



Genetics of attention deficit hyperactivity disorder

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Abstract

Decades of research show that genes play a vital role in the etiology of attention deficit hyperactivity disorder (ADHD) and its comorbidity with other disorders. Family, twin, and adoption studies show that ADHD runs in families. ADHD's high heritability of 74% motivated the search for ADHD susceptibility genes. Genetic linkage studies show that the effects of DNA risk variants on ADHD must, individually, be very small. Genome-wide association studies (GWAS) have implicated several genetic loci at the genome-wide level of statistical significance. These studies also show that about a third of ADHD's heritability is due to a polygenic component comprising many common variants each having small effects. From studies of copy number variants we have also learned that the rare insertions or deletions account for part of ADHD's heritability. These findings have implicated new biological pathways that may eventually have implications for treatment development.

Attention deficit hyperactivity disorder (ADHD) is a childhood-onset condition with impairing symptoms of inattention, impulsivity, and hyperactivity. Decades of research have documented and replicated key facts about the disorder (for a review, see ref. [1]). It occurs in about 5% of children with little geographic or cross-cultural variation in prevalence and often co-occurs with other conditions, including mood, anxiety, conduct, learning, and substance use disorders. Longitudinal studies show that two-thirds of ADHD youth will continue to have impairing symptoms of ADHD in adulthood. People with ADHD are at risk for a wide range of functional impairments: school failure, peer rejection, injuries due to accidents, criminal behavior, occupational failure, divorce, suicide, and premature death. Although many details of ADHD's pathophysiology are unknown, neuropsychological and neuroimaging studies implicate brain circuits regulating executive functioning, reward processing, timing, and temporal information processing.

This article reviews data about the role that genes play in the etiology of ADHD from two perspectives. Family, twin, and adoption studies provide a firm foundation for asserting that genes are involved in the etiology of ADHD. The view from molecular genetics provides a basis for understanding mechanisms whereby genes affect biological pathways that lead to ADHD.

Family, twin and adoption studies of ADHD

Evidence for heritability from family, adoption, and twin studies

A study of 894 ADHD probands and 1135 of their siblings aged 5–17 years old found a ninefold increased risk of ADHD in siblings of ADHD probands compared with siblings of controls [2]. Adoption studies suggest that the familial factors of ADHD are attributable to genetic factors rather than shared environmental factors [3, 4] with the most recent one reporting rates of ADHD to be greater among biological relatives of non-adopted ADHD children than adoptive relatives of adopted ADHD children. The adoptive relatives had a risk for ADHD like the risk in relatives of control children [4].

Twin studies rely on the difference between the within-pair similarities of monozygotic (MZ) twin pairs, who are genetically identical, and dizygotic (DZ) twin pairs, who share, on average, 50% of their segregating genes. The

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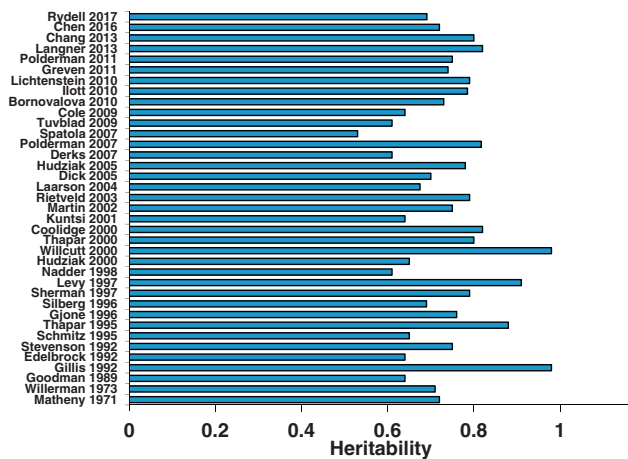


Fig. 1 Heritability of ADHD from twin studies of ADHD diagnoses or symptom counts [153–173]

mean heritability across 37 twin studies of ADHD or measures of inattentiveness and hyperactivity is 74% (Fig. 1). A similar heritability estimate of around 80% was seen in a study of MZ and DZ twins, full siblings, and maternal and paternal half-siblings [5]. The heritability is similar in males and females and for the inattentive and hyperactive-impulsive components of ADHD [6–8].

