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## Measured Gene by Environment Interaction in Relation to Attention-Deficit/Hyperactivity Disorder (ADHD)

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### Abstract

**Objective**—Summarize and evaluate the state of knowledge regarding the role of measured gene by environment interactions in relation to ADHD.

**Method**—A selective review of methodological issues is followed by a systematic search for relevant articles on measured GxE; the search yielded 16 studies, which are discussed in qualitative fashion.

**Results**—Relatively consistent evidence points to the interaction of genotype with psychosocial factors in the development of ADHD. The next step is to identify the mechanisms on the environment side and the gene combinations on the genetic side accounting for this effect. By contrast, evidence for gene-environment interactions involving pre- and peri-natal risk factors is generally negative or unreplicated. The aggregate effect size for psychosocial interaction with genotype is more than double that for the interaction of pre- and perinatal risks with genotype. Only a small fraction of candidate environments and gene markers have been studied, and multivariate methods to integrate multiple gene or environment markers have yet to be implemented.

**Conclusions**—GxE appears likely to prove fruitful in understanding the etiology of ADHD. Findings to date already suggest new avenues of investigation particularly involving psychosocial mechanisms and their interplay with genotype. Further pursuit of theoretically promising leads is recommended.

### Keywords

ADHD; GxE; gene-by-environment interaction; gene; environment

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For decades, theorists have posited that psychopathology develops as a confluence of genetic and experiential factors; some models, such as the diathesis stress model, have relied on this logic. Indeed, the interplay between gene activity and environmental opportunity throughout

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development is inescapable. Yet, distinct from this truism is the reality that specific genotypes and specific environments may interact—that is, they may mechanistically amplify or dampen one another's expression. Some environments are probably damaging only to some individuals because of genotype. Alternately, some genotypes are advantageous, but only in certain environments. Such effects have been observed for some time in fields such as infectious disease, but historically remained in the realm of speculation for psychiatric disorders.

More recently, however, psychiatric genetics and developmental psychopathology have been energized by what we call “measured gene by environment” (GxE) studies. In these studies, specific measured gene markers and specific environmental effects are studied in tandem for statistical interaction. A related approach, though less often utilized, relies on quantitative methods to assess the moderation of latent genetic and environmental variance components by a measured environment variable via twin or adoption data.

An available literature documents the growth of this interest in GxE and its reasons, along with a range of conceptual and methodological considerations.<sup>1–3</sup> Among the most compelling motivations for studying GxE is that, in ADHD as in most psychiatric disorders, main effects of currently observable gene markers account for only a small fraction of the substantial heritability observed in twin studies. Measured GxE holds out the hope of identifying stronger etiological signals, the conditions under which particular genes have major effects, and the genotypes for which particular environments have major effects for a subset of the population—any of these would constitute genuine breakthroughs in mapping the multiple causal pathways involved in ADHD as well as other behavioral disorders.

For that and other reasons, and despite the methodological and inferential hazards that we note later, measured GxE has become a compelling approach to understanding the etiology and developmental course of most psychiatric disorders. In child psychiatry, interest has been ignited by findings regarding interactions of life stresses and the serotonin transporter gene promoter polymorphism (5HTTLPR) in depression<sup>4</sup> and a functional promoter polymorphism in the monoamine oxidase A gene (MAOA) and child maltreatment in conduct disorder.<sup>5</sup>

In the case of ADHD, no striking finding has similarly galvanized interest. However, ADHD research on GxE is now sufficiently far along that it is time to take stock of the initial forays into this field. In this review we (a) briefly outline conceptual issues that pertain to ADHD, some of them uniquely so, (b) examine and summarize the existing empirical literature using measured GxE studies of ADHD, and (c) offer our suggestions for next steps and issues in this exciting area of research.

## General Methodological Issues in GxE

Methodological issues in GxE research have been frequently reviewed and are readily available to interested readers.<sup>1–3,6,7</sup> Therefore, here we only briefly note particularly salient methodological issues that directly affect our ability to interpret the existing ADHD literature.

An over-arching issue is the substantial danger of false positive findings. One rather neglected issue involves measurement or statistical artifact. Under some conditions (depending on allele frequency and on measurement approach) the false positive rate for identifying GxE effects can exceed 50%.<sup>8</sup> In particular, GxE studies examining DNA markers with very low minor allele frequencies (i.e., <10% in population) with artificially dichotomized binary outcome measures will result in unbalanced cell sizes, resulting in an increased potential for false-positive significance tests of  $p < .05$ . In such situations, replication affords little assurance of accurate findings. Space does not permit this level of scrutiny here, but we emphasize ADHD effects apparent in studies using categorical as well as scaled outcomes. Similarly, there is often unclear protection against multiple testing artifact or else inadequate statistical power for

the number of tests conducted. The results presented later include studies with uncorrected findings that may not survive appropriate correction; we do not point this out in every instance. The problem of low power can be remedied by larger sample sizes of course, as well as by more reliable and accurate measurement, including use of latent variables or latent GxE approaches.<sup>1</sup> Theoretically justified tests provide a further protection against chance findings.

