to more carefully delineate the mechanisms of risk going from genes to brain to behavior, and in conjunction with the environment. The falling cost of genome-wide genotyping arrays that cover both common and rare genetic variation (currently <100 USD) means that it is now financially feasible to collect genotypic data on samples for which there are detailed longitudinal developmental data. This permits examination of important process-oriented questions about the biological and psychological mechanisms through which genetic risk has its effect on genotype (e.g., through deficits in social information processing or structural or functional brain differences; Crick and Dodge, 1994; Huebner et al., 2008). Although a precision medicine approach for psychiatric disorders has yet to be realized (Collins and Varmus, 2015), identifying these mechanisms may provide critical insights about how to best implement prevention and intervention efforts so that the right people are intervened with at the right time.

Fourth, genetically informed data can be leveraged to test causal hypotheses about purported risk factors for conduct disorder. Although our review has primarily focused on how genetic and environmental risk factors come together to predict conduct disorder, it is also important to note that genetically informed designs can also be used to test competing hypotheses about causation versus correlation due to confounding familial factors (D'Onofrio et al., 2013). Testing causal hypotheses about risk factors is central to identifying the appropriate targets for conduct disorder intervention and prevention efforts, and ultimately reducing the burden of these behaviors on individuals and societies. For example, if the association between *OXTR* methylation at birth and callous-unemotional traits in adolescence (Cecil et al., 2014) is causal, environmental interventions aimed at changing methylation patterns (e.g., through exercise, pharmaceutical intervention, or other manipulations) may be reasonable. The power of quasi-causal designs comes from comparison of sibling pairs who are discordant on a factor of interest. Under a causal model, if the risk factor has a causal impact on the phenotype, the exposed sibling would have a higher rate of conduct disorder compared to the non-exposed sibling. Under a non-causal model, where the risk factor is confounded by familial factors (genetic or environmental), the exposed sibling and the unexposed sibling would show similar rates of conduct disorder. Accordingly, genetically informed designs can give important insights about the risk factors to prioritize in prevention and intervention efforts.

In summary, a rich history of research suggests that a complex matrix of genetic and environmental factors contribute to conduct disorder. As behavior genetic research on conduct disorder expands beyond studies of heritability, the importance of characterizing the probabilistic and interdependent influences of genetic predispositions and environmental risk factors to better understand the mechanisms of risk from genes to behavior is becoming increasingly clear. This enhanced etiological understanding will inform the ultimate goal of developing effective interventions for this socially and personally costly disorder.

Acknowledgements

Support for this work came from National Institutes of Health Grants F32AA022269, K01AA024152, K02AA018755, U10AA008401, R01DA070312, and R01AA015416. The contents of the paper are solely the responsibility of the authors and do not necessarily represent the official views of the funders.

Please cite this article in press as: Salvatore, J.E., Dick, D.M., Genetic influences on conduct disorder. Neurosci. Biobehav. Rev. (2016), http://dx.doi.org/10.1016/j.neubiorev.2016.06.034

References

Agrawal, A., Edenberg, H.J., Foroud, T., Bierut, L.J., Dunne, G., Hinrichs, A.L., Nurnberger, J.I., Crowe, R., Kuperman, S., Schuckit, M.A., Begleiter, H., Porjesz, B., Dick, D.M., 2006. Association of GABRA2 with drug dependence in the collaborative study of the genetics of alcoholism sample. Behav. Genet. 36, 640–650, http://dx.doi.org/10.1007/s10519-006-9069-4.

American Psychiatric Association, 1987. Diagnostic and Statistical Manual of Mental Disorders, revised third edition. American Psychiatric Association, Washington, D.C.

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), Washington D.C.

Anckarsater, H., Lundstrom, S., Kollberg, L., Kerekes, N., Palm, C., Carlstrom, E., Langstrom, N., Magnusson, P.K.E., Halldner, L., Bolte, S., Gillberg, C., Gumpert, C., Rastam, M., Lichtenstein, P., 2011. The child and adolescent twin study in Sweden (CATSS). Twin Res. Hum. Genet. 14, 495–508, http://dx.doi.org/10.1375/twin.14.6.495.

Anney, R.J., Lasky-Su, J., O'Dushlaine, C., Kenny, E., Neale, B.M., Mulligan, A., Franke, B., Zhou, K., Chen, W., Christiansen, H., Arias-Vasquez, A., Banaschewski, T., Buitelaar, J., Ebstein, R., Miranda, A., Mulas, F., Oades, R.D., Roeyers, H., Rothenberger, A., Sergeant, J., Sonuga-Barke, E., Steinhausen, H., Asherson, P., Faraone, S.V., Gill, M., 2008. Conduct disorder and ADHD: evaluation of conduct problems as a categorical and quantitative trait in the international multicentre ADHD genetics study. Am. J. Med. Genet. B Neuropsychiatr. Genet. 147b, 1369–1378, http://dx.doi.org/10.1002/ajmg.b.30871.