Only a few of the twin studies in Fig. 1 used categorical measures of ADHD [9–12]. Their heritability estimates range from 77 to 88%, which is consistent with the larger number of studies using symptom count measures of ADHD. Twin studies have explored whether ADHD is best viewed as a categorical disorder or as an extreme of a continuous trait. A study of 16,366 Swedish twins found a strong genetic link between the extreme and the sub-threshold variation of DSM-IV ADHD symptoms [13]. This study confirmed an early study of 583 same-sexed twin pairs using ADHD-III-R symptoms [14]. Both studies suggest that the diagnosis of ADHD is the extreme of a continuous distribution of ADHD symptoms in the population and that the etiologic factors involved in the disorder also account for the full range of symptoms. These data are consistent with clinical studies showing the clinical implications of subthreshold ADHD [15].

ADHD's clinical features and course

Reporter effects

Parent and teacher ratings of ADHD symptoms result in high heritability estimates (70–80%) [6]. In contrast, studies using self-ratings in adolescence and adulthood show lower heritabilities (<50%) [16–19]. Two twin studies examined these rater effects [20, 21]. They showed that self-ratings, as well as different-parent and different-teacher ratings within twin pairs, were associated with lower heritability estimates

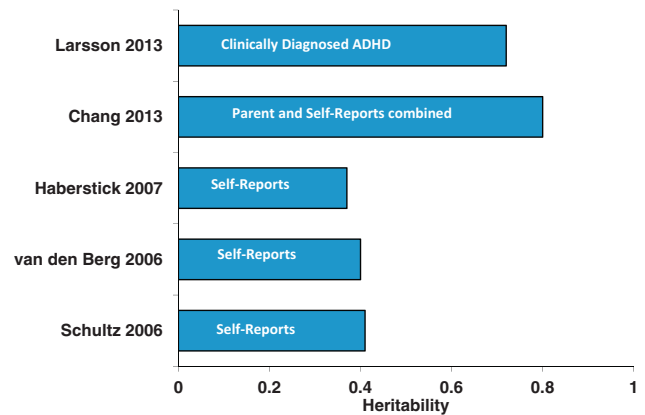


Fig. 2 Heritability of ADHD in adults depends on method of diagnosis

(~30–40%) compared with heritabilities based on same-parent and same-teacher ratings (~70–80%) [20–22]. Low reliability of self-reports may explain why heritability estimates are lower in studies of self-rated ADHD symptoms. Using different informants for ADHD symptom ratings of each twin in a pair introduces rater effects (i.e., each rater experiences and reports different ADHD symptoms) or rater bias (i.e., a rater consistently over- or underestimates ADHD symptoms or similarities between twins). These effects could explain why heritability estimates are lower in studies relying on different informants for each twin in a pair compared with studies using the same raters [23].

Developmental effects

The first twin studies of ADHD in adults used self-reports and estimated heritability at 30–40% (Fig. 2), (e.g. [24]), which is substantially lower than the heritability among children and adolescents. In contrast, one study estimated heritability to be 80% after combining self and parent ratings into a composite index of ADHD. Another study found the heritability of clinically diagnosed ADHD in adults to be 72% [25]. These findings (Fig. 2) suggest that the heritability of ADHD is stable during the transition from childhood into adulthood. They explain previous reports of low heritability for ADHD symptoms in adults as due to measurement error from rater effects. The higher heritabilities for clinically diagnosed adult ADHD confirm family studies suggesting that persistent ADHD is highly familial [5, 26, 27].

Twin studies show that both stable and dynamic genetic risk factors influence ADHD over the course of the development from childhood to early adulthood [7, 28–30]. These study findings explain the developmental structure of genetic risk factors for ADHD with both stable and dynamic processes. The stable component of the genetic risk suggests that persistent ADHD and its pediatric form are genetically linked. The dynamic component suggests that

the set of genetic variants accounting for the onset of ADHD differs from those accounting for the persistence and remission of the disorder. For a review of the genetics of adult ADHD, see Franke et al. [26].

