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Genetic risk factors and gene–environment interactions in adult and childhood attention-deficit/hyperactivity disorder

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Attention-deficit/hyperactivity disorder (ADHD) is a common and highly heritable neurodevelopmental disorder. In recent years, genetic studies have revealed several risk gene variants associated with ADHD; however, these variants could only be partly replicated and are responsible for only a fraction of the whole heritability of ADHD estimated from family and twin studies. One factor that could potentially explain the 'missing heritability' of ADHD is that childhood and adult or persistent ADHD could be genetically distinct subtypes, which therefore need to be analyzed separately. Another approach to identify this missing heritability could be combining the investigation of both common and rare gene risk variants as well as polygenic risk scores. Finally, environmental factors are also thought to play an important role in the etiology of ADHD, acting either independently of the genetic background or more likely in gene–environment interactions. Environmental factors might additionally convey their influence by epigenetic mechanisms, which are relatively underexplored in ADHD. The aforementioned mechanisms might also influence the response of patients with ADHD to stimulant and other ADHD medication. We conducted a selective review with a focus on risk genes of childhood and adult ADHD, gene–environment interactions, and pharmacogenetics studies on medication response in childhood and adult ADHD.

Keywords: attention-deficit/hyperactivity disorder, common variant, epigenetics, gene×environment interactions, pharmacogenetics, rare variant, risk genes

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is one of the psychiatric disorders with the highest heritability, and a population prevalence estimated to be ~4–7% in children (Polanczyk *et al*., 2014) and between 2.5 and 3.4% in the adult population (Fayyad *et al*., 2007; Simon *et al*., 2009; Ramos-Quiroga *et al*., 2014a, 2014b). It has been estimated that at least 15% of children diagnosed with ADHD (childhood ADHD) will continue to retain a full diagnosis by the age of 25 years, ~40% will show just a partial remission and continue to experience impairing symptoms, and ~40% will have a complete remission (Franke *et al*., 2018). It is currently under debate whether ADHD diagnosed in adulthood (adult ADHD) could have arisen de novo (Moffitt *et al*., 2015) or whether there was a pre-existing subdiagnosis threshold ADHD in childhood (Franke *et al*., 2018).

Several biological mechanisms have been implicated in the etiology of ADHD. These include dopaminergic, serotoninergic, and glutamate signaling and synaptic vesicle, neurite outgrowth, and cell adhesion pathways (Bonvicini et al., 2016a, 2016b). Comparative enrichment analysis of the most significantly enriched functions for ADHD genome-wide associated genes added cell–cell communication, oxidative stress response , multicellular organismal development, and nervous system development to this list, consistent with the idea that the pathophysiology of ADHD is neurodevelopmental (Hawi *et al*., 2015). Further combined analysis of ADHD candidate genes suggested that synaptic transmission, catecholamine metabolic processes, cell migration, and G-protein signaling pathways may also play a role in ADHD etiology (Cristino *et al*., 2014). Calcium channel signaling may additionally contribute, as genes involved in this process have been linked with five major psychiatric dis-orders, including ADHD (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). The involvement of neurodevelopmental and noradrenergic pathways in ADHD has been supported by findings from a recent review of the literature on childhood ADHD pharmacogenetics, which revealed that these systems specifically responded to methylphenidate (MPH) treatment (Bruxel *et al*., 2014). However, this study found no or contrasting results for dopaminergic and serotoninergic signaling. A common problem when studying the etiology of ADHD is that distinctions are not usually made between childhood ADHD and adult or persisting ADHD, which may have distinct etiologies, and therefore contradictory results are often reported. Fewer studies have solely focused on the adult form of the disorder, resulting in a lack of knowledge regarding its specific pathophysiology (Bonvicini et al., 2016a, 2016b).

Recent genetic studies investigating rare and common variants have reinforced the role of genetic variants playing a part in the pathogenesis of ADHD. However, there is emerging evidence that different gene variants might be involved in the childhood and adult forms (Franke *et al.*, 2010). Furthermore, an increasing amount of studies show gene–gene and gene–environment interactions (G×Es) regarding the pathomechanisms of ADHD. In addition, there are several studies about genetic influence of treatment response in ADHD. This selective review focused on the recent developments regarding genetic risk variants in adult and childhood ADHD as well as studies on G×E and genetic factors associated with treatment response in adult and childhood ADHD.

Attention-deficit/hyperactivity disorder heritability

Classical genetic studies have shown that ADHD is strongly heritable, with heritability for childhood ADHD estimated to average 75% (Faraone and Mick, 2010). Initial estimates of heritability for adult ADHD were, however, much lower, at ~30–50% (Boomsma *et al.*, 2010; Kan *et al.*, 2013; Larsson *et al.*, 2013), despite evidence having suggested that adult ADHD possesses a much stronger genetic component (Biederman et al., 1995, 1996; Faraone et al., 2000a, 2000b). Recent literature on the genetic component of adult ADHD shows considerable differences in the estimated hereditability between studies (Brikell *et al.*, 2015), but estimates are still lower than for childhood ADHD. It is thought that this decrease in adult ADHD heritability is unlikely to reflect a true developmental change but may instead be because of rater effects (Bonvicini et al., 2016a, 2016b). Only assessment by others is used for the individuals in childhood ADHD studies (e.g. parent/teacher), whereas adult ADHD studies rely mostly on self-reporting of symptoms. Studies using a self-rating scale report significant lower estimated heritability than the ones using rating from the parents or teachers (Brikell *et al.*, 2015). When a cross-informant approach was taken to control for rater effects, the heritability of adult ADHD appeared comparable to childhood ADHD (Brikell *et al.*, 2015). It is, thus, believed that the heritability of ADHD in adulthood may actually be comparable to childhood ADHD (Bonvicini et al., 2016a, 2016b).

Although sex prevalence differs in childhood ADHD, with males overrepresented (≤80%), in adult ADHD, there is an equal male to female ratio (Kooij *et al.*, 2010), and overall heritability estimates are not affected by sex. Furthermore, systematic review of the literature shows no association between sex and the persistence or remittance of ADHD symptoms (Caye *et al.*, 2016). It has recently been investigated whether sex-specific heterogeneity and higher burden of risk, two putative genetic mechanisms underlying sex bias, were significantly increased in female patients with ADHD and could thus explain the unbalanced ratio (Martin *et al.*, 2018). The authors show a clear polygenic contribution from common autosomal genetic variants in both females and males with ADHD and no significantly higher burden of genetic risk variants in females compared with males. In addition, they did show a greater familiar burden in terms of risk, with siblings of female patients with ADHD at higher risk for ADHD than siblings of male patients. Moreover, female patients with ADHD seem to be at a higher risk of developing comorbidities such as autism spectrum disorders (ASDs) and congenital malformations (Martin *et al.*, 2018). Both results might imply some degree of clinical heterogeneity. Besides possible genetic differences between male and female patients with ADHD, other potential explanations for the different sex ratios in childhood and adult ADHD have also been proposed. First, it is possible that girls with ADHD are underdiagnosed because of differing symptomatology in comparison with the boys (Mowlem *et al.*, 2018). There are also findings that pubertal hormonal changes can augment subthreshold ADHD symptoms in girls, who could not be previously diagnosed using the age-of-onset *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. criteria of 7 years old (Murray *et al.*, 2018). Further research should be done to determine sex-specific differences in ADHD in all areas of the disorder.