Bakermans-Kranenburg, M.J., van Ijzendoorn, M.H., 2015. The hidden efficacy of interventions: gene x environment experiments from a differential susceptibility perspective. Annu. Rev. Psychol. 66, 381–409, http://dx.doi.org/10.1146/annurev-psych-010814-015407.

Begleiter, H., Reich, T., Hesselbrock, V., Porjesz, B., Li, T.K., Schuckit, M.A., Edenberg, H.J., Rice, J.P., 1995. The collaborative study on the genetics of alcoholism. Alcohol Health Res. W 19, 228–236.

Belsky, J., Jonassaint, C., Pluess, M., Stanton, M., Brummett, B., Williams, R., 2009. Vulnerability genes or plasticity genes? Mol. Psychiatr. 14, 746–754, http://dx.doi.org/10.1038/mp.2009.44.

Blair, R.J., Leibenluft, E., Pine, D.S., 2014. Conduct disorder and callous-unemotional traits in youth. N. Engl. J. Med. 371, 2207–2216, http://dx.doi.org/10.1056/NEJMra1315612.

Bosker, F.J., Hartman, C.A., Nolte, I.M., Prins, B.P., Terpstra, P., Posthuma, D., van Veen, T., Willemsen, G., DeRijk, R.H., de Geus, E.J., Hoogendijk, W.J., Sullivan, P.F., Penninx, B.W., Boomsma, D.I., Snieder, H., Nolen, W.A., 2011. Poor replication of candidate genes for major depressive disorder using genome-wide association data. Mol. Psychiatry 16, 516–532, http://dx.doi.org/10.1038/mp.2010.38.

Broms, U., Wedenoja, J., Largeau, M.R., Korhonen, T., Pitkaniemi, J., Keskitalo-Vuokko, K., Happola, A., Heikkila, K.H., Heikkila, K., Ripatti, S., Sarin, A.P., Salminen, O., Paunio, T., Pergadia, M.L., Madden, P.A., Kaprio, J., Loukola, A., 2012. Analysis of detailed phenotype profiles reveals CHRNA5-CHRNA3-CHRNB4 gene cluster association with several nicotine dependence traits. Nicotine Tob. Res. 14, 720–733, http://dx.doi.org/10.1093/ntr/ntr283.

Burt, S.A., Klump, K.L., 2014. Parent-child conflict as an etiological moderator of childhood conduct problems: an example of a 'bioecological' gene-environment interaction. Psychol. Med. 44, 1065–1076, http://dx.doi.org/10.1017/S0033291713001190.

Burt, S.A., 2009. Are there meaningful etiological differences within antisocial behavior? Results of a meta-analysis. Clin. Psychol. Rev. 29, 163–178, http://dx.doi.org/10.1016/j.cpr.2008.12.004.

Bush, W.S., Haines, J., 2010. Overview of linkage analysis in complex traits. Curr. Protoc. Hum. Genet., http://dx.doi.org/10.1002/0471142905. hg0109s64, editorial board, Jonathan L. Haines. [et al.] Chapter 1, Unit 1 9 1–18.

Button, T.M.M., Corley, R.P., Rhee, S.H., Hewitt, J.K., Young, S.E., Stallings, M.C., 2007. Delinquent peer affiliation and conduct problems: a twin study. J. Abnorm. Psychol. 116, 554–564, http://dx.doi.org/10.1037/0021-843x.116.3.554.

Canino, G., Polanczyk, G., Bauermeister, J.J., Rohde, L.A., Frick, P.J., 2010. Does the prevalence of CD and ODD vary across cultures? Soc. Psychiatry Psychiatr. Epidemiol. 45, 695–704, http://dx.doi.org/10.1007/s00127-010-0242-y.

Caspi, A., Moffitt, T.E., 2006. Gene-environment interactions in psychiatry: joining forces with neuroscience. Nat. Rev. Neurosci. 7, 583–590, http://dx.doi.org/10.1038/nrn1925.

Caspi, A., McClay, J., Moffitt, T.E., Mill, J., Martin, J., Craig, I.W., Taylor, A., Poulton, R., 2002. Role of genotype in the cycle of violence in maltreated children. Science 297, 851–854, http://dx.doi.org/10.1126/science.1072290.

Cecil, C.A.M., Lysenko, L.J., Jaffee, S.R., Pingault, J.B., Smith, R.G., Relton, C.L., Woodward, G., McArdle, W., Mill, J., Barker, E.D., 2014. Environmental risk, Oxytocin Receptor Gene (OXTR) methylation and youth callous-unemotional traits: a 13-year longitudinal study. Mol. Psychiatr. 19, 1071–1077, http://dx.doi.org/10.1038/mp.2014.95.