Psychiatric comorbidity

Multivariate twin and sibling studies have found a general genetic factor that influences ADHD and a broad spectrum of neuropsychiatric conditions [31, 32]. These studies have shown that a latent shared genetic factor accounts for up to 45% of co-variance across childhood externalizing, internalizing, and phobia symptoms [31, 33] and 31% of co-variance in childhood neurodevelopmental symptoms [34]. Similar results have been reported for register-based clinical diagnoses, with one study showing that a general genetic factor explained 10–36% of disorder liability across several psychiatric diagnoses [32]. Two studies have assessed the contribution of measured genetic variants for a general psychopathology dimension. One study estimated the SNP-heritability as 18% for maternal ratings of total problems on the Child Behavior Checklist, which measures internalizing, externalizing, and attention problems [35]. Similarly, another study estimated the SNP heritability as 38% for a general psychopathology factor derived from childhood psychopathology symptoms assessed by multiple raters [36]. These studies also support spectrum-specific genetic factors, such as genetic factors that load specifically on externalizing disorders [31]. The finding of externalizing-specific genetic factors for ADHD is consistent with a large number of twin and family studies demonstrating genetic overlaps of ADHD with oppositional-defiant disorder symptoms [37], conduct disorder [38], antisocial behavior [39], and substance use problems [40–42].

Twin studies have tested for genetic overlap between ADHD and autism spectrum disorders (ASD) [43, 44], which often co-occur [45]. Studies of community samples of youth, from the United States of America [46], the United Kingdom [47], and Sweden [11, 48] show that genetic factors influence this comorbidity. Ronald et al. [47] found genetic correlations between ADHD and ASD above 0.50. Similar results have been found in adult twin studies [49]. A register-based study in Sweden found that individuals with ASD and their relatives were at increased risk of ADHD. The pattern of association across relatives supported the existence of a genetic overlap between clinically ascertained ASD and ADHD [50]. Some features of ASD are differentially linked to either the inattentive or the hyperactive-impulsive components of ADHD [51, 52]. For instance, Polderman et al. [51] found that the symptoms reflecting the repetitive and restricted aspects of ASD showed the strongest genetic association with ADHD and a Swedish twin study found that the subcomponents of

ADHD and ASD are influenced by specific genetic factors [48].

Fewer studies have explored how genetic factors contribute to the co-occurrence between ADHD and internalizing disorders. A large family study found an increased risk of attempted and completed suicide in first- and second-degree relatives of ADHD probands [53]. The pattern of familial risks across different levels of relatedness suggests that shared genetic factors are important for these associations [53]. Family studies that studied the association between ADHD and depression suggest that the co-occurrence is influenced by shared familial factors [54, 55]. Twin studies of this issue suggest that shared genetic factors explain the overlap of ADHD with depression, anxiety, and internalizing symptoms [56–60]. For example, Cole et al. [59] found that shared genetic factors explained most of the association between traits of ADHD and depression. Similar results were found by Spatola et al. [60], who used a multivariate twin analysis to study the overlap between different subscales of the Child Behavior Check List (CBCL), such as affective problems, anxiety problems, and attention-deficit/hyperactivity problems.

In contrast to the wealth of information about the familial co-transmission of ADHD and many other disorders, very little is known about ADHD's familial links to intellectual disability (ID). A meta-analysis reported that the intelligence quotient (IQ) of youth with ADHD is nine points lower than typically developing peers [61] and much evidence suggests it is valid to diagnose ADHD in the context of ID [62]. Faraone et al. [63] studied the genetic association of ADHD and ID in Swedish medical registry data. Individuals with ID were at increased risk for ADHD and relatives of ID cases had an increased risk for ADHD compared with relatives of those without ID. Model fitting analyses attributed 91% of the correlation between the liabilities of ADHD and ID to genetic factors. This work attributes nearly all the comorbidity between ADHD and ID to genetic factors. Only a few twin and family studies have explored how genetic factors contribute to non-psychiatric comorbidity. The literature suggests novel etiologic links with asthma [64], obesity [65], and epilepsy [66].

The search for common genetic variants

Genetic linkage studies

Genetic linkage was the first genome-wide method applied to ADHD. This method searches the genome for evidence that a segment of DNA is transmitted with a disorder within families. A review of the linkage literature found substantial disagreement about which chromosomal regions are linked to ADHD [67]. Although there is some overlap in

“suggestive” findings, no finding met genome-wide significance [68]. To make sense of these results, Zhou et al. [69] applied Genome Scan Meta-Analysis. They found genome-wide significant linkage for a region on chromosome 16 between 64 Mb and 83 Mb. Because the linkage method only detects genetic variants that have large effects, the paucity of significant findings for other loci suggests that common DNA variants having a large effect on ADHD are unlikely to exist. Nearly all ADHD linkage studies have selected either sibling pairs or small families from outbred populations. Another approach is to assess for linkage in multigenerational population isolates. Arcos-Burgos et al. [70] used this strategy to study 16 multi-generational families from Colombia. In some of these families, they found evidence supporting linkage to chromosomes 4q13.2, 5q33.3, 8q11.23, 11q22, and 17p11. one region implicated *LPHN3*. For a review of supporting evidence, see ref. [71].