In conclusion, heritability estimates remain consistent across the age-span, familial effects seem all to be genetic in origin (no shared environmental influences), and the proportion of shared genetic effects between inattention and hyperactivity–impulsivity is 60–70% (Franke *et al.*, 2012).

Genetic basis of attention-deficit/hyperactivity disorder

The heritability estimates reported in the previous paragraph show a strong genetic contribution to the etiology of ADHD. Over the past decades, many efforts have been made to understand the genetic basis of complex diseases such ADHD and have progressed in parallel to scientific advancement and development of new genetic techniques. Early genetic studies were influenced by the 'common disease common variant' hypothesis, which proposes that the main genetic disease drivers are common genetic variations with allelic frequencies above 5% that additionally show low penetrance in the common population. On the contrary, the 'common disease rare variant' hypothesis, where multiple rare variations (≤5% frequency) combine together to significantly affect the risk for common conditions, represents an alternative approach to molecular genetic research of psychiatric diseases (Hawi *et al.*, 2015). These hypotheses are interconnected with candidate gene investigations and pedigree analysis as well as genome-wide association studies (GWAS) as main investigative approaches (Hayman and Fernandez, 2018). We will shortly summarize the

different approaches to discover risk genes in ADHD in general and then focus on different and shared risk genes in adult and childhood ADHD as well as pharmacogenetics studies and G×E.

Genetic linkage analysis

Among the classical tools to investigate genetic contribution, genetic linkage analyses have contributed to the understanding of many diseases. On the basis of the assumption that genes in physically proximity on a chromosome remain linked during meiosis (Pulst, 1999), this method is especially useful for identification of genetic risk factors with large effect sizes in families with a high burden of ADHD. Promising candidate genes or gene regions that have been identified using linkage studies include a significant region in chromosome 16q (Zhou *et al.*, 2008). However, results from linkage analysis on ADHD families have failed to be replicated across the studies, suggesting that if at all, only very few genes of larger effect size contribute to the ADHD phenotype (Faraone *et al.*, 2008).

Candidate genes association studies

Another classical tool that has contributed to the understanding of ADHD genetics is candidate gene investigation. Candidate gene association studies are hypothesis-driven association analyses, with genes selected a priori by researching the literature for association with the disorder. The investigated genes were therefore derived from gene knock-out in animal studies or were variations in genes with known biological function directly or indirectly connected with the investigated trait. Association with ADHD was found in genes of the serotonergic, dopaminergic, and nitrinergic systems and in genes that play a role in synaptic plasticity (serotonin transporter *5HTT* and tryptophan hydroxylases *TPH1* and *TPH2* (Grevet *et al.*, 2007). Furthermore, associations were identified between ADHD and the dopamine transporter *DAT1 = SLC6A3*, dopamine receptors *DRD4* and *DRD5* (Ohadi *et al.*, 2006; Lasky-Su *et al.*, 2008a, 2008b, 2008c), neuronal isoform of the nitric oxide synthase (*NOS1*) (Franke *et al.*, 2009; Reif *et al.*, 2009), synaptosomal-associated protein (*SNAP25*) (Hawi *et al.*, 2015), G-protein-coupled receptor kinase interacting ArfGAP 1 (*GIT1*), and cannabinoid receptor gene 1 (*CNR1*) (Arcos-Burgos *et al.*, 2010; Ribases *et al.*, 2011; Jain *et al.*, 2012). More recently, Hayman and Fernandez (2018) selected 105 genes from the literature that were proven to have a nominal statistical significance with ADHD. After pathway, network, and protein–protein interaction analyses, they identified 14 core candidate genes that displayed significantly more connectivity than expected by chance. These genes clustered in three groups, with enrichment in nitric oxide synthase and α-1 adrenergic pathways, and showed expression enrichment in the cerebellum and in the cortex (Hayman and Fernandez, 2018).

Although useful, this type of classical study has largely been criticized because, being based on a priori hypothesis, it might fail to include all possible causative genes and might be prone to a selection bias (Zhu and Zhao, 2007). Moreover, given some technical limitations with the genotyping techniques used in the past, the selection of the investigated gene variants in some cases could have been more in relation to a technical ease in genotyping rather than a causal connection with the disease (Tabor *et al.*, 2002). It needs to be pointed out that, in general, significant findings of association in many candidate gene studies have not been replicated when followed up in subsequent association studies, an outcome that might be connected with variations of the study design or selection of polymorphism that are not likely to be causative (Ioannidis *et al.*, 2001). These limitations are the main reason of the transition to hypothesis-free approaches.

Genome-wide association studies

GWAS investigate common genetic variants that occur in more than 1% of the population, mostly focusing on single nucleotide polymorphisms (SNPs). In the past decades, a total of 10 ADHD GWAS have been conducted (Franke *et al.*, 2018; Demontis *et al.*, 2019). GWAS have identified the involvement of genes mainly involved in or functionally related to neurotransmission, such as *PARK2*, *SLC6A3*, *DRD4*, *DRD5*, *SLC6A4*, *HTR1B*, *SNAP25*, *DIRAS2*, *LPHN3*, and *NOS1*, as well as other genetic loci possibly involved (5p13, 14q12, and 17p11) (Arcos-Burgos and Muenke, 2010; Reif *et al.*, 2011; Hawi *et al.*, 2015). A recent GWAS reported the *CDH13* and *LPHN3 = ADGRL3* genes as the most promising ADHD risk genes. *CDH13* codes for the protein cadherin-13 which seems to be involved in neuronal growth processes and cell adhesion and was found to be associated with ADHD in two independent samples (Lesch *et al.*, 2008; Lasky-Su *et al.*, 2008a, 2008b, 2008c; Salatino-Oliveira *et al.*, 2015). *ADGRL3* codes for the protein latrophilin-3. *LPHN3* was originally postulated as an ADHD risk gene because of fine mapping of a chromosome region significantly linked with ADHD and has been replicated in GWAS in independent samples (Arcos-Burgos *et al.*, 2010; Jain *et al.*, 2012). Additionally, *LPHN3* is the most brain-specific subtype and is expressed in brain regions associated with ADHD such as the amygdala. It is implicated in axon guidance, the development of glutamergic synapses, and synaptic plasticity (Sudhof, 2001; Silva *et al.*, 2011; Ranaivoson *et al.*, 2015). Despite these initial insights into the function of LPHN3, there remains a lack of physiological data, and it is currently unclear how variants of this gene may contribute to the development of adult ADHD. Glucose–fructose oxidoreductase-domain containing 1, electron transport (*GFOD1*), has also been reported to be associated with ADHD (Lasky-Su *et al.*, 2008a, 2008b, 2008c), although its physiological