Collins, F.S., Varmus, H., 2015. A new initiative on precision medicine. N. Engl. J. Med. 372, 793–795, http://dx.doi.org/10.1056/NEJMp1500523.

Collins, A.L., Kim, Y., Sklar, P., O'Donovan, M.C., Sullivan, P.F., 2012. Hypothesis-driven candidate genes for schizophrenia compared to genome-wide association results. Psychol. Med. 42, 607–616, http://dx.doi.org/10.1017/s0033291711001607.

Costello, E.J., Angold, A., 2001. Bad behaviour: an historical perspective on disorders of conduct. In: Hill, J., Maughan, B. (Eds.), Conduct Disorders in Childhood and Adolescence. Cambridge University Press, Cambridge, United Kingdom, pp. 1–31.

Covault, J., Gelernter, J., Hesselbrock, V., Nellissery, M., Kranzler, H.R., 2004. Allelic and haplotypic association of GABRA2 with alcohol dependence. Am. J. Med. Genet. B Neuropsychiatr. Genet. 129B, 104–109, http://dx.doi.org/10.1002/ajmg.b.30091.

Crick, N.R., Dodge, K.A., 1994. A review and reformulation of social information-processing mechanisms in children's social adjustment. Psychol. Bull. 115, http://dx.doi.org/10.1037//0033-2909.115.1.74, 74–74.

D'Onofrio, B.M., Lahey, B.B., Turkheimer, E., Lichtenstein, P., 2013. Critical need for family-based, quasi-experimental designs in integrating genetic and social science research. Am. J. Public Health 103, 46–55, http://dx.doi.org/10.2105/ajph.2013.301252.

Dadds, M.R., Moul, C., Cauchi, A., Dobson-Stone, C., Hawes, D.J., Brennan, J., Ebstein, R.E., 2014. Methylation of the oxytocin receptor gene and oxytocin blood levels in the development of psychopathy. Dev. Psychopathol. 26, 33–40, http://dx.doi.org/10.1017/s0954579413000497.

Dick, D.M., Li, T.K., Edenberg, H.J., Hesselbrock, V., Kramer, J., Kuperman, S., Porjesz, B., Bucholz, K., Goate, A., Nurnberger, J., Foroud, T., 2004. A genome-wide screen for genes influencing conduct disorder. Mol. Psychiatry 9, 81–86, http://dx.doi.org/10.1038/sj.mp.4001368.

Dick, D.M., Bierut, L., Hinrichs, A., Fox, L., Bucholz, K.K., Kramer, J., Kuperman, S., Hesselbrock, V., Schuckit, M., Almasy, L., Tischfield, J., Porjesz, B., Begleiter, H., Nurnberger, J., Xuei, X.L., Edenberg, H.J., Foroud, T., 2006. The role of GABRA2 in risk for conduct disorder and alcohol and drug dependence across developmental stages. Behav. Genet. 36, 577–590, http://dx.doi.org/10.1007/s10519-005-9041-8.

Dick, D.M., Pagan, J.L., Viken, R., Purcell, S., Kaprio, J., Pulkkinen, L., Rose, R.J., 2007. Changing environmental influences on substance use across development. Twin Res. Hum. Genet. 10, 315–326, http://dx.doi.org/10.1375/twin.10.2.315.

Dick, D.M., Aliev, F., Wang, J.C., Grucza, R.A., Schuckit, M., Kuperman, S., Kramer, J., Hinrichs, A., Bertelsen, S., Budde, J.P., Hesselbrock, V., Porjesz, B., Edenberg, H.J., Bierut, L.J., Goate, A., 2008. Using dimensional models of externalizing psychopathology to aid in gene identification. Arch. Gen. Psychiatry 65, 310–318, http://dx.doi.org/10.1001/archpsyc.65.3.310.

Dick, D.M., Latendresse, S.J., Lansford, J.E., Budde, J.P., Goate, A., Dodge, K.A., Pettit, G.S., Bates, J.E., 2009. Role of GABRA2 in trajectories of externalizing behavior across development and evidence of moderation by parental monitoring. Arch. Gen. Psychiatry 66, 649–657, http://dx.doi.org/10.1001/archgenpsychiatry.2009.48.

Dick, D.M., Meyers, J., Aliev, F., Nurnberger Jr., J., Kramer, J., Kuperman, S., Porjesz, B., Tischfield, J., Edenberg, H.J., Foroud, T., Schuckit, M., Goate, A., Hesselbrock, V., Bierut, L., 2010. Evidence for genes on chromosome 2 contributing to alcohol dependence with conduct disorder and suicide attempts. Am. J. Med. Genet. B Neuropsychiatr. Genet. 153b, 1179–1188, http://dx.doi.org/10.1002/ajmg.b.31089.