Candidate gene association studies

Early molecular genetic studies of ADHD sought to associate ADHD with genes that had some a priori plausibility as being involved in its etiology. Because the drugs that treat ADHD target dopaminergic or noradrenergic transmission, many studies examined “candidate genes” in these pathways. Results were frequently contradictory [26, 67]. In the meta-analyses of Gizer et al. [72], eight candidate DNA variants showed a statistically significant association with ADHD across multiple studies. These variants implicated six genes: the serotonin transporter gene (*5HTT*), the dopamine transporter gene (*DAT1*), the D4 dopamine receptor gene (*DRD4*), the D5 dopamine receptor gene (*DRD5*), the serotonin 1B receptor gene (*HTR1B*) and a gene coding for a synaptic vesicle regulating protein known as *SNAP25*. A meta-analysis covering all genetic association studies of adults with ADHD reported a significant association between adult ADHD and *BAIAP2* (brain-specific angiogenesis inhibitor 1-associated protein 2). *BAIAP2* is involved in neuronal proliferation, survival, and maturation and dendritic spine morphogenesis and may affect neuronal growth-cone guidance. These findings were significant even after Bonferroni correction [73]. For both the child and adult meta-analyses, the strength of each association, as measured by the odds ratio, is small, less than 1.5.

Many studies examined the dopamine transporter gene (*SLC6A3*), especially a 40-base pair variable number of tandem repeats regulatory polymorphism located in the 3'-untranslated region of the gene. This variant produces two common alleles with 9- and 10-repeats (9R and 10R). In humans, the 10R allele of this polymorphism has been associated with ADHD in youth [67] while the 9R allele is associated with ADHD in adults [74]. A meta-analysis

showed that the 9R allele is associated with increased DAT activity in human adults as measured by positron emission tomography [75].

Genome-wide significant common variants

Genome-wide association studies (GWAS) scan the entire genome to detect common DNA variants having very small etiologic effects. By “common” we mean greater than 1% of the population. To do this, GWAS assay hundreds of thousands or even millions of single nucleotide polymorphisms (SNPs). Doing so has a statistical cost: to assert genome-wide statistical significance, an observed association must have a *p* value less than 0.00000005. This stringent *p* value needs very large samples.

The initial GWAS of ADHD [76–86] did not discover any DNA variants that achieved genome-wide significance, even when most of these samples were combined in meta-analysis having a sample size of 2064 trios (two parents and an ADHD child), 896 ADHD patients, and 2455 controls [87]. That study did find statistical significance for a group of candidate genes previously nominated by members of the International Multisite ADHD Genetics (IMAGE) project [88]. For a review of early GWAS studies, see Franke et al. [89]. Examination of the “molecular landscape” derived from the top findings from these initial GWAS studies along with other data concluded that genes regulating directed neurite outgrowth were strongly implicated in the etiology of ADHD [90]. Pathway and gene set analyses of GWAS data implicated pathways involved in the regulation of neurotransmitter release, neurite outgrowth and axon guidance as contributors to the etiology of ADHD [91–93].

A consortium of ADHD researchers completed a GWAS meta-analysis of 12 studies comprising 20,183 people with ADHD and 35,191 controls. For methodologic details about the studies contributing data to this meta-analysis, see Demontis et al. [94]. Twelve loci achieved genome-wide significance. None of the genome-wide significant SNPs showed significant heterogeneity between studies. Among the implicated genes, *FOXP2* is especially notable because prior work had implicated it in adult ADHD (Ribases, 2012 #26445) and in speech and language disorders [95]. A *FOXP2* knockout mouse study found that the gene regulates dopamine in ADHD-associated brain regions [96].

As described by Demontis et al. [94], other genes implicated by the genome-wide significant loci have relevant biological roles. *DUSP6* regulates neurotransmitter homeostasis by affecting dopamine levels in the synapses. *SEMA6D* is expressed in the brain. It regulates neuronal wiring during embryonic development. *ST3GAL3* harbors missense mutations associated with ID. *LINC00461* is expressed in brain and includes variants associated with educational attainment. Another gene implicated at that

locus is *MEF2C*, which has been associated with ID and several psychiatric disorders.