role is still unclear. Furthermore, several genes of voltage-gated ion channels have been identified in ADHD GWAS, for example, *KCNIP4*, *KCNIP1*, and *KCNC1*. However, these genes have also been implicated in other psychiatric disorders such as schizophrenia and bipolar disorder (Lewis *et al.*, 2003; Lesch *et al.*, 2008; Neale *et al.*, 2008; Lasky-Su *et al.*, 2008a, 2008b, 2008c; Weissflog *et al.*, 2013). *GRM5*, coding for the glutamate receptor, and *SPOCK3* (Jain *et al.*, 2012; Lesch *et al.*, 2013; Weber *et al.*, 2014a, 2014b) have also been reported as promising ADHD risk genes from GWAS. *SPOCK3* codes for a Ca^{2+}-binding extracellular heparan/chondroitin-sulfate-proteoglycan which seems to play a role in inhibition of neurite growth potentially by matrix-metalloproteinases (Nakada *et al.*, 2001; Yamamoto *et al.*, 2014). Furthermore, both copy number variants and SNPs in *FBXO33* and the gene coding for the acetylcholine-metabolizing butyrylcholinesterase (*BCHE*) and *DIRAS2* have been associated with ADHD (Reif *et al.*, 2011; Jacob *et al.*, 2013; Weber et al., 2014a, 2014b; Sanchez-Mora *et al.*, 2015). *FBXO33* codes for a member of the F-box protein family and interacts as a substrate recognition protein within a protein–ubiquitin ligase complex, which plays a role in the proteasomal degradation of proteins (Lin *et al.*, 2015). The acetylcholine-metabolizing butyrylcholinesterase or pseudocholinesterase is a nonspecific cholinesterase which hydrolysis various cholinesters and is produced in the liver (Lockridge, 1988). *DIRAS2* codes for a Ras GTPase whose function is largely unknown. Highest expression of *DIRAS2* in the human brain could be shown in the hippocampus and the cerebral cortex. The same study reported that Diras2 concentration increased during mouse brain development from prenatal to late postnatal stages. It appears to be coexpressed in glutamatergic and catecholaminergic neurons, which supports the evidence of *DIRAS2* as a candidate gene for ADHD (Grunewald *et al.*, 2018). Previously, it also could be showed that the *DIRAS2* risk allele leads to increased expression of the reporter gene and influences prefrontal functions in a Go/noGo task in children with ADHD (Grunewald *et al.*, 2016). Unfortunately, there has been very little replication of GWAS findings, and there is only limited overlap in findings among the different GWAS. A possible explanation for this is related to the multifactorial nature of the disorder and strong heterogeneity in symptoms; their extremely large cohorts might be required to surpass the threshold of genome-wide significance. To account for this, Demontis *et al.* (2019) recently performed a genome-wide association meta-analysis of previous GWAS studies, resulting in larger sample numbers (20 183 ADHD cases and 35 191 controls). By using this approach, they identified 12 independent loci that surpassed genome-wide significance (Demontis *et al.*, 2019). Further studies investigating which genes or gene variants are responsible for the highly significant association between ADHD and the identified loci are needed.

Polygenic risk score

To explain and quantify the contribution of the multiple risk variants revealed by GWAS to psychiatric disorders, the concept of polygenic risk scores was introduced (International Schizophrenia *et al.*, 2009). The polygenic risk score (PRS; also known as genome-wide score) reflects the sum of all risk alleles weighted for the evidence of risk of the variant itself (Zheutlin and Ross, 2018), facilitating investigation of the interaction and synergistic effects of multiple common risk variants (Middeldorp *et al.*, 2011; Martin et al., 2015a, 2015b). This allows researchers to estimate the contribution of variants that exert small effects on ADHD phenotype, and it has been shown that PRS predicts both hyperactivity and inattention traits in the general population in children (Hamshere *et al.*, 2013) and also in children with ASD (Martin *et al.*, 2014). This approach is also very beneficial in exploring the shared genetic basis of ADHD and comorbid somatic and psychiatric conditions. In a large GWAS including 20 138 ADHD cases and 35 191 healthy controls, PRS for ADHD was predicted by a higher body mass index, depression, neuroticism, anxiety, risk taking, alcohol misuse, and smoking (Du Rietz *et al.*, 2018).

Rare genetic variants

Rare genetic variants are present in less than 1% of the population. As common variants only explain approximately one-third of ADHD heritability, rare genetic variants need to be explored to determine whether they may contribute to this 'missing heritability' (Faraone *et al.*, 2005). In the past years, attention has been focused on rare copy number variants (CNVs). CNVs are large genomic structural variations comprising deletions, duplications, triplications, and translocations in comparison with a reference genome (Stankiewicz and Lupski, 2010). CNVs compose ~13% of the human genome, arise more frequently than SNPs (Ruderfer *et al.*, 2016) and can be inherited or arise de novo (Stankiewicz and Lupski, 2010). CNVs are believed to play a role in several neuropsychiatric and neurodevelopmental diseases. The deletion or duplication of a relatively large genomic segment, which can cover one or several genes, might have a greater effect on gene function compared with SNP (Lew *et al.*, 2018). The exact mechanism by which CNVs affect phenotype is still unclear and could involve gene dosage effects, positional effects, or the unmasking of a recessive mutation of the remaining allele (in the case of deletion CNVs). In addition, they could potentially delete regulatory elements or disrupt coding sequences (Stankiewicz and Lupski, 2010).

In patients with ASD, it has been consistently shown that there is a larger load of CNVs compared with the normal population (Glessner *et al.*, 2009). Several studies have investigated if an increase in the overall rare CNV burden is also present in patients with ADHD.

This was confirmed in both young ADHD populations (Yang *et al.*, 2013; Stergiakouli *et al.*, 2015; Martin et al., 2015a, 2015b; Demontis *et al.*, 2016) and in adults (Lesch *et al.*, 2011; Ramos-Quiroga *et al.*, 2014a, 2014b). It has, therefore, been proposed that the risk for ADHD follows a polygenic liability threshold model, in which individuals with rare large CNVs require a lower number of common genetic risk variants present for developing ADHD (Martin et al., 2015a, 2015b).

CNVs in single genes have also been associated with ADHD, for example, in the *PARK2* and *NPY* genes, as well as the glutamate receptor genes *GRM1*, *GRM5*, *GRM7*, and *GRM8* (Lesch *et al.*, 2011; Jarick *et al.*, 2014; Hawi *et al.*, 2015). CNVs in the *PARK2* locus (chr6: 162 659 756–162 767 019 – NCBI36/hg18) were first reported in an American ADHD cohort (Elia *et al.*, 2010). Some years later, a genome-wide analysis by Jarick *et al.* (2014) using a White population carrying rare CNVs also identified *PARK2* as a candidate ADHD gene. The study showed that patients with ADHD have an increased incidence of CNVs in the coding region (exon 2 or exon 3) of *PARK2*. Additionally, the study reported an increased length of rare CNVs in the ADHD sample compared with the controls. *PARK2* has also been proposed as a candidate for ASD, a neurodevelopmental disorder that often co-occurs in patients with ADHD (Yin *et al.*, 2016).