Dick, D.M., Aliev, F., Krueger, R.F., Edwards, A., Agrawal, A., Lynskey, M., Lin, P., Schuckit, M., Hesselbrock, V., Nurnberger Jr., J., Almasy, L., Porjesz, B., Edenberg, H.J., Bucholz, K., Kramer, J., Kuperman, S., Bierut, L., 2011. Genome-wide association study of conduct disorder symptomatology. Mol. Psychiatry 16, 800–808, http://dx.doi.org/10.1038/mp.2010.73.

Dick, D.M., Aliev, F., Latendresse, S., Porjesz, B., Schuckit, M., Rangaswamy, M., Hesselbrock, V., Edenberg, H., Nurnberger, J., Agrawal, A., Bierut, L., Wang, J., Bucholz, K., Kuperman, S., Kramer, J., 2013. How phenotype and developmental stage affect the genes we find: GABRA2 and impulsivity. Twin Res. Hum. Genet. 16, 661–669, http://dx.doi.org/10.1017/thg.2013.20.

Dick, D.M., Agrawal, A., Keller, M.C., Adkins, A., Aliev, F., Monroe, S., Hewitt, J.K., Kendler, K.S., Sher, K.J., 2015. Candidate gene-environment interaction research: reflections and recommendations. Perspect. Psychol. Sci. 10, 37–59, http://dx.doi.org/10.1177/1745691614556682.

Duncan, L., Keller, M.C., 2011. A critical review of the first ten years of measured gene-by-environment interaction research in psychiatry. Am. J. Psychiatry 168, 1041–1049, http://dx.doi.org/10.1176/appi.ajp.2011.11020191.

Eaves, L., Silberg, J.L., Meyer, J.M., Maes, H.H., Simonoff, E., Pickles, A., Neale, M.C., Reynolds, C.A., Erikson, M.T., Heath, A.C., Loeber, R., Truett, K.R., Hewitt, J.K., Rutter, M., 1997. Genetics and developmental psychopathology: 2. The main effects of genes and environment on behavioral problems in the Virginia Twin Study of Adolescent Behavioral Development. J. Child Psychol. Psychiatry 38, 965–980, http://dx.doi.org/10.1111/j.1469-7610.1997.tb01614.x.

Ebstein, R.P., Israel, S., Chew, S.H., Zhong, S., Knafo, A., 2010. Genetics of human social behavior. Neuron 65, 831–844, http://dx.doi.org/10.1016/j.neuron.2010.02.020.

Edenberg, H.J., Dick, D.M., Xuei, X., Tian, H., Almasy, L., Bauer, L.O., Crowe, R., Goate, A., Hesselbrock, V., Jones, K.A., Kwon, J., Li, T.K., Nurnberger Jr., J.I., O'Connor, S.J., Reich, T., Rice, J., Schuckit, M., Porjesz, B., Foroud, T., Begleiter, H., 2004. Variations in GABRA2, encoding the α2 subunit of the GABA-A receptor are associated with alcohol dependence and with brain oscillations. Am. J. Hum. Genet. 74, 705–714, http://dx.doi.org/10.1086/383283.

El-Sayed, A.M., Koenen, K.C., Galea, S., 2013. Putting the 'epi' into epigenetics research in psychiatry. J. Epidemiol. Community Health 67, 610–616, http://dx.doi.org/10.1136/jech-2013-202430.

Elkins, I.J., McGue, M., Iacono, W.G., 2007. Prospective effects of attention-deficit/hyperactivity disorder, conduct disorder, and sex on adolescent substance use and abuse. Arch. Gen. Psychiatry 64, 1145–1152, http://dx.doi.org/10.1001/archpsyc.64.10.1145.

Please cite this article in press as: Salvatore, J.E., Dick, D.M., Genetic influences on conduct disorder. Neurosci. Biobehav. Rev. (2016), http://dx.doi.org/10.1016/j.neubiorev.2016.06.034

Enoch, M.A., Hodgkinson, C.A., Yuan, Q., Albaugh, B., Virkkunen, M., Goldman, D., 2009. GABRG1 and GABRA2 as independent predictors for alcoholism in two populations. Neuropsychopharmacology 34, 1245–1254, http://dx.doi.org/10.1038/npp.2008.171.

Enoch, M.A., 2008. The role of GABA(A) receptors in the development of alcoholism. Pharmacol. Biochem. Behav. 90, 95–104, http://dx.doi.org/10.1016/j.pbb.2008.03.007.

Erskine, H.E., Ferrari, A.J., Polanczyk, G.V., Moffitt, T.E., Murray, C.J., Vos, T., Whiteford, H.A., Scott, J.G., 2014. The global burden of conduct disorder and attention-deficit/hyperactivity disorder in 2010. J. Child Psychol. Psychiatry 55, 328–336, http://dx.doi.org/10.1111/jcpp.12186.

Ficks, C.A., Waldman, I.D., 2014. Candidate genes for aggression and antisocial behavior: a meta-analysis of association studies of the 5HTTLPR and MAOA-uVNTR. Behav. Genet., http://dx.doi.org/10.1007/s10519-014-9661-y.