Another crucial artifact source in GxE research is that the psychosocial moderator may not be genetically independent of the outcome variable. In fact, “environmental” measures often are, at least in part, influenced by genetic factors.<sup>9</sup> Such findings are typically interpreted as evidence of gene-environment correlations (rGE). rGE are defined via non-random/genetically-influenced exposure to particular experiences. For example, children may exhibit ADHD due to genetic influences, but also evoke more negative reactions from their parents,<sup>10</sup> further influencing their ADHD symptoms via an evocative rGE. Crucial for our purposes is that rGE can masquerade as GxE.<sup>1</sup> Building on the example above, if an ineffective parenting style stems in part from genes common to ADHD, then the potentiation of genetic influences at high levels of “environmental” risk could be a reflection of rGE processes, rather than true GxE. Fortunately, many GxE studies have examined association between genetic and environmental measures in their study. Yet the lack of such a correlation at one particular locus does not mean that rGE effects can be fully ruled out. Other unmeasured genetic markers may be associated with both the environmental moderator and the outcome. Twin or adoption designs, using latent GxE methods that simultaneously consider rGE using measured environments, are important as complementary studies to molecular approaches, so that such possibilities can be fully evaluated. They remain underutilized.

Another underutilized approach has been to compare results for concordant and discordant twin pairs. Such studies have as yet failed to examine measured environments. However, studies of discordant twins reveal that brain structural and functional alterations associated with ADHD are distinct for environmental versus genetic influences, and demonstrate environmental modulation of genetic influences on ADHD.<sup>11–13</sup> These data underscore the importance of identifying environmental effects in ADHD.

## Issues Pertinent to ADHD

### Etiological Structure

ADHD differs from depression and externalizing behaviors in regard to its etiological structure. Depression, conduct disorder, and oppositional defiant disorder all tend to show a pattern of moderate heritability, with small-to-moderate shared or common environment effects.<sup>14,15</sup> ADHD, in contrast, has higher heritability with small non-shared environment effects and null shared environment effects,<sup>15,16</sup> although it remains possible that shared environment effects are masked by rater contrast effects or other artifact. This pattern of very high heritability may have initially misled the field into overlooking GxE research on ADHD. This would be unfortunate, because a critical, if somewhat non-intuitive, indicator of possible GxE is moderate-to-high heritability of the phenotype in question<sup>1</sup>. Because some types of gene-environment interplay increase monozygotic (identical) twin similarity relative to dizygotic (fraternal) twin similarity, GxE (as well as some rGE) is contained within the genetic proportion of variance in standard behavioral genetic analyses.

To illustrate hypothetically: if parental divorce provokes behavior problems only in genetically vulnerable children, then even in the absence of any genetic main effect on behavior problems we would see that MZ twins are more similar than DZ twins. A dramatic real example comes from the history of infectious disease. Human leukocyte antigen and other markers are now associated with susceptibility to infectious disease<sup>17</sup>. As a result of such effects, monozygotic twins are far more likely to be concordant for tuberculosis than dizygotic twins, yielding

estimates of heritability for tuberculosis of .6 or higher.<sup>18,19</sup> This result obviously reflects heritability of susceptibility interacting with pathogen exposure. (Note that although monozygotic twins affiliate more than dizygotic twins, this particular example likely survives evaluation of those confounding effects<sup>18</sup>). Despite major limitations to using infectious disease as a model for psychopathology, it is quite possible that disorders like ADHD also reflect genetic liability interacting with environmental triggers. In the case of psychopathology these triggers are viewed not as necessary (the way they are in infectious disease) but as probabilistic. In all, higher heritability coefficients are suggestive of more, rather than less, GxE. Accordingly, GxE may be especially appropriate for understanding ADHD.

With this in mind, how are genes and environments to be selected for study? One approach is to examine “candidates” (both “G” and “E”) that have shown some evidence of a main effect on the disorder or its constituent symptoms, to see if these effects are magnified by interactions among them. Note, however, that although this is one opening strategy, interactions can completely mask main effects. Thus, premature closure of a candidate list based only on main effects is likely ill-advised.