An increased load of rare variants has also been shown in the *DRD4* 7R allele in childhood (Grady *et al.*, 2003) and persistent ADHD (Tovo-Rodrigues *et al.*, 2012). Furthermore, there are several rare chromosomal anomalies whose carriers show ADHD-like symptoms among a defined syndrome complex, including 22q11.2 deletion syndrome, Turner syndrome, and Klinefelter syndrome (Cederlof *et al.*, 2014; Green *et al.*, 2015; Niarchou *et al.*, 2015).

Combined approaches investigating common and rare genetic variants

A recent study investigating three families with several family members affected by childhood and adult ADHD combined linkage analysis and whole-exome-sequencing approaches to analyze the cumulative role of common and rare genetic variants in persistent ADHD in 9365 individuals (Corominas *et al.*, 2018). The *AAED1* and *ATAD2* genes were identified as being significantly associated with persistent ADHD. The *AAED1* gene codes for the AhpC/TSA antioxidant enzyme domain-containing 1 protein, which binds and interacts with the protein kinase C-α-binding protein (PICK1) (Huttlin *et al.*, 2015). PICK1 is a regulator of the dopamine transporter (Torres, 2006). *ATAD2* codes for ATPase family AAA domain-containing protein 2, although it is currently unclear what possible role the gene product may play in the development of ADHD.

Comparison of risk genes associated with childhood and adult attention-deficit/hyperactivity disorder

As mentioned previously, there is still an ongoing debate as to whether there is a distinct adult-onset form of ADHD, and whether different genes may be involved in childhood and adult ADHD. There are only a few studies that investigate childhood and persisting and/or adult ADHD separately (Table 1), and until now, to the best of our knowledge, no review has directly compared risk genes between childhood ADHD and adult ADHD. The dopaminergic system, as already stated, has been repeatedly implicated in ADHD etiology. Specifically, the 10-repeat allele of the *DAT1* 3′-UTR VNTR (10-6 SLC6A3-haplotype) has been consistently associated with childhood ADHD (Cook *et al.*, 1995; Gill *et al.*, 1997; Curran *et al.*, 2001). However, this risk allele does not appear to be associated with adult ADHD in European (Franke *et al.*, 2008), German (Bruggemann *et al.*, 2007), Brazilian (Aparecida da Silva *et al.*, 2011), or Norwegian patient cohorts (Johansson *et al.*, 2008). Contradictory results have been found for the six-repeat allele of the VNTR in intron 8 of the gene (9-6 *SLC6A3*-haplotype), with one study reporting an association with adult ADHD (Franke *et al.*, 2008) and another finding no association with adult ADHD (Bruggemann *et al.*, 2007). A recent review and meta-analysis of candidate gene studies could not find an overall significant association between ADHD and the dopamine transporter gene after strict Bonferroni correction. However, carriers of the *DAT* 9R allele had nominally increased rates of adult ADHD, as well as the 6/6 homozygote genotype of 30-bp variable number tandem repeat (VNTR). Moreover, this meta-analysis also reported negative association with ADHD for *DRD4* 48-bp VNTR. Moreover, in contrast to studies in children, the *COMT* val66met variant showed no association with persistent ADHD. However, a gene that is potentially more specifically associated with adult ADHD was investigated in this meta-analysis using three different samples (Ribases *et al.*, 2009). This gene is *BAIAP2* (or *IRSp53*) and encodes the brain-specific angiogenesis inhibitor 1-associated protein 2, which is an adapter protein that links membrane bound G-proteins to cytoplasmic effector proteins. BAIAP2 functions as an insulin receptor tyrosine kinase substrate and might play a role for insulin in the central nervous system. It may also affect neuronal growth-cone guidance (Kang *et al.*, 2016). Interestingly, *Baiap2* expression in rat brain is influenced by MPH treatment (Bonvicini et al., 2016a, 2016b; Quansah *et al.*, 2017).

Some studies have shown increased aggressive scores and emotional dysfunction in children with ADHD carrier of the *COMT* Val158Met polymorphism (rs4680) (Caspi *et al.*, 2008; Fowler *et al.*, 2009), but a meta-analysis of association studies indicated no association with ADHD (Sun *et al.*, 2014; Lee and Song, 2018). Association studies in an adult ADHD cohort failed to reveal a significant

Table 1 Comparison of risk gene variants in childhood and adult attention-deficit/hyperactivity disorder

Genes	Variant	Association with disorder/symptom severity		References
		cADHD	aADHD	
DAT1=SLC6A3	3′-UTR VNTR 10R	Yes	No	Cook *et al.* (1995), Gill *et al.* (1997), Curran *et al.* (2001), Bruggemann *et al.* (2007), Franke *et al.* (2008), Johansson *et al.* (2010), Aparecida da Silva *et al.* (2011)
DAT1=SLC6A3	6-Repeat allele of the VNTR in intron 8	Yes	Inconsistent results	Bruggemann *et al.* (2007), Laucht *et al.* (2007), Franke *et al.* (2008)
COMT	COMT Val158Met polymorphisms (rs4680)	Inconsistent results	No	Caspi *et al.* (2008), Muller *et al.* (2008), Retz *et al.* (2008), Fowler *et al.* (2009), Sun *et al.* (2014), Bonvicini et al. (2016a, 2016b., Lee and Song (2018)
DRD4	DRD4 7-repeat allele	Yes	Inconsistent results	LaHoste *et al.* (1996), Muglia *et al.* (2000), Faraone *et al.* (2001), Grady *et al.* (2003), Arcos-Burgos *et al.* (2004), Johansson *et al.* (2008), Biederman *et al.* (2009), Muller *et al.* (2010), Sanchez-Mora *et al.* (2011), Tovo-Rodrigues *et al.* (2012)
SLC6A4=5HTT	Several SNPs	Inconsistent results	No	Johann *et al.* (2003), Grevet *et al.* (2007), Gizer *et al.* (2009), Landaas *et al.* (2010), Fonseca *et al.* (2015)
TPH1 and *TPH2*	Several SNPs	Inconsistent results	No	Tang *et al.* (2001), Lasky-Su *et al.* (2005), Sheehan et al. (2005, 2007), Johansson *et al.* (2010)
ADGRL3=LPHN3	rs6551665	Yes	Yes and also various other SNPs	Arcos-Burgos *et al.* (2002), Arcos-Burgos *et al.* (2010), Ribases *et al.* (2011), Hwang *et al.* (2015)
NOS1	Several variants	No	Yes	Reif *et al.* (2009), Weber *et al.* (2015), Salatino-Oliveira *et al.* (2016)
CDH3	Several variants	Yes	Yes	Lesch *et al.* (2008), Romanos *et al.* (2008), Zhou *et al.* (2008), Lasky-Su *et al.* (2008a, 2008b, 2008c), Neale *et al.* (2010), Salatino-Oliveira *et al.* (2015)