Foroud, T., Edenberg, H.J., Goate, A., Rice, J., Flury, L., Koller, D.L., Bierut, L.J., Conneally, P.M., Nurnberger, J.I., Bucholz, K.K., Li, T.K., Hesselbrock, V., Crowe, R., Schuckit, M., Porjesz, B., Begleiter, H., Reich, T., 2000. Alcoholism susceptibility loci: confirmation studies in a replicate sample and further mapping. Alcohol Clin. Exp. Res. 24, 933–945, http://dx.doi.org/10.1111/j.1530-0277.2000.tb04634.x.

Foster, E.M., Jones, D.E., 2005. The high costs of aggression: public expenditures resulting from conduct disorder. Am. J. Public Health 95, 1767–1772, http://dx.doi.org/10.2105/AJPH.2004.061424.

Frick, P.J., Ellis, M., 1999. Callous-unemotional traits and subtypes of conduct disorder. Clin. Child Fam. Psychol. Rev. 2, 149–168, http://dx.doi.org/10.1023/A:1021803005547.

Gelernter, J., Kranzler, H.R., Sherva, R., Almasy, L., Koesterer, R., Smith, A.H., Anton, R., Preuss, U.W., Ridinger, M., Rujescu, D., Wodarz, N., Zill, P., Zhao, H., Farrer, L.A., 2013. Genome-wide association study of alcohol dependence: significant findings in African- and European-Americans including novel risk loci. Mol. Psychiatry 19, 41–49, http://dx.doi.org/10.1038/mp.2013.145.

Gelhorn, H.L., Stallings, M.C., Young, S.E., Corley, R.P., Rhee, S.H., Hewitt, J.K., 2005. Genetic and environmental influences on conduct disorder: symptom, domain and full-scale analyses. J. Child Psychol. Psychiatry 46, 580–591, http://dx.doi.org/10.1111/j.1469-7610.2004.00373.x.

Gelhorn, H., Stallings, M., Young, S., Corley, R., Rhee, S.H., Hopfer, C., Hevitt, J., 2006. Common and specific genetic influences on aggressive and nonaggressive conduct disorder domains. J. Am. Acad. Child Adolesc. Psychiatry 45, 570–577, http://dx.doi.org/10.1097/01.chi.0000198596.76443.b0.

Gunter, T.D., Vaughn, M.G., Philibert, R.A., 2010. Behavioral genetics in antisocial spectrum disorders and psychopathy: a review of the recent literature. Behav. Sci. Law 28, 148–173, http://dx.doi.org/10.1002/bsl.923.

Haber, J.R., Bucholz, K.K., Jacob, T., Grant, J.D., Scherrer, J.F., Sartor, C.E., Duncan, A.E., Heath, A., 2010. Effect of paternal alcohol and drug dependence on offspring conduct disorder: gene-environment interplay. J. Stud. Alcohol Drugs 71, 652–663, http://dx.doi.org/10.15288/jsad.2010.71.652.

Hesselbrock, V., Dick, D., Hesselbrock, M., Foroud, T., Schuckit, M., Edenberg, H., Bucholz, K., Kramer, J., Reich, T., Goate, A., Bierut, L., Rice, J.P., Nurnberger, J.I., 2004. The search for genetic risk factors associated with suicidal behavior. Alcohol Clin. Exp. Res. 28, 70S–76S, http://dx.doi.org/10.1097/01.alc.0000127416.92128.b0.

Huebner, T., Vloet, T.D., Marx, I., Konrad, K., Fink, G.R., Herpertz, S.C., Herpertz-Dahlmann, B., 2008. Morphometric brain abnormalities in boys with conduct disorder. J. Am. Acad. Child Adolesc. Psychiatry 47, 540–547, http://dx.doi.org/10.1097/CHI.0b013e3181676545.

INSERM Collective Expertise Centre, 2005. Conduct disorder in children and adolescents. Institut national de la santé et de la recherche médicale, Paris.

Jacobson, K.C., Prescott, C.A., Kendler, K.S., 2002. Sex differences in the genetic and environmental influences on the development of antisocial behavior. Dev. Psychopathol. 14, 395–416, http://dx.doi.org/10.1017/s0954579402002110.

Jain, M., Palacio, L.G., Castellanos, F.X., Palacio, J.D., Pineda, D., Restrepo, M.I., Munoz, J.F., Lopera, F., Wallis, D., Berg, K., Bailey-Wilson, J.E., Arcos-Burgos, M., Muenke, M., 2007. Attention-deficit/hyperactivity disorder and comorbid disruptive behavior disorders: evidence of pleiotropy and new susceptibility loci. Biol. Psychiatry 61, 1329–1339, http://dx.doi.org/10.1016/j.biopsych.2006.06.026.