Yet in the case of ADHD, numerous such candidates are available for initial examination. On the genetic side, more success has emerged for ADHD than most psychiatric disorders in the identification of associated gene markers. Results of a recent meta-analysis<sup>20</sup> are summarized in Table 1. These markers either show reliable meta-analytic main effects, heterogeneity of effect (which could indicate, among other possibilities, presence of GxE), or both. Candidate chromosomal regions have also been identified in meta-analysis of GWA studies, particularly on chromosome 16.<sup>21</sup> In addition, the search is now on for multiple rare variants (e.g., copy number variants) that may occur in some families with ADHD. Clearly there will be no shortage of genetic markers to pursue in ADHD.

Unlike genes, which are relatively defined for our purposes (despite ongoing controversy about their boundaries), “environment” is poorly defined and has very different connotations in different health and medical sub-literatures. Here, we use the term environment to indicate any biological or psychosocial experience, or proxy thereof, impinging on the child (as we noted earlier, these can be correlated with genotype and not always purely environmental). A systematic analysis of which environments are likely candidates for ADHD is needed (and is currently lacking) to ground this type of research theoretically. Nigg<sup>19</sup> provided the most comprehensive effort to evaluate relevant environments on theoretical and empirical grounds. That review showed that the candidates for environmental effect on ADHD range from well supported to highly speculative in regard to their potential to yield major GxE findings. In Table 2, we informally summarize and catalogue the most often suggested environmental contributors to ADHD, grouped by pre-, peri-, and post-natal timing in development. The candidate environments listed are in many instances correlated or even overlapping (e.g., low birth weight increases risk for perinatal problems). Yet their joint influence is not well understood.

Also apparent in this table is that the candidate environments vary widely in their suitability and potential for explaining ADHD as part of a putative interaction model. The most promising for discovering powerful interaction effects are those that can be very reliably measured (greatly enhancing chances of finding an effect if one exists), and occur in a broad swath of the population (thus carrying the potential to have a large population attributable fraction or percent of cases explainable if an interaction exists). Yet, for the most part the suggested environmental candidates are not specific to ADHD—they confer risk for a range of adverse behavioral, emotional, and health outcomes. Thus, even if GxE is identified in ADHD, the developmental staging through which effects relate to ADHD versus other outcomes—either as mediators or as examples of multi-finality—will remain to be understood.

The key challenges in understanding main effects of these environmental contributors also confront understanding their role via GxE. For pre- and peri-natal factors, it remains unclear how long those effects persist in development. Outcomes appear to be sufficiently influenced by subsequent events that, by the time a child reaches school age, main effects of mild to moderate perinatal insults are difficult to detect.<sup>22</sup> The same mechanisms also may render it difficult to show interaction effects. In the case of post-natal or psychosocial factors, on the other hand, the directionality of effects will remain a perennial concern in most studies (due in part to potential for rGE as well as bidirectional causality).

Overall, most studies of ADHD have not considered the likely magnitude of different environmental measures in systematic fashion. Environmental measures tend to have more robust main effects than do individual gene markers, probably because environmental measures tend to represent an aggregation of multiple processes and mechanisms. Their reliability and mechanistic specificity nonetheless remain rate-limiting steps in discovering how they interact with the genome. Thus, there will be considerable need in coming years for studies to examine a range of candidate environmental measures, to allow them to compete against one another, to identify highly reliable environmental probes (including more use of latent variable modeling strategies in GxE designs), and to identify their functional overlaps, all while considering that rGE may also be important in the ADHD story.

### Conceptual Basis

It is unclear whether ADHD should be studied as a category or a dimension (or combination of dimensions); it may be argued that the diagnosis represents an extreme on a continuous dimension of behaviors. While some studies have examined symptom dimensions, many examined only ADHD diagnostic groupings or proxies for ADHD diagnosis. More differentiation of effects may ensue if symptom dimensions are considered, as has been illustrated by neuropsychological studies showing that certain cognitive problems are related to symptoms of inattention rather than hyperactivity-impulsivity.<sup>23</sup> One possibility is that GxE involving pre- and peri-natal influences relate primarily to hyperactivity, whereas subsequent psychosocial effects interact with genotype primarily in regard to inattention.