Studies are listed in which children and adolescents or adults were analyzed separately or in which a comparison between those groups was carried out.
aADHD, adult attention-deficit/hyperactivity disorder; *ADGRL3*, adhesion G-protein-coupled receptor L3 (*LPHN3*); cADHD, childhood attention-deficit/hyperactivity disorder; *CDH13*, cadherin-13 (*CDHH, P105*); *COMT*, catechol-O-methyltransferase; *DRD4*, dopamine receptor D4 (*D4DR*); *NOS1*,nitric oxide synthase 1 (*NOS*); *SLC6A3*, solute carrier family 6 member 3 (*DAT, DAT1*); *SLC6A4*, solute carrier family 6 member 4 (*5HTT, SERT, 5-HTTLPR*); SNP, single nucleotide polymorphism; *TPH1*, tryptophan hydroxylase 1 (*TPRH, TRPH*); *TPH2*, tryptophan hydroxylase 2 (*NTPH, ADHD7*); UTR, untranslated region; VNTR, variable number tandem repeat.

association of common variants in *COMT* gene (Bonvicini et al., 2016a, 2016b) and symptom severity (Muller *et al.*, 2008; Retz *et al.*, 2008). A high prevalence of rare dopamine receptor D4 alleles has been reported in children diagnosed with ADHD (Grady *et al.*, 2003), especially the *DRD4* 7-repeat allele (7R allele) (LaHoste *et al.*, 1996; Faraone *et al.*, 2001; Arcos-Burgos *et al.*, 2004). This polymorphism has additionally been shown associated with a more persistent course of ADHD (Biederman *et al.*, 2009). However, findings regarding the association between the DRD4 7-allele and adult ADHD are contradictory. An excess of rare variants in the allele was reported in adult ADHD (Muglia *et al.*, 2000; Tovo-Rodrigues *et al.*, 2012) but was not replicated (Johansson *et al.*, 2008; Sanchez-Mora *et al.*, 2011). In addition, genetic variations in this gene were not significantly associated with severity of ADHD symptoms in adults (Muller *et al.*, 2010).

In the serotonergic system, significant associations were identified for several candidate genes by meta-analytic review of the literature (Gizer *et al.*, 2009). However, no associations were reported for polymorphisms in the *SLC6A4* gene in Colombian patients with childhood ADHD (Fonseca *et al.*, 2015). Common variants in *SLC6A4* were also not found associated with adult ADHD (Johann *et al.*, 2003; Grevet *et al.*, 2007; Landaas *et al.*, 2010). *TPH2* was suggested to be a susceptibility locus for childhood ADHD (Lasky-Su *et al.*, 2008a, 2008b, 2008c), and SNPs in this gene have been positively associated with childhood ADHD in both an Irish sample (rs1843809 and rs1386493; Sheehan *et al.*, 2005) and German sample (rs4570625 and rs11178997; Walitza *et al.*, 2005). However, these results could not be replicated in a Chinese Han (Tang *et al.*, 2001) or a White sample (Sheehan *et al.*, 2007). Furthermore, common variants in the *TPH1* and *TPH2* gene regions were not found associated with persistent ADHD (Johansson *et al.*, 2010). In the nitrinergic system, *NOS1* ex1f-VNTR was associated with adult ADHD as well as a wide range of impulsive behaviors in adults but not in children (Reif *et al.*, 2009; Weber *et al.*, 2015; Salatino-Oliveira *et al.*, 2016).

Children with ADHD reportedly have an increased presence of the *ADGRL3* rs6551665 GG genotype (Hwang *et al.*, 2015), but further studies are needed to confirm this finding. Other SNPs within *ADGRL3* have also been shown to be associated with adult ADHD (Arcos-Burgos *et al.*, 2002; Ribases *et al.*, 2011). Common variants in the *CDH13* gene have been reported by a Genome-Wide Association Scan of Quantitative Traits (Lasky-Su *et al.*, 2008a, 2008b, 2008c) and a case–control GWAS (Neale *et al.*, 2010) to be associated with childhood ADHD. Additionally, the *CDH13* rs11150556 CC genotype was associated with increased hyperactive and impulsive symptoms in youths with ADHD (Salatino-Oliveira *et al.*, 2015). Meta-analysis of linkage results derived from seven independent studies using both children and adult patients with ADHD revealed that the chromosomal

region that contains the *CDH13* gene was nominally associated with both childhood ADHD and adult ADHD (Zhou *et al.*, 2008), a finding that was later confirmed by another study (Romanos *et al.*, 2008). Finally, a specific association between *CDH13* and adult ADHD was reported in a GWAS (Lesch *et al.*, 2008). An overview of comparisons between genetic risk variants implicated in childhood and adult ADHD is shown in Table 1.

Genetic markers for treatment response

Medical treatment with stimulants such as MPH and amphetamine, as well as the nonstimulant drug atomoxetine, which targets the norepinephrine system, is helpful in alleviating symptoms in a substantial proportion of patients with ADHD. However, ~50% patients are nonresponders or partial responders to stimulant medication, and a large number of patients stop taking stimulant medication because of various adverse effects (e.g. weight loss, abdominal pain, sleep disturbances, headaches, irritability, and decreased appetite; Storebo *et al.*, 2018). In adult ADHD patients effects sizes of stimulants and other medication are ~ 30–50% decreased compared with children and adolescents (Cortese *et al.*, 2018). Predictive tests for medication response would therefore be beneficial, to reduce patient suffering by reducing treatment of nonresponders/partial responders.

A meta-analysis containing 36 pharmacogenetic studies on MPH response in children and adolescents with ADHD has previously been performed. Several (mostly common) genetic variants were significantly associated with treatment response, including SNPs in the *ADRA2A*, *COMT*, and *SLC6A2* genes and VNTRs in the *DRD4* and *SLC6A3* genes (Myer *et al.*, 2017). Variants of the *ADGRL3* (=*LPHN3*) gene have additionally been correlated with MPH treatment response. It was originally reported that a significant association existed between the rs6551665 SNP and treatment response in childhood ADHD, with G-allele carriers showing a quicker response to MPH in the inattentive symptom domain (Arcos-Burgos *et al.*, 2010). In contrast to these findings, a later study found that the G allele of this SNP was significantly associated with poor treatment response in childhood ADHD, which the authors suggest could be because of population structures within the different populations studied (Labbe *et al.*, 2012). However, this study also observed that the G allele of the rs6858066 SNP conferred risk for childhood ADHD and improved treatment response. A different haplotype consisting of the rs6813183, rs1355368, and rs734644 SNPs was recently identified for childhood ADHD risk, and carriers were also observed to respond faster to MPH treatment (Bruxel *et al.*, 2015). Finally, one study investigated the possible effects of the rs6551655, rs1947274, and rs6858066 SNP haplotype on MPH treatment response in childhood ADHD whilst taking into account maternal stress and smoking (Choudhry *et al.*, 2012). The authors reported that this haplotype was associated with a significant improvement in symptom improvement owing to treatment, providing further evidence that *ADGRL3* (=*LPHN3*) variants may serve as MPH treatment response markers (Choudhry *et al.*, 2012).