The consortium conducted several gene set analyses including three sets of genes regulated by *FOXP2*: (1) genes enriched in wild-type versus control *FOXP2* knockout mouse brains; (2) genes showing differential expression in wild-type versus *FOXP2* knockout mouse brains; and (3) genes enriched in basal ganglia or inferior frontal cortex from human fetal brain samples. None of these sets were associated with ADHD. Also, non-significant was a set of candidate genes for ADHD previously proposed by a panel of ADHD experts [88]. Among these, only *SLC9A9* showed a weak association with ADHD. No Gene Ontology gene sets attained statistical significance but a set of genes showing high intolerance to loss of function did associate with ADHD.

Common variant ADHD as a polygenic disorder

The GWAS analyses also showed that much of ADHD's heritability is due to the polygenic effects of many common variants each having very small effects. The SNP heritability was 0.22, which is about one-third of ADHD's heritability computed from twin studies [97]. The polygenic architecture for ADHD was confirmed by estimating polygenic risk scores in one subset of the sample and showing that it predicted ADHD, in a dose-dependent manner, in a validation subset. As seen for other psychiatric disorders [98], the variance explained by these risk scores was low (5.5%).

Further evidence for the validity of the ADHD's polygenic background comes from analyses showing that the relevant SNPs were enriched for annotations implicating conserved regions of the genome (which are known to have biological significance) and for regulatory elements specific to the central nervous system. The discovery of a polygenic susceptibility to ADHD does not show which DNA variants comprise the susceptibility. It does, however, support the idea that more genome-wide significant variants will be discovered in larger samples.

Martin et al. [99] showed that ADHD's polygenic liability derived from a clinical sample predicted ASD traits in a population sample, which confirms twin study data [48, 51] and gene set analyses [100] showing genetic overlap between ADHD and ASDs. The polygenic liability score derived from Martin et al.'s ADHD case-control clinical sample also predicted both inattention and hyperactivity in the general population. This latter finding was replicated by Groen-Blokhuis et al. [101] who found that ADHD polygenic risk scores significantly predicted both parent and teacher ratings of attention in preschool- and school-aged children in the population. Likewise, Stergiakouli et al. [102] showed that the polygenic liability for ADHD traits in

a population sample predicted ADHD clinical diagnoses in a case-control study. These results confirmed conclusions from twin studies that the liability for clinically defined ADHD is the extreme of a trait that varies continuously in the population [13].

Other polygenic score studies are confirming cross-disorder genetic associations previously predicted by family and twin studies. We have long known that ADHD co-occurs with conduct disorder. Both family and twin studies have implicated shared genes in this association [38, 103–105]. Consistent with this prior work, Hamshere et al. [106] reported a high polygenic risk for ADHD among children with comorbid conduct problems. In a large population study, Larsson et al. [107] reported that the relatives of ADHD individuals had an increased risk for schizophrenia and bipolar disorder. Consistent with that report, the polygenic risk score derived from a large GWAS of schizophrenia significantly discriminated ADHD cases from controls [108]. This discrimination was strongest for alleles that were risk alleles for both adult schizophrenia and adult bipolar disorder, which confirms prior family and twin data suggesting a genetic link between ADHD and bipolar disorder [109]. Moreover, a joint GWAS of ADHD and bipolar disorder reported a significant correlation between the polygenic scores of ADHD and bipolar disorder and also identified genome-wide significant loci for the two disorders [110]. Similarly, prior reports of familial co-transmission of ADHD and depression [54] have been extended by showing shared SNP heritability between the two disorders [98]. Using a novel drug challenge paradigm, Hart et al. [111] found that the polygenic scores for both schizophrenia and ADHD were associated with the euphoric response to amphetamine, which suggests that the genetic association between these disorders may be due to variants in the neural systems regulating the euphoric response to amphetamine.