Moreover, if ADHD is conceptualized as rooted in perturbed development processes—for example, abnormal development of self regulation—then a developmental account mandates consideration of epigenetics (that is, how gene expression depends on experiences) and of genotype by environment interplay. Such effects must be considered both in the amplification of the disorder over time<sup>24</sup> and perhaps also in protection and avoidance of secondary complications such as externalizing psychopathology.<sup>25</sup> Crucial from this perspective is to consider how self regulation (including such broad-brush abilities as attention, cognitive control, and impulse control) develops. Such development is mediated via complex interchanges among children and caregivers as well as rapid consolidation of neural networks governed both by genetic programming and response to expectable and extreme environments. Those extreme environments may include pre- or peri-natal insults or post-natal social or biological challenges. Of course, environments can also be protective in relation to genetic risk or in relation to other environmental risks; likewise, genes can confer protection,<sup>25</sup> as well as risk, or might confer responsivity to the environment.<sup>26</sup> Self-regulation also develops in a manner that may be nonlinear across development, with periods of consolidation and periods of rapid change. Incorporation of developmental considerations into GxE studies has scarcely been conceived as yet in the field.

Finally, the range of environmental and genetic candidates for ADHD likely includes both relatively specific and non-specific candidate contributors. Most genetic and environmental factors studied to date appear to be correlated with outcomes in addition to ADHD, though it remains possible that ADHD is a gateway into those outcomes due to its early emergence.

Studies that examine multiple endpoints and consider their inter-correlation and developmental timing will be of value,<sup>27</sup> as will studies that consider correlates of constituent domains (e.g., inattention and its overlap with learning disabilities; hyperactivity/impulsivity and its overlap with oppositional and aggressive behaviors).

## Approach to the Current Literature and Selection of Studies

The methodological approach to this review was as follows. Literature searches were conducted in MEDLINE using “gene by environment”, “GxE”, “ADHD”, “and Externalizing”. Reference sections of recent papers were also scanned. Researchers in the field were contacted to inquire about missed or in press papers, including announcements to all the researchers participating in the International ADHD Molecular Genetics Network.<sup>28</sup> Studies identified were then examined to determine if they constituted an empirical study with measured environment and measured genotype. The review was restricted to studies of humans, although it is important to note a burgeoning literature looking at gene by environment interaction, as well as at gene expression, in animal models related to ADHD. Due to space constraints, we omit studies of related phenotypes such as externalizing behavior and conduct disorder. However, it is important to note that just like environmental effects, similar genetic findings have occurred across much of psychiatry—virtually no genetic findings are unique to one psychiatric disorder. The same may prove true of GxE effects. The present review also places little emphasis on quantitative studies (i.e., twin or behavior genetic studies) in part because there are relatively few that examined measured environment while looking at GxE in ADHD, although for reasons noted earlier, they remain important.

## Discussion

The resulting studies identified are summarized in Table 3. It summarizes 16 studies that examined ADHD as an outcome. Although several gene markers were examined, only three were examined in multiple studies. (1) The DRD4 Exon III VNTR (a 48 base pair repeat often referred to by the number of repeats, such as the “7 repeat” or “4-repeat” variant) generally yielded negative findings, but did show unreplicated interactions with season of birth and with maternal smoking. (2) The DAT1 VNTR in the 3’ untranslated region (a 40 base pair sequence that is likewise often referred to by the number of repeat sequences, hence “9 repeat” or “10 repeat”) and a 30 base pair VNTR on intron 8 (“5 repeat” and “6 repeat” variants are most common) yielded interaction findings in both psychosocial studies, but mostly negative results with regard to prenatal risk variables. Finally, (3) the serotonin transporter promoter polymorphism (5HTTLPR) yielded replicated positive findings with psychosocial risk factors but not with prenatal experiences.

Note that environmental main effects were usually significant but gene main effects usually non-significant in these studies. Due to the otherwise very wide variation in target environments and genes, we could consider only very limited data pooling (below). To this end, despite their obvious heterogeneity, we organized the studies into two major groups for review based on the type of environment they examined.

The first group examined psychosocial moderators of ADHD, with the main focus on psychosocial adversity (usually a composite of multiple adversity indicators such as low income, in-home conflict, and large family size), but some studies examining quality of interactions in the home specifically (parenting, marital quality, or expressed emotion measures). This is useful because studies of processes in the home may identify mediators of adversity effects that are amenable to intervention. The studies in this first group show initial replication, across multiple sampling types and multiple measure types, regarding the interplay of psychosocial measures and genotype in likelihood of having ADHD or in number of ADHD

symptoms, particularly for measures of behavioral inattention. The effects are primarily for DAT1 and for 5-HTT. The conclusion that psychosocial factors interact with genotype in ADHD is supported by two twin studies that examined latent GxE while considering rGE and measured environment effects.<sup>29,30</sup> One of these<sup>30</sup> converges with a molecular study of interaction of genotype with child perception of marital conflict.<sup>31</sup> This last finding provides an initial hint that the pattern of data may move from non-specific psychosocial measures to specific mechanisms.