Kendler, K.S., Baker, J.H., 2007. Genetic influences on measures of the environment: a systematic review. Psychol. Med. 37, 615–626, http://dx.doi.org/10.1017/s0033291706009524.

Kendler, K.S., Prescott, C.A., Myers, J., Neale, M.C., 2003. The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. Arch. Gen. Psychiatry 60, 929–937, http://dx.doi.org/10.1001/archpsyc.60.9.929.

Kendler, K.S., Kuo, P.H., Webb, B.T., Kalsi, G., Neale, M.C., Sullivan, P.F., Walsh, D., Patterson, D.G., Riley, B., Prescott, C.A., 2006. A joint genomewide linkage analysis of symptoms of alcohol dependence and conduct disorder. Alcohol Clin. Exp. Res. 30, 1972–1977, http://dx.doi.org/10.1111/j.1530-0277.2006.00243.x.

Kendler, K.S., Jacobson, K., Myers, J.M., Eaves, L.J., 2008. A genetically informative developmental study of the relationship between conduct disorder and peer deviance in males. Psychol. Med. 38, 1001–1011, http://dx.doi.org/10.1017/s0033291707001821.

Kendler, K.S., Aggen, S.H., Patrick, C.J., 2013. Familial influences on conduct disorder reflect 2 genetic factors and 1 shared environmental factor. JAMA Psychiatry 70, 78–86, http://dx.doi.org/10.1001/jamapsychiatry.2013.267.

Krueger, R.F., Hicks, B.M., Patrick, C.J., Carlson, S.R., Iacono, W.G., McGue, M., 2002. Etiological connections among substance dependence, antisocial behavior, and personality: modeling the externalizing spectrum. J. Abnorm. Psychol. 111, 411–424, http://dx.doi.org/10.1037//0021-843X.111.3.411.

Lander, E., Kruglyak, L., 1995. Genetic dissection of complex traits: guidelines for interpreting and reporting linkage results. Nat. Genet. 11, 241–247, http://dx.doi.org/10.1038/ng1195-241.

Legrand, L.N., Keyes, M., McGue, M., Iacono, W.G., Krueger, R.F., 2008. Rural environments reduce the genetic influence on adolescent substance use and rule-breaking behavior. Psychol. Med. 38, 1341–1350, http://dx.doi.org/10.1017/s0033291707001596.

Loeber, R., Burke, J.D., Lahey, B.B., Winters, A., Zera, M., 2000. Oppositional defiant and conduct disorder: a review of the past 10 years. I. J. Am. Acad. Child Adolesc. Psychiatry 39, 1468–1484.

McAdams, T.A., Gregory, A.M., Eley, T.C., 2013. Genes of experience: explaining the heritability of putative environmental variables through their association with behavioural and emotional traits. Behav. Genet. 43, 314–328, http://dx.doi.org/10.1007/s10519-013-9591-0.

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

Meier, M.H., Slutske, W.S., Heath, A.C., Martin, N.G., 2011. Sex differences in the genetic and environmental influences on childhood conduct disorder and adult antisocial behavior. J. Abnorm. Psychol. 120, 377–388, http://dx.doi.org/10.1037/a0022303.

Melroy, W.E., Stephens, S.H., Sakai, J.T., Kamens, H.M., McQueen, M.B., Corley, R.P., Stallings, M.C., Hopfer, C.J., Krauter, K.S., Brown, S.A., Hewitt, J.K., Ehringer, M.A., 2014. Examination of genetic variation in GABRA2 with conduct disorder and alcohol abuse and dependence in a longitudinal study. Behav. Genet. 44, 356–367, http://dx.doi.org/10.1007/s10519-014-9653-y.

Moffitt, T.E., 1993. Adolescence-limited and life-course-persistent antisocial behavior: a developmental taxonomy. Psychol. Rev. 100, 674–701, http://dx.doi.org/10.1037//0033-295X.100.4.674.

Neale, M.C., Roysamb, E., Jacobson, K., 2006. Multivariate genetic analysis of sex limitation and G×E interaction. Twin Res. Hum. Genet. 9, 481–489, http://dx.doi.org/10.1375/183242706778024937.

Pappa, I., St Pourcain, B., Benke, K., Cavadino, A., Hakulinen, C., Nivard, M.G., Nolte, I.M., Tiesler, C.M., Bakermans-Kranenburg, M.J., Davies, G.E., Evans, D.M., Geoffroy, M.C., Grallert, H., Groen-Blokhuis, M.M., Hudziak, J.J., Kemp, J.P., Keltikangas-Jarvinen, L., McMahon, G., Mileva-Seitz, V.R., Motazedi, E., Power, C., Raitakari, O.T., Ring, S.M., Rivadeneira, F., Rodriguez, A., Scheet, P.A., Seppala, I., Snieder, H., Standl, M., Thiering, E., Timpson, N.J., Veenstra, R., Velders, F.P., Whitehouse, A.J., Smith, G.D., Heinrich, J., Hypponen, E., Lehtimaki, T., Middeldorp, C.M., Oldehinkel, A.J., Pennell, C.E., Boomsma, D.I., Tiemeier, H., 2015. A genome-wide approach to children's aggressive behavior: the EAGLE consortium. Am. J. Med. Genet. B Neuropsychiatr. Genet., http://dx.doi.org/10.1002/ajmg.b.32333.