Using GWAS results from many studies, it is possible to compute genetic correlations that indicate the degree to which the polygenic architectures of two disorders or traits overlap. When Demontis et al. [94] correlated ADHD's polygenic risk with 220 disorders and traits, many highly significant correlations emerged. Figure 3 shows some of the most significant of these correlations (each passing the Bonferroni significance threshold). Some of these genetic correlations fit with prior expectations (e.g., with neuroticism, depression and the cross disorder GWAS). Others are consistent with the clinical epidemiology of ADHD (e.g., with obesity, IQ, smoking and school achievement). In some cases, these significant correlations offer new directions for understanding comorbidity. For example, some have interpreted the comorbidity between ADHD and obesity, which has been confirmed via meta-analysis [112], as being caused by the impulsivity associated with ADHD. The genetic correlation data suggest that shared genetic risk

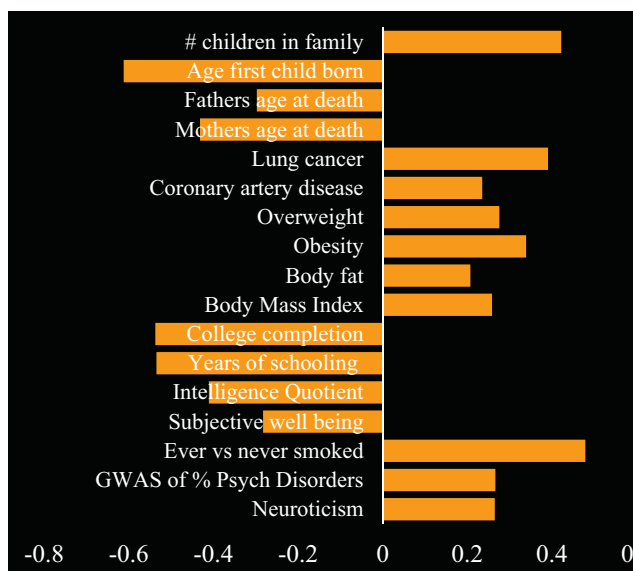


Fig. 3 Genetic correlations of ADHD with other traits based on LD score regression

factors, and an underlying shared pathophysiology, account for this comorbidity.

Some of the genetic correlations in Fig. 3 are entirely novel. These include ADHD's genetic correlations with medical outcomes (lung cancer, coronary artery disease, parents' age at death) and with demographics (number of children in the family, age first child born). There are, however, some consistent findings in the prior literature, which suggest that people with ADHD are more likely to have larger families [113] and more likely to die prematurely [114].

The search for rare genetic variants

Initially, information about rare DNA variants (<1% of the population) came from reports of syndromic chromosomal anomalies associated with multiple medical and psychiatric problems along with ADHD. Examples are velo-cardio facial syndrome fragile-X syndrome, Turner syndrome, tuberous sclerosis, neurofibromatosis, Klinefelter syndrome, and Williams syndrome (Fig. 4). In a single family, a pericentric inversion of chromosome 3 co-segregating with ADHD symptoms [115, 116] implicated *SLC9A9*. Mutations of that gene lead to an animal model of ADHD [117, 118] and have been associated with both autism [119, 120] and ADHD [121].

The common variant genotyping arrays used in GWAS studies can detect large copy number variants (CNVs). Because CNVs often delete or duplicate a large genomic segment spanning part of a gene or even entire genes, they often have clear implications for gene functioning. Studies