Further, although some studies reported uncorrected p values, null finding in this set of psychosocial studies were arguably attributable to lack of power. The only GWA study<sup>32</sup> had several intriguing findings, but none survived the stringent correction necessary in the GWA study. Suggestive findings may warrant confirmatory follow up, including a suggestive finding for a marker within the serotonin transporter gene.

The second group of studies examined presumptive indicators of early neurological insult (represented invariably by low birth weight, prenatal cigarette or alcohol exposure, or season of birth, which we put in this group due to its presumed mechanism of effect via infectious exposure during pregnancy). Here, the picture is much less consistent. Effects were few and when found, tended to occur for hyperactivity (and often, for disruptive behavior as well). When interactions were observed, replications generally failed.

In light of the tendency of new literatures to entail reporting of positive findings early on and null findings only later, the null findings must give pause regarding claims about genotype interaction with prenatal cigarette exposure in ADHD. Indeed, recent questions about the initially exciting GxE effects in depression<sup>4</sup> encourage caution for ADHD effects too. On the other hand, it is striking that all of the negative findings for an interaction with prenatal cigarette exposure relied on retrospective report of maternal smoking; the two prospective studies both identified an interaction of smoking and genotype. Single study findings with interesting theoretical support include the finding that CHRNA4 interacts with prenatal cigarette exposure. Replication efforts on this marker are needed. Beneficial now would be a quantitative study looking at interaction of maternal smoking with latent genotype in a twin design.

Table 4 summarizes the most important findings embedded in Table 3 in regard to domains covered in multiple studies. As it documents, there is initial replication for gene  $\times$  environment interaction for psychosocial factors, particularly for inattention symptoms. Table 4 also documents that from a box-score perspective, interactions of particular genotypes with pre- and peri-natal risk factors are not supported for ADHD. As more studies accumulate and reliable meta-analytic estimates can be generated, this conclusion may be overturned. Finally, the table presents initial estimates of interaction effect sizes, which may help guide future studies with regard to power requirements. Overall, the effect sizes for interactions is almost twice as large for psychosocial than pre- and perinatal environmental measures in the age ranges studied.

Other studies (not included in the tables) have asked, not about ADHD *per se*, but about amplification of symptoms once a child has ADHD. Two cross sectional studies found positive interactions, one involving low birth weight and the COMT Val/met marker;<sup>33</sup> the other looking at maternal expressed emotion and finding interactions with marker sets on DAT1 and 5-HT but not DRD4.<sup>34</sup> Another consideration is that positive effects also may suggest plasticity rather than vulnerability.<sup>26</sup> Further scrutiny of these effects and possibilities will be valuable.

The following themes can be drawn from this initial empirical literature, each of which commends to us a future direction that warrants serious consideration in this field. First, the initial forays into GxE effects in ADHD have been highly encouraging. As a group, these studies indicate that identification of such effects in relation to ADHD is feasible, that some

effects are reproducible, and that this approach therefore is promising for defining a next generation of etiological studies on ADHD. Following directly from this point, this literature indicates that refocusing on environmental influences in ADHD, within a GxE approach, may be extremely important.

Second, the etiological influences on inattention versus hyperactivity may be distinct, as indicated in a recent meta-analysis of twin and adoption studies.<sup>16</sup> More scrutiny of this possibility in future studies, particularly in relation to the timing of environmental events (with early events possibly influencing hyperactivity and later events influencing inattention), will help to constrain this area of research. Such an effort may be enhanced by application of cognitive endophenotypes, such as executive functioning, for the inattention domain. Although such measures have been heavily studied in relation to environmental risks and genetic main effects, they are largely untouched in GxE studies.

Third, the same genes may be relevant to ADHD in relation to different environmental influences, but it is not clear whether these effects are at the same point in development or influence the same behavioral outcomes. It will be crucial for research to more sharply constrain the timing of effects or the timing of outcomes. The age range of the outcomes measured in these studies was either “old” (adolescence or adulthood) or very wide.<sup>27</sup>

Fourth, this line of work continues to face fundamental challenges from lack of consensus operational criteria for ADHD. Integration of effects across different reporters, availability of competing phenotype models (e.g., latent class analyses), and use of different kinds of measures in different research centers all weigh against successful replication. Fortunately, despite these obstacles, a consistent picture of genetic effects has emerged and environmental correlations are likewise emerging. Nonetheless, definitional issues need addressing.