Studies have also investigated the use of genetic variants as response markers to other ADHD medications. Four SNPs in the dopamine β-hydroxylase gene (*DBH*) were found nominally associated with atomoxetine response status in a Chinese sample of 153 children and adolescents with ADHD (rs1076150, rs2873804, rs1548364, and rs2519154). The association between rs2519154 and atomoxetine response remained significant after correction for multiple comparisons (Fang *et al.*, 2015). Ramoz *et al.* (2009) also investigated atomoxetine response in association with *SLC6A2* and *CYP2D6* gene SNPs. The genomic regions spanning exons 2 and 4–9 of *SLC6A2* were shown to be significantly associated with atomoxetine response in two independent samples. However, no association was found for the *CYP2D6* gene (Ramoz *et al.*, 2009). Another study from the Chinese group found that rs3785143 and rs2279805 SNPs in *SLC6A2* were significantly associated with atomoxetine response and/or remission (Yang *et al.*, 2012).

Several studies have been conducted regarding the pharmacokinetics of cytochrome P450 polymorphisms and atomoxetine (for a review, see Yu et al., 2016a, 2016b). However, the studies mostly investigated the metabolism of atomoxetine and blood concentration in poor, extensive, high and ultrarapid metabolizers, and not on treatment response versus nonresponse. There are very few studies investigating genetic markers for amphetamine response. A study including 56 children and adolescents with ADHD suggested that patients with the 9/9 genotype of the *SLC6A* gene responded worse than 10/10 and 9/10 genotype carriers (Stein *et al.*, 2014). However, further research is needed.

In adult patients with ADHD, Contini *et al.* (2012) did not find an association of genetic variants in the *SLC6A4*, *HTR1B*, *TPH2*, *DBH*, *DRD4*, *COMT*, or *SNAP25* genes with MPH treatment response in 164 adult patients. A systematic review of five pharmacogenetic studies in the same adult ADHD group reported only one significant association with MPH response, which was a SNP in the dopamine transporter gene (*DAT*=*SLC6A3*; Contini *et al.*, 2013). A more recent review and meta-analysis found five pharmacogenetic studies specifically investigating genetic variants in the *SLC6A3* gene available for analysis, but the authors included only two, both of which investigated the 40-bp VNTR. However, no association was found between this VNTR and MPH treatment response in adult ADHD, nor between variants in the *DRD4* and *SLC6A2* genes and MPH response. Negative findings were also reported for *ADRA2A* (rs1800544, rs1800545, and rs553668; Bonvicini et al., 2016a, 2016b).

To our best knowledge, there are no pharmacogenetics studies on treatment response investigating atomoxetine or amphetamine salts specifically in adult ADHD. There are only studies on amphetamine effects in association with genetic variants in healthy adult participants, with a focus on susceptibility for drug abuse (Lott *et al.*, 2005).

Gene–environment interaction

Environmental risk factors for attention-deficit/hyperactivity disorder

Ronald *et al.* (2010) describe that ~1% of variance in ADHD symptoms in 2-year-old children is explained by maternal prenatal stress (Bale, 2014; Class *et al.*, 2014), whereas environmental factors as a whole are thought to explain 22% of ADHD variance (Faraone *et al.*, 2005; Nikolas and Burt, 2010). Mothers of children with ADHD were observed to have elevated gestational psychosocial stress, and prenatal anxiety and depression was suggested to contribute up to 10–15% of the burden associated with behavioral and emotional negative outcomes (Talge *et al.*, 2007). A Swedish register study reported that maternal prenatal stress in the third trimester led to an increased risk for ADHD (adjusted hazard ratio: 1.31, 95% confidence interval: 1.04–1.66; Class *et al.*, 2014). However, those risk factors were not specific for ADHD but also other developmental disorders and neuropsychiatric disorders later in life (Talge *et al.*, 2007). Despite this, the findings of an association between maternal stress during pregnancy remain consistent across the literature, suggesting that this is a robust environmental risk factor for ADHD.

Exposure to various environmental toxins (such as manganese), food additives, and sugars have also been reported as risk factors for the development of ADHD (Collipp *et al.*, 1983; Bateman *et al.*, 2004; Choi *et al.*, 2015). Elevated blood lead concentrations have been observed significantly correlated with ADHD in children, and children with concentrations above 2.0 μg/dl had a 4.1-fold higher ADHD risk (Braun *et al.*, 2006). Exposure to lead and polychlorinated biphenyls has also been shown to cause cognitive deficits and inhibited attention and executive functions, reflective of childhood ADHD (Eubig *et al.*, 2010). The different exposures appeared to have differential effects, as lead mostly disrupted attention processes, whereas polychlorinated biphenyls appeared to effect response inhibition greater than attention. Perinatal mercury exposure has also been suggested as a risk factor for ADHD, and a recent meta-analysis showed a significant association between exposure and ADHD (Yoshimasu *et al.*, 2014). However, the same study found that exposure of embryos or young children to vaccines containing thimerosal (a mercury-containing organic compound) were not associated with ADHD. Because of such conflicting findings, and lack of valid scientific evidence (Casas *et al.*, 2015; Tewar *et al.*, 2016; Yu et al., 2016a, 2016b), there are still ongoing discussions as to whether exposure to such environmental toxins can contribute to ADHD etiology. Further scientific studies relating to these substances are needed to clarify whether an association between exposure and ADHD might exist, particularly as many children who are exposed do not go develop ADHD (Banerjee *et al.*, 2007).

Postnatal ADHD risk factors have been suggested to be a low Apgar score at 5 m (Li *et al.*, 2011; Schwenke *et al.*, 2018) as well as preterm and post-term birth (Silva *et al.*, 2011). Other potential external contributors to ADHD risk include disadvantaged households (Pennington *et al.*, 2009), higher levels of parental conflict (Nikolas *et al.*, 2012) and lower levels of parental involvement (Nikolas *et al.*, 2015). Maltreatment, emotional trauma and sexual abuse have also been associated with ADHD risk (Famularo *et al.*, 1992; McLeer *et al.*, 1994). In support of previous findings, a prospective cohort study using a large sample size from the general population identified three psychosocial risk factors that were associated with ADHD: maternal depression, nonintact family, and a paternal history of antisocial behavior (Galera *et al.*, 2011).