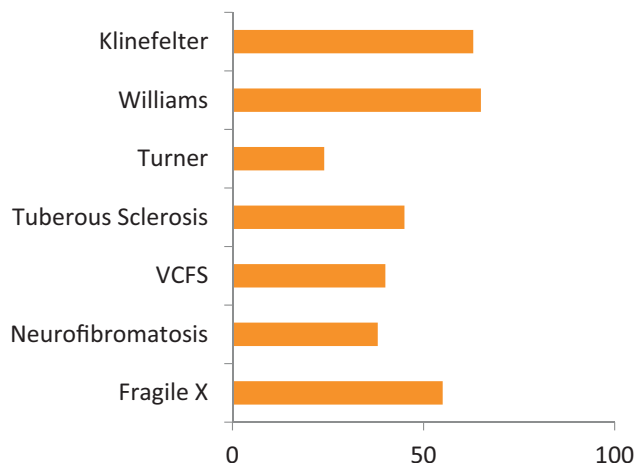


Fig. 4 Prevalence of ADHD in rare genetic syndromes

of CNVs in ADHD assessed ADHD youth and controls for the presence of large (>500 kb), rare CNVs [77, 122–127]. Each study, except one, found an odds ratio greater than one, indicating a greater burden of large, rare CNVs among ADHD patients compared with controls. The discrepant study used a different definition of burden [125]. Only three studies found a statistically significant burden among ADHD patients for large CNVs (for a summary, see Thapar et al. [128]). As their review shows, deletions and duplications are equally over-represented in ADHD samples although statistical significance emerged only for duplications. Thapar et al. also found enrichment for duplications (but not deletions) previously implicated in schizophrenia and, to a lesser extent, ASDs. The top biological pathways implicated by these CNV studies were: respiratory electron transport, organonitrogen compound catabolic process, transmembrane transporter activity, carbohydrate derivative catabolic process, ligand-gated ion channel activity, methyltransferase activity, transmembrane transport and ion gated channel activity.

A study of 489 ADHD patients and 1285 controls found rare CNVs in the parkinson protein two gene (*PARK2*) [123]. The result was significant after empirical correction for genome-wide testing. *PARK2* regulates the cell's ubiquitin-proteasome system which helps dispose damaged, misshapen, and excess proteins. Two other genes involved in this pathway (*FBXO33* and *RNF122*) had been implicated in other studies [84, 129]. A study of adult ADHD did not find a significant effect for large CNVs, but did find a significant effect for small CNVs [126].

The CNV studies have implicated several biological pathways. Williams et al. [127] found that ADHD patients harbored duplications in the alpha-7 nicotinic acetylcholine receptor gene (*CHRNA7*) and showed that the finding replicated in four independent cohorts from the United Kingdom, the United States, and Canada. Another

replication was reported in an Italian sample [130]. The implication of the nicotinic system is particularly interesting given that nicotinic neurons modulate dopaminergic neurons, ADHD patients have a high rate of smoking [131] and nicotine administration reduces ADHD symptoms [132]. In a sample of 99 children and adolescents with severe ADHD, Lesch et al. [124] found several CNVs, including a 3 Mb duplication on chromosome 7p15.2-15.3 harboring neuropeptide Y (*NPY*). Investigation of other family members yielded an association of this duplication with increased *NPY* plasma concentrations and functional magnetic imaging assessed brain abnormalities.

Thapar et al. [128] reported biological pathway studies of ADHD CNV data pooled from five studies. These CNV data were enriched for genes previously implicated in schizophrenia, Fragile X intellectual disability and, to a lesser degree, autism. Several biological pathways were significantly enriched in the ADHD CNV findings, most notably ion channel pathways, which had been implicated in cross-disorder analyses of ADHD, autism, schizophrenia, bipolar disorder, and depression [133]. The CNV analyses also pointed to pathways regulating immune functioning and oxidative stress. These pathways had previously been implicated in ADHD by non-genetic studies, (e.g. refs. [134–136]).

Elia et al. [122] showed that CNVs impacting metabolic glutamate receptor genes were significantly enriched across multiple cohorts of patients. Supporting evidence came from Akutagawa-Martins et al. [137] who reported that CNVs in glutamatergic genes were associated with the cognitive and clinical impairments of ADHD. In a pharmacogenomics GWAS, an SNP in glutamate receptor gene *GRM7* was one of the most significant findings [138]. Glutamatergic defects have been observed in a rat model of ADHD [139, 140] and magnetic resonance spectroscopy in humans shows dysregulation of glutamate and glutamate/glutamine concentrations in ADHD patients (e.g. ref. [141]).

An exome sequencing study of ADHD [121] reported results for 123 adults with persistent ADHD and 82 healthy controls. Significantly more cases than controls had a rare missense or disruptive variant in a set of ADHD candidate genes. In an exome sequencing study of ADHD patients without a family history of ADHD, Kim et al. [142] reported six de novo missense SNVs in brain-expressed genes: *TBC1D9*, *DAGLA*, *QARS*, *CSMD2*, *TRPM2*, and *WDR83*. They also sequenced 26 genes implicated in ID and ASDs but found only one potentially deleterious variant. In an exome chip study, Zayats et al. [143] assayed a sample of 1846 cases and 7519 controls to search for rare genetic variants. They detected four study-wide significant loci that implicated four genes known to be expressed in the brain during prenatal stages of development: *NT5DC1*, *SEC23IP*, *PSD*, and *ZCCHC4*. Hawi et al. [144] found

novel rare variants in the *BDNF* gene by sequencing 117 genes in 152 youth with ADHD and 188 controls.

Pharmacogenetics of ADHD

Several studies have clarified the genetics of the metabolism of ADHD patients. Some patients are slow metabolizers of atomoxetine due to variants in the cytochrome P450 isoenzyme 2D6, which is regulated by the *CYP2D6* gene. As a result, the half-life of atomoxetine ranges from 5.2 h in rapid metabolizers to 21.6 h in slow metabolizers [145]. Some work has looked into *CES1* variants regarding the regulation of methylphenidate metabolism and *CYP2D6*/*CYP3A4* variants and the metabolism of ADHD, but the evidence base has not generated consistent results for either children [146] or adults [73].

Myer et al. [147] used meta-analysis to evaluate pharmacogenetic studies of the efficacy response to methylphenidate for the treatment of ADHD. They found 36 studies comprising 3647 ADHD youth treated with methylphenidate. Statistically significant effects were found for: rs1800544 in *ADRA2A* (odds ratio (OR): 1.69; confidence interval (CI): 1.12–2.55), rs4680 *COMT* (OR: 1.40; CI: 1.04–1.87), rs5569 *SLC6A2* (OR: 1.73; CI: 1.26–2.37), and rs28386840 *SLC6A2* (OR: 2.93; CI: 1.76–4.90), and repeat variants *VNTR 4 DRD4* (OR: 1.66; CI: 1.16–2.37) and *VNTR 10 SLC6A3* (OR: 0.74; CI: 0.60–0.90). The following variants did not reach statistical significance: rs1947274 *LPHN3* (OR: 0.95; CI: 0.71–1.26), rs5661665 *LPHN3* (OR: 1.07; CI: 0.84–1.37) and *VNTR 7 DRD4* (OR: 0.68; confidence interval: 0.47–1.00). The significant findings were not due to publication biases. Although the odds ratios are small, these findings suggest that a personalized medicine approach to ADHD is a reasonable goal of future research.

Conclusions and future directions

There can be no doubt that DNA variants in genes or regulatory regions increase the risk for ADHD. In rare cases, a single genetic defect may lead to ADHD in the absence of other DNA variants. We do not know how many of these rare variants exist or if such variants require environmental triggers for ADHD to emerge. It is equally clear that no common DNA variants are necessary and sufficient causes of ADHD. Genome-wide association studies show that a genetic susceptibility to ADHD comprised of many common DNA variants accounts for about one-third of the twin study estimates of ADHD's heritability. We do not know yet which variants or how many of them make up the polygenic component. The heritability that cannot be

explained by main effects of rare or common variants is likely due to gene–gene interactions, gene–environment interactions or gene–environment correlations.

The convincing evidence for genes as risk factors for ADHD does not exclude the environment as a source of etiology. The fact that twin estimates of heritability are less than 100% asserts quite strongly that environmental factors must be involved. ADHD's heritability is high, and that estimate encompasses gene by environment interaction. Thus, it is possible that such interactions will account for much of ADHD's etiology. Environmental risk factors likely work through epigenetic mechanisms, which have barely been studied in ADHD [148]. The importance of the environment can also be seen in the fact that, as for other complex genetic disorders, much of ADHD's heritability is explained by SNPs in regulatory regions rather than coding regions [149].

Another hypothesis for future research to explore is the possibility that ADHD is an omnigenic disorder. The omnigenic model of Boyle et al. [150] posits the existence of a small number of “core genes” having “biologically interpretable roles in disease” along with a much greater quantity of “peripheral genes” regulating the core genes. Because there are many more peripheral genes, they account for a greater proportion of the variability in heritability than do the core genes. Because core genes are more likely than peripheral genes to be relevant for developing biomarkers and treatment targets, separating these two classes from one another will require more research.

Gene discovery for ADHD has succeeded but has left us with unexpected results. None of the genome-wide significant findings had been predicted a priori and a set of ADHD candidate genes, implicated primarily by the disorder's neuropharmacology, did not reach statistical significance. These findings challenge the idea that the core of ADHD's pathophysiology rests within the machinery of catecholaminergic transmission. Instead, it is possible that the catecholaminergic dysregulation believed to underlie ADHD is a secondary compensation to ADHD's primary etiology (see discussion by Hess et al. [151]).

In the years to come, we can expect breakthroughs in the