It is also promising that one replicated pattern of findings already emerges from this nascent literature: dopaminergic and serotonergic genotypes interact with psychosocial factors in influencing severity of ADHD symptoms in childhood. Pursuit of this effect is warranted to better evaluate particular mechanisms at lower levels of analysis. They may hold promise for eventual treatment matching. The other intriguing, though more speculative, possibility to emerge from the literature so far is that the same genes interact with different triggers to influence distinct components of the syndrome at different points in development. If that guess is right, we would infer that early insult (pre- or peri-natal) interacts with genotype to influence hyperactivity. Later developmental pressures (psychosocial factors) interact with genotype to influence inattention. Hypotheses of this sort, that consider developmental processes and that take into account the commonality of the environmental effects, will be of considerable interest.

Overall, the study of gene by environment interaction in a highly heritable disorder such as ADHD introduces its own challenges and requires further analysis of relevant environments. Yet, interactions appear probable in relation to ADHD, even though only a small fraction of the relevant genes and environments have yet been studied in a GxE approach. Despite the very real possibility of false-positives or artifact in these early stages of investigation, the initial findings suggest the major conclusion that the study of measured GxE is likely to be fruitful and yield new discoveries about ADHD etiology. This exciting field is only at the beginning of a long series of investigations that will cover many new areas of the genome and connect these with more sophisticated measures of the developmental environment to begin to map causal pathways with greater specificity. The results of work in this arena promises to be both intriguing and exciting for some time to come.

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Table 1

Candidate genetic markers in Attention-Deficit/Hyperactivity Disorder

Gene	Marker	Locus	# studies	Functional	Main Effect	Heterogeneity
DAT1	VNTR	3'UTR	34	Y	1.12*	yes
DAT1	VNTR	Intron 8	5	?	1.25*	yes
DAT1	rs27072	3'UTR	7	N	1.20***	no
DRD4	VNTR	Exon III	26	Y?	1.33*****	yes
DRD4	Ins/Del	Promoter	8	?	1.05	yes
DRD4	rs180955	Promoter	5	?	1.21***	yes
DRD2	TaqI	3' Flanking	6	?	1.65	yes
DRD5	Dinucleotide Repeat	5' Flanking	9	?	1.23***	no
DBH	TaqI	Intron 5	6		1.12	yes
5HTT	5HTTLPR	Promoter	19	Y	1.17***	yes
HTR1B	rs6296	Exon I	9	?	1.11***	no
THP2	rs1843809	Intron 5	4	?	1.15	yes
THP2	rs1386493	Intron 5	4	?	1.04	yes
MAOA	VNTR	Promoter	4		1.02	yes
CHRNA4	rs2273506	Exon II	4	?	1.19 <sup>+</sup>	yes
CHRNA4	rs6090384	Intron II	4	?	1.28 <sup>+</sup>	yes
SNAP25	rs3746544	3' UTR	7	?	1.15*	yes

Note: Effect sizes reported as odds ratios taken from Gizer, Ficks, & Waldman<sup>14</sup>. Meta-analytic significance is coded as

\* ( $p \leq .05$ ),

\*\* ( $p \leq .01$ ),

\*\*\* ( $p \leq .001$ ),

\*\*\*\* ( $p < .0001$ ),

<sup>+</sup> ( $p \leq .10$ ). No mark indicates non-significant. 5HTT = 5-HTTLPR (serotonin transporter), N = no; UTR = Untranslated Region; VNTR = Variable Number Tandem Repeat Y = yes.