Despite the wealth of evidence documenting strong associations between specific environmental risk factors and the development of ADHD, caution must be taken when interpreting the results, as there are a number of confounding variables inherent to this area of study. These include methodological differences between studies, the possibility of observer bias, and relying on retrospective assessment for important data, which is often subjective. Furthermore, it is rare that specific risk factors exist in isolation without the confounding influence of other potential environmental factors. It is therefore difficult to test whether individual risk factors have discriminable effects on ADHD risk, or whether a combination of risk factors is required, or even if potential environmental risk factors may be substitutable for one another. Future studies should aim to analyze multiple risk factors, including possible secondary and tertiary factors, and use a prospective or longitudinal design to capture any changes in environmental influence over time.

Gene–environment interaction

G×Es are becoming increasingly recognized as important in the pathogenesis of ADHD, but this area is currently underinvestigated (Nigg *et al.*, 2010). It is thought that this neglection is owing to ADHD's unique etiology, as previous research has showed strong genetic contributions, and thereby the effect of environmental factors as well as G×Es has been underestimated (Gould *et al.*, 2017). When assessing the interplay of genetic variation and environmental factors, it is also important to try to disentangle G×E and gene–environment correlation. However, there are still very few studies on either topic, but this is something to bear in mind for designing and

analyzing future studies (Briley *et al.*, 2018). Of the few studies that have been published, ~50% have focused on two polymorphisms: the *DAT1* 3′-UTR VNTR and the *DRD4* exon 3 VNTR. In the first study examining the possible role of G×E in ADHD, it was found that the *DAT1* VNTR genotype interacted with fetal smoking exposure to predict oppositional and hyperactive–impulsive symptoms (Kahn *et al.*, 2003). A later study went on to show that interactions between *DAT1* and maternal prenatal smoking were significant, particularly a nine-repeat allele, which almost doubled the risk of developing ADHD (Neuman *et al.*, 2007). Further studies reported conflicting results, with one study supporting a G×E for *DAT1* and prenatal smoking but only in boys (Altink *et al.*, 2008) and another observing no influence of interactions between smoking and ADHD risk (Langley *et al.*, 2008). It has also been reported that there is an interaction between *DAT1* VNTR alleles and maternal alcohol use, as the risk of developing childhood ADHD was found to be higher when the mother had consumed alcohol during pregnancy (Brookes *et al.*, 2006). In contrast to this, another study found no evidence of such an interaction (Brookes *et al.*, 2006; Laucht *et al.*, 2007; Langley *et al.*, 2008).

Studies examining the potential interaction between the *DRD4* VNTR and environment on ADHD risk found that the risk of developing hyperkinetic conduct disorder symptoms was decreased in children born in the winter, whereas risk was increased in summer-born children (Seeger *et al.*, 2004). The authors suggested that this interaction may occur because of seasonal factors such as temperature and number of daylight hours. However, a recent study was not able to replicate these findings, as the interaction was no longer significant after correction for the large number of statistical tests performed (Brookes *et al.*, 2008). Further studies focused on the possible interactions between the *DRD4* VNTR and perinatal risk factors such as maternal smoking and alcohol use. One study found that the combined effects of both exposures increased ADHD risk higher than the predictors' main effects (Neuman *et al.*, 2007), and children carrying the risk allele had double the risk of developing ADHD if their mother had smoked prenatally compared with children with neither risk factor. A replication study reported conflicting results, whereby no interaction was found between the *DRD4* genotype and maternal smoking on parental-reported childhood ADHD symptoms; however, there was evidence of an interaction between these factors on teacher-reported inattentive symptoms, highlighting the importance of potential observer bias (Altink *et al.*, 2008). A later study also reported no interaction between maternal alcohol use, smoking or low birth weight and the *DRD4* genotype on ADHD risk, although the study sample size was small in comparison with the previous studies and was therefore statistically underpowered (Langley *et al.*, 2008).

Other genes have also been investigated for their interaction with environmental factors. The *DRD2* Taq1 A2 allele has been found to interact with the mother's marital stability, as homozygous children were at higher risk for ADHD when their mothers were never married, separated or divorced (Waldman, 2007). An exon 5 C-substitution in the nicotinic acetylcholine receptor (*CHRN4A*) gene has been reported to interact with maternal smoking to increase ADHD risk, and the authors also demonstrated a gene–gene–environment interaction on ADHD risk between this allele, the previously mentioned *DRD4* VNTR allele and smoking of the mother during pregnancy (Todd and Neuman, 2007). It has also been found that children carriers of the *COMT* risk allele appeared more susceptible to ADHD symptoms when they had a lower birth weight (Thapar *et al.*, 2005). Finally, *ADGRL3* (=*LPHN3*) risk variants have also been shown to interact with the environment, with one common variant (rs2345039) found to increase the risk of ADHD when combined with maternal stress during pregnancy (Choudhry *et al.*, 2012).

There are several limitations to performing G×E studies, which are general to studies of this type and not specifically related to ADHD. First, correlation does not equal cause, and thus environmental characteristics can be a consequence of the target disorder and a direct cause. Furthermore, certain environmental factors may be secondary and reflect other related primary environmental variables, making it difficult to determine which factor is influencing disease risk. For example, maternal smoking and alcohol use may reflect increased levels of maternal stress. Finally, environmental factors may actually have an underlying genetic cause (Ficks and Waldman, 2009). It is possible that the same gene that influences the disorder in the child may also be the same gene that influences the parental environmental; for example, a mother may smoke because of a genetic predisposition to impulsive tendencies, and transfer this genetic predisposition to her child, making them more likely to be diagnosed with ADHD (Skoglund *et al.*, 2014). These second two points demonstrate the importance of properly controlling for confounding variables, which unfortunately most G×E literature has so far failed to do, as demonstrated by Keller (2014). In his paper, he analytically shows that entering potential confounding variables as covariates in general linear models does not control for the effects these variables may have on the G×E interaction, and instead these variables should be entered as covariate-by-environment and covariate-by-gene interactions in the same model as the G×E interaction. Therefore, previous reports of significant G×E interactions should be interpreted with caution.

Although contradictory findings have been reported for some G×E, the evidence suggests that significant interactions do exist and have a large role to play in ADHD

Table 2 Gene–environment interactions for attention-deficit/hyperactivity disorder risk

Environmental risk factors	Gene(s)	References
Prenatal smoking	*DAT1* 3′-UTR VNTR *DRD4* exon 3 VNTR *CHRN4A* exon 5 C-substitution	Kahn *et al.* (2003), Neuman *et al.* (2007), Todd and Neuman (2007), Altink *et al.* (2008), Langley *et al.* (2008)
Maternal alcohol use during pregnancy	*DAT1* 3′-UTR VNTR *DRD4* exon 3 VNTR	Brookes *et al.* (2006), Langley *et al.* (2008)
Low birth weight	*COMT*	Thapar *et al.* (2005)
Birth season	*DRD4* exon 3 VNTR	Brookes *et al.* (2008)
Maternal stress	*ADGRL3*	Choudhry *et al.* (2012)
Maternal marital status	*DRD2* Taq1 A2	Waldman (2007)

UTR, untranslated region; VNTR, variable number tandem repeat.

susceptibility. G×E can no longer be overlooked, and future studies should aim to replicate previous results to validate the data, preferably using much a larger sample size. They should also be rigorously designed to address some of the aforementioned limitations. An overlook of possible G×E is presented in Table 2.