Pluess, M., Belsky, J., 2013. Vantage sensitivity: individual differences in response to positive experiences. Psychol. Bull. 139, 901–916, http://dx.doi.org/10.1037/a0030196.

Polderman, T.J., Benyamin, B., de Leeuw, C.A., Sullivan, P.F., van Bochoven, A., Visscher, P.M., Posthuma, D., 2015. Meta-analysis of the heritability of human traits based on fifty years of twin studies. Nat. Genet. 47, 702–709, http://dx.doi.org/10.1038/ng.3285.

Provencal, N., Suderman, M.J., Caramaschi, D., Wang, D., Hallett, M., Vitaro, F., Tremblay, R.E., Szyf, M., 2013. Differential DNA methylation regions in cytokine and transcription factor genomic loci associate with childhood physical aggression. PLoS One 8, e71691, http://dx.doi.org/10.1371/journal.pone.0071691.

Purcell, S., 2002. Variance components models for gene-environment interaction in twin analysis. Twin Res. 5, 554–571.

Rathouz, P.J., Van Hulle, C.A., Rodgers, J.L., Waldman, I.D., Lahey, B.B., 2008. Specification, testing, and interpretation of gene-by-measured-environment interaction models in the presence of gene-environment correlation. Behav. Genet. 38, 301–315, http://dx.doi.org/10.1007/s10519-008-9193-4.

Rhee, S.H., Waldman, I.D., 2002. Genetic and environmental influences on antisocial behavior: a meta-analysis of twin and adoption studies. Psychol. Bull. 128, 490–529, http://dx.doi.org/10.1037//0033-2909.128.3.490.

Sakai, J.T., Stallings, M.C., Crowley, T.J., Gelhorn, H.L., McQueen, M.B., Ehringer, M.A., 2010. Test of association between GABRA2 (SNP rs279871) and adolescent conduct/alcohol use disorders utilizing a sample of clinic referred youth with serious substance and conduct problems, controls and available first degree relatives. Drug Alcohol Depend. 106, 199–203, http://dx.doi.org/10.1016/j.drugalcdep.2009.08.015.

Scarr, S., McCartney, K., 1983. How people make their own environments: a theory of genotype greater than environment effects. Child Dev. 54, 424–435, http://dx.doi.org/10.2307/1129703.

Schizophrenia Working Group of the Psychiatric Genomics, C., 2014. Biological insights from 108 schizophrenia-associated genetic loci. Nature 511, 421–427, http://dx.doi.org/10.1038/nature13595.

Shanahan, M.J., Hofer, S.M., 2005. Social context in gene-environment interactions: retrospect and prospect. J. Gerontol. Ser. B Psychol. Sci. Soc. Sci. 60B, 65–76, http://dx.doi.org/10.1093/geronb/60.Special_Issue_1.65.

Slutske, W.S., Heath, A.C., Dinwiddie, S.H., Madden, P.A.F., Bucholz, K.K., Dunne, M.P., Statham, D.J., Martin, N.G., 1998. Common genetic risk factors for conduct

Please cite this article in press as: Salvatore, J.E., Dick, D.M., Genetic influences on conduct disorder. Neurosci. Biobehav. Rev. (2016), http://dx.doi.org/10.1016/j.neubiorev.2016.06.034