**Table 2**  
 Example Scalable Environmental Effect Candidates for Attention-Deficit/Hyperactivity Disorder (ADHD)

Candidate (citation)	Measurement Qualities		Association		Incidence
	Method	Reliability	Human	Animal	
Prenatal: Cigarette <sup>19,35,36</sup>	cotinine/report	high/low	2	2	15%
Prenatal: Alcohol <sup>19,36,37</sup>	report, blood	low/moderate	3	2	15%
Prenatal: POP <sup>19,36</sup>	blood	moderate	3	2	50–100%
Prenatal: maternal stress <sup>35,38,39</sup>	report	low	2	2	minority
Peri: LBW <sup>19</sup>	weight	high	1	n/a	10%
Peri: PDIC <sup>40</sup>	rating	moderate	3	n/a	5–10%
Peri: hypoxic ischemia <sup>41</sup>	cardiac/MRI	moderate	4	n/a	minority
Peri: parenchymal lesion <sup>42</sup>	ultrasound	moderate	3	n/a	minority
Post: lead-high (> 10 ug/dL) <sup>19</sup>	blood	high	1	2	5%
Post: lead-low (1–10 ug/dL) <sup>43</sup>	blood	high	1	4	50–100%
Post: manganese <sup>19</sup>	blood	high	2	4	20%
Post: mercury <sup>19</sup>	blood	high	3	3	10%
Post: diet-additives <sup>19</sup>	blood	high	3	4	50–100%
Post: diet-fats <sup>19</sup>	report	low	2	2	50–100%
Post: parenting <sup>19</sup>	report/obs	moderate	2	n/a	minority
Post: family/marital conflict <sup>19</sup>	report/obs	moderate	2	?	minority
Post: adversity <sup>44</sup>	report	low-moderate	1	n/a	minority
Post: maltreatment <sup>36</sup>	report	low-moderate	2	n/a	minority
Post: TV/video <sup>19</sup>	report	low/moderate	3	na	50%–100%

**Note:** Hypoxia/ischemia or neonatal encephalopathy that is moderate (but not severe) and that excludes cerebral palsy. Association rating by the authors based on their judgment of: 1=well replicated or somewhat specific association; 2=replicated or experimental finding but non-specific to ADHD; 3=conflicting findings, likely complex associations, 4=few data/non-convincing association; “stress” includes a wide range of moderate stressors some of which are common and some uncommon. “Incidence” reflects the authors’ estimate of occurrence of the risk factor in the general population of the U.S.A based on the studies cited; in most cases these are quite imprecise estimates. Conclusions in the table are based on reviews of the literature or on selected studies as cited in the table. Adversity = composite psychosocial adversity excluding severe trauma or severe deprivation; fam=family; LBW=low birth weight; obs=observations; PDIC=pregnancy, delivery, and infancy complications; Peri = perinatal events; Post=post-natal events; POP=persistent organic pollutants.

Table 3

Studies Examining Attention-Deficit/Hyperactivity Disorder (ADHD) as the Outcome and Using Measured Gene (G) and Measured Environment (E) as Predictors

Study(Year)	Gene (Single/multiple Markers)	Env	N	Age	Design	Outcome Measure	Results		Interaction
							G	E	
<u>Family/psychosocial moderators</u>									
Lasky-Su (2007) <sup>45</sup>	(M)	BDNF	701	6-18	CL	KSADS-E-ADHD Sx	+/-	+	+ inattention
Laucht (2007) <sup>46</sup>	(M)	DAT1	305	15	P	at least 1 ADHD sx	-	+	+ adversity
Nikolas (in press) <sup>31</sup>	(S)	5HTT	304	6-18	CC	Conners, ADHD RS	-	+	+ marital conflict, inatt and hyp
Retz (2008) <sup>47</sup>	(S)	5HTT	184	18-50*	CL	self report ADHD sx	+	+	+ adversity
Stevens (2009) <sup>48</sup>	(S)	DAT1-8	217	15	P	SDQ; CAPA ADHD sx	-	+	+ adversity with haplotype
		DRD4					-		null effect DRD4
Sonuga-Barke (2008) <sup>32</sup>	(M)	GWAS	909**	5-17	SIB	ADHD, CD symptoms	-	+	null for genome wide
Waldman (2007) <sup>49</sup>	(M)	DRD2	697	4-18	SIB	ADHD status parent rep	+/-	+	+ marital instability
<u>Pre-perinatal moderators</u>									
Alink (2008) <sup>50</sup>	(S)	DRD4	946	6-17	SIB(r)	ADHD dx by Conners	+	+	null findings (CG)
Becker (2008) <sup>51</sup>	(S)	DAT1	305	15	P(p)	KSADS-E-ADHD, sx	-	-	+ hyperactive only, males
Brookes (2006) <sup>52</sup>	(M)	DAT1	396	5-15	CL(r)	CAPA, KSAD-ADHD	+	+	+ alcohol; - smoking
Brookes (2008) <sup>53</sup>	(S)	DRDR	1110**	4-15	CL	ADHD-C, CAPA	+	-	null after correction
Kahn (2003) <sup>54</sup>	(S)	DAT1	161	5	P(p)	Conners symptoms	-	+	+ hyperactivity only
Langley(2007) <sup>55</sup>	(S)	DRD4	266	5-13*	CL(r)	CAPA ADHD, ODD	-	+	null findings
		DAT1					-	+	CG* DAT for ODD
		DRD5					-	+	null findings
		5HTT					-	+	null findings
Neuman (2007) <sup>56</sup>	(S)	DAT1	1540	7-19	TW(r)	ADHD (par interview)	-	+(CG)	+smoking
		DRD4					-		+ smoking
Seeger (2004) <sup>57,58</sup>	(S)	DRD4	227		CC(r)	HKD+CD	-	-	+ SEA
Todd (2007) <sup>58</sup>	(M)	CHRNA4	1441	7-19*	P(r)	LCA ADHD	-	+	+ smoking

**Note: Environmental marker codes:** A = adversity index (e.g. Rutter), AL = prenatal alcohol exposure; CG = pre-natal cigarette exposure; ED = parental education level; EE = parental expressed emotion; LBW=low birth weight; M=marital stability or marital conflict; P = parenting style or problems; SEA = season of birth; SES = socioeconomic status.

**Genetic markers codes:** S=single marker study (in which case the default marker is indicated by the following genetic codes); M = multiple marker study generally including the default marker plus additional markers on that gene. DAT1=3' UTR VNTR 40 bp in length; 10 repeat (480-bp) and 9 repeat (440 bp) most studied. DAT1-8 = 30 bp VNTR in intron 8 (5 and 6 repeats most common); DRD4 = Exon III VNTR (48 bp, most commonly studied are 7 repeat and 4 repeat). DRD4-I = Insertion/Deletion in promoter region (120 bp and 240 bp alleles), also called the DRDR insertion deletion. DRD5 = DRD5 CAN marker; 5-HTT = Serotonin transporter 5-HTTLPR; BDNF = brain derived neurotrophic factor (11p14.1; Val66met polymorphism is most commonly studied but the one study here conducted a multiple marker approach); GWAS = genome wide association study; CHRNA4 = Neuronal acetylcholine receptor subunit alpha-4

**Design Codes:** For prenatal risk factors, studies were also coded as (r) = retrospective or (p) = prospective from either pregnancy or infancy. CC = case control design; CL = clinically disordered group, no control group; P = prospective, community based cohort; SIB = ADHD and unaffected siblings (e.g., the IMAGE study); TWIN = population based twin sample, cross sectional analyses.

**Outcome Measure Codes:** In the measures columns, the footnote indicators indicate the following:

\* = age range estimated, age range not reported; + = observational measures of parenting behavior;

\*\* = Sonuga-Barke et al (2008)<sup>32</sup> had 909 child-parent trios and Brookes et al (2008)<sup>53</sup> had 1110 trios.

ADHD-C = ADHD Combined; CAPA = Child and Adolescent Psychiatric Assessment (a structured clinical interview); CBCL=parent rated child behavior checklist; Conners = Conners ADHD Rating Scale (parent or teacher version); EXT = externalizing composite scale; HKD+CD = ICD-10 criteria for hyperkinetic disorder and conduct disorder; K-SADS = Kiddie Schedule Affective Disorders and Schizophrenia; K-SADS-E = Kiddie Schedule Affective Disorders and Schizophrenia Epidemiological version; LCA = latent class analysis; ODD = Oppositional defiant disorder; SDQ = Strengths and Difficulties Questionnaire; YSR=youth self report version of the Child Behavior Checklist.

**Results Codes:** + means a significant main effect, - means no significant main effect, +/- means a marginal or qualified main effect.

**Interaction Codes:** inatt = inattention; hyp = hyperactivity

**Table 4**  
 Replicated findings on Gene × Environment (G×E) of Attention-Deficit/Hyperactivity Disorder

Environmental probe	Developmental period	Gene probe	“Box Score”		Effect Size	
			Pos	Neg	d	OR
Mostly Positive (Pos) findings						
Psychosocial factors	post-natal	DAT1	n=246,48	n=132	.56	2.76
Psychosocial factors	post-natal	5HTT	n=231,47	n=0	.54	2.66
Total for psychosocial factors and genotype						
			4	1	.54	2.56
Mostly Negative (Neg) findings						
			Pos	Neg	d	OR
Cigarette exposure	pre-natal	DRD4(VNTR)	n=156	n=250,55	.14	1.29
Cigarette exposure	pre-natal	DAT1	n=254,56	n=252,55	.27	1.63
Alcohol exposure	pre-natal	DAT1	n=153	n=255,56	.16	1.34
Total for cigarette exposure and genotype						
			3	4	.19	1.41

Note: Interaction effect size was converted to d and to odds ratio (OR) for all studies using *ClinTools Software*<sup>59</sup>. Effect sizes were calculated for the relevant interaction term in each study, and then weighted by sample size. Effect sizes for psychosocial factors and for prenatal cigarette exposure were then averaged respectively.