Epigenetics

Many of the aforementioned environmental risk factors are believed to be involved in epigenetic modifications. Epigenetic changes might have a greater effect during key developmental time points, a notion that fits well with the prevalence of prenatal, perinatal, and postnatal risk factors associated with ADHD, and the fact that ADHD is a neurodevelopmental disorder (Mill and Petronis, 2008). In fact, these susceptible stages of brain development are characterized by high mitotic activity, and therefore any environmentally induced epigenetic changes are more likely to be propagated to the cell progeny (Spiers *et al.*, 2015). Epigenetic modifications include chromatin modifications such as cytosine methylation in CpG islands that is associated with gene silencing and chromatin compaction; histone modifications such as acetylation, methylation, and phosphorylation; and RNA-mediated modifications such as small interfering RNAs that can suppress the activity of specific genes by targeted RNA interference and micro-RNA (miRNA) (Mill and Petronis, 2008).

Micro-RNA

MiRNAs are short, noncoding, highly conservative RNAs which play a role in gene regulation at the post-transcriptional level (He and Hannon, 2004). Several miRNAs have been found to modulate genes that have been associated with ADHD, such *BDNF*, *DAT1*, *HTR2C*, *HTR1B*, and *SNAP25*. Furthermore, changes in peripheral miRNA concentration have been found in both animal models and human patients with ADHD (Srivastav *et al.*, 2017). Specifically, genetic variants around the miR-183-96-182 cluster locus and in miR-641 binding sites in the *SNAP25* gene have been associated with ADHD and impulsivity (Nemeth *et al.*, 2013; Sanchez-Mora *et al.*, 2013). Reduced peripheral miR-107 levels could be specifically observed in ADHD and have been proposed as a useful diagnostic marker (Kandemir *et al.*, 2014). In a study from Garcia-Martinez *et al.* (2016), adult ADHD was associated with SNPs in the miR-34b/c cluster, and in the 3′-UTRs of three target genes (*MET*, *NOTCH2*, and *HMGA2*), which have been associated with ASDs (although not ADHD). In addition, an overexpression of miR-34c-3p in peripheral blood monocyte cells has been shown in ADHD. Another genetic variant that has been linked to ADHD is rs4938723, which is localized in the promotor region of pri-miR-34b/c. This variant is functional and influences peripheral gene expression, as the rs4938723 T allele has been observed to lead to reduced miR-34b and miR-34c levels in peripheral blood monocyte cells of patients with ADHD (Garcia-Martinez *et al.*, 2016).

Methylation

DNA methylation is the most frequently studied epigenetic mechanism in the pathophysiology of psychiatric and stress-related disorders. Hypermethylation generally leads to reduced gene expression (Egger *et al.*, 2004). The role of DNA methylation has been extensively studied in post-traumatic stress disorder, major depression and other stress-related disorders (Weder et al., 2014a, 2014b), but could also contribute to the risk of developing ADHD. A study in monozygotic twins, of whom only one twin was having ADHD, revealed several differentially methylated genes between ADHD and non-ADHD siblings (Chen *et al.*, 2017). A modulating effect of *DAT1* methylation on MPH response in children with ADHD was also recently reported (Ding *et al.*, 2016). In adult patients with ADHD, an interaction was reported between severe maltreatment in childhood, gene methylation and genetic variants in the *5-HT3A* gene with severity of ADHD symptoms, bipolar disorder, and borderline personality disorder (Perroud *et al.*, 2016). In children with ADHD, differential methylation patterns in dopaminergic and serotonergic genes have been associated with symptom severity (van Mil *et al.*, 2014). Another study revealed interaction between increased methylation of the promotor region of the serotonin-transporter gene (*5HTT*), severity of ADHD symptoms, and changes in the cortical thickness in occipitofrontal brain regions (Park *et al.*, 2015).

So far, most epigenetic studies have been conducted in childhood ADHD (Dadds *et al.*, 2016; Wilmot *et al.*, 2016). A recent study by Wilmot *et al.* (2016) has shown an increased CpG methylation in peripheral tissue of male children with ADHD. Enrichment analysis suggested the involvement of genes (*VIPR2* and *MYT1L*) linked to inflammatory processes and modulation of monoamine and cholinergic neurotransmission (Wilmot *et al.*, 2016). Walton *et al.* (2017) performed a genome-wide analysis of DNA methylation from childhood ADHD patient blood

samples. They report an association of ADHD symptom trajectories at birth for multiple genomic locations (*SKI*, *ZNF544*, *ST3GAL3*, and *PEX2*), but none of these genes maintained an association at the age of 7 years (Walton *et al.*, 2017). Further studies investigating the potential role of epigenetics in childhood ADHD need to be performed, as well as initial studies assessing epigenetic changes in adult ADHD. In addition, future studies on epigenetic mechanisms need to replicate the previous findings in independent cohorts and need to be designed more rigorous regarding the tissue investigated and confounders that could potentially influence epigenetic mechanisms like smoking, age, and sex. In many cases, it is not clear, if changes that can be seen in peripheral tissue correlate with brain tissue and are meaningful in either explaining pathomechanisms of ADHD or useful as diagnostic biomarkers.

Discussion and conclusion

From the wealth of evidence arising from family, twin, and adoption studies, it is clear that ADHD is a heritable disorder. However, the common genetic variants that are currently known explain only up to one-third of the risk of developing ADHD. Recent studies have therefore aimed to combine approaches investigating both common and rare variants, to discover the missing genetic factors in ADHD. Generating polygenic risk scores has also already proven useful in detecting genetic risk load of ADHD-associated genes. Future studies should aim to clarify the role of the coded proteins and associated pathways of identified genetic risk variants in conveying their risk to the development of ADHD. Environmental factors may also contribute to the risk of the disorder, potentially in interaction with genetic risk variants, and they also require further study. It may be possible to introduce strategic interventions or educate mothers about environmental risk factors to lower the risk of ADHD for the new-born in the future, if conclusive factors can be identified. However, studies using specific designs to disentangle the genetic risk from the environmental factors and clarifying the mode of interplay between genetic and environmental factors are needed, for example, exposed versus nonexposed siblings (Altink *et al.*, 2008). Epigenetic mechanisms might play a role to confer the environmental risks to patients. However, studies of DNA methylation (especially in adult ADHD) are still scarce. G×Es might also play a role in response to ADHD medication. Future studies should use translational approaches to model and clarify the complex gene–environment development interactions in the pathomechanisms of ADHD, using data from multiomic and brain imaging human studies, animal models and human-derived cellular models. Machine-learn algorithms and other bioinformatical tools will also be needed to process the resulting big and complex data to gain further insight into childhood and adult ADHD.

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Conflicts of interest

S.K.S. and A.R. are consultants to Shire and have received author's honoraria from Medice Arzneimittel Pütter GmbH. For the remaining authors, there are no conflicts of interest.

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