disorder and alcohol dependence. J. Abnorm. Psychol. 107, 363–374, http://dx.doi.org/10.1037/0021-843X.107.3.363.
Stallings, M.C., Corley, R.P., Dennehey, B., Hewitt, J.K., Krauter, K.S., Lessem, J.M., Mikulich-Gilbertson, S.K., Rhee, S.H., Smolen, A., Young, S.E., Crowley, T.J., 2005. A genome-wide search for quantitative trait loci that influence antisocial drug dependence in adolescence. Arch. Gen. Psychiatry 62, 1042–1051, http://dx.doi.org/10.1001/archpsyc.62.9.1042.
Thomasson, H.R., Edenberg, H.J., Crabb, D.W., Mai, X.L., Jerome, R.E., Li, T.K., Wang, S.P., Lin, Y.T., Lu, R.B., Yin, S.J., 1991. Alcohol and aldehyde dehydrogenase genotypes and alcoholism in Chinese men. Am. J. Hum. Genet. 48, 667–681.
Tielbeek, J.J., Medland, S.E., Benyamin, B., Byrne, E.M., Heath, A.C., Madden, P.A., Martin, N.G., Wray, N.R., Verweij, K.J., 2012. Unraveling the genetic etiology of adult antisocial behavior: a genome-wide association study. PLoS One 7, e45086, http://dx.doi.org/10.1371/journal.pone.0045086.
Tobacco and Genetics Consortium, 2010. Genome-wide meta-analyses identify multiple loci associated with smoking behavior. Nat. Genet. 42, http://dx.doi.org/10.1038/ng.571.
Tremblay, R.E., 2008. Understanding development and prevention of chronic physical aggression: towards experimental epigenetic studies. Philos. Trans. R. Soc. B Biol. Sci. 363, 2613–2622, http://dx.doi.org/10.1098/rstb.2008.0030.
van Goozen, S.H., Fairchild, G., Snoek, H., Harold, G.T., 2007. The evidence for a neurobiological model of childhood antisocial behavior. Psychol. Bull. 133, 149–182, http://dx.doi.org/10.1037/0033-2909.133.1.149.
van der Sluis, S., Posthuma, D., Dolan, C.V., 2012. A note on false positives and power in G×E modelling of twin data. Behav. Genet. 42, 170–186, http://dx.doi.org/10.1007/s10519-011-9480-3.
Veroude, K., Zhang-James, Y., Fernàndez-Castillo, N., Bakker, M.J., Cormand, B., Faraone, S.V., 2015. Genetics of aggressive behavior: an overview. Am. J. Med. Genet. B Neuropsychiatr. Genet. 171, 3–43, http://dx.doi.org/10.1002/ajmg.b.32364.
Villafuerte, S., Trucco, E.M., Heitzeg, M.M., Burmeister, M., Zucker, R.A., 2014. Genetic variation in moderates peer influence on externalizing behavior in adolescents. Brain Behav., http://dx.doi.org/10.1002/brb3.291.
Vrieze, S.I., Feng, S., Miller, M.B., Hicks, B.M., Pankratz, N., Abecasis, G.R., Iacono, W.G., McGue, M., 2014. Rare nonsynonymous exonic variants in addiction and behavioral disinhibition. Biol. Psychiatry 75, 783–789, http://dx.doi.org/10.1016/j.biopsych.2013.08.027.
Walum, H., Lichtenstein, P., Neiderhiser, J.M., Reiss, D., Ganiban, J.M., Spotts, E.L., Pedersen, N.L., Anckarsater, H., Larsson, H., Westberg, L., 2012. Variation in the oxytocin receptor gene is associated with pair-bonding and social behavior. Biol. Psychiatry 71, 419–426, http://dx.doi.org/10.1016/j.biopsych.2011.09.002.
Willour, V.L., Zandi, P.P., Badner, J.A., Steele, J., Miao, K., Lopez, V., MacKinnon, D.F., Mondimore, F.M., Schweizer, B., McInnis, M.G., Miller, E.B., Depaulo Jr., J.R., Gershon, E.S., McMahon, F.J., Potash, J.B., 2007. Attempted suicide in bipolar disorder pedigrees: evidence for linkage to 2p12. Biol. Psychiatry 61, 725–727, http://dx.doi.org/10.1016/j.biopsych.2006.05.014.
Wray, N.R., Lee, S.H., Mehta, D., Vinkhuyzen, A.A., Dudbridge, F., Middeldorp, C.M., 2014. Research review: polygenic methods and their application to psychiatric traits. J. Child Psychol. Psychiatry 55, 1068–1087, http://dx.doi.org/10.1111/jcpp.12295.
Young, S.E., Stallings, M.C., Corley, R.P., Krauter, K.S., Hewitt, J.K., 2000. Genetic and environmental influences on behavioral disinhibition. Am. J. Med. Genet. 96, 684–695, http://dx.doi.org/10.1002/1096-8628(20001009)96:5<684:aid-ajmg16>3.0.co;2-g.
Zhang-James, Y., Faraone, S.V., 2015. Genetic architecture for human aggression: a study of gene-phenotype relationship in OMIM. Am. J. Med. Genet. B Neuropsychiatr. Genet., http://dx.doi.org/10.1002/ajmg.b.32363.
Zintzaras, E., 2012. Gamma-aminobutyric acid A receptor, alpha-2 (GABRA2) variants as individual markers for alcoholism: a meta-analysis. Psychiatr. Genet. 22, 189–196, http://dx.doi.org/10.1097/YPG.0b013e328353ae53.
Zubenko, G.S., Maher, B.S., Hughes 3rd, H.B., Zubenko, W.N., Scott Stiffler, J., Marazita, M.L., 2004. Genome-wide linkage survey for genetic loci that affect the risk of suicide attempts in families with recurrent, early-onset, major depression. Am. J. Med. Genet. B Neuropsychiatr. Genet. 129B, 47–54, http://dx.doi.org/10.1002/ajmg.b.30092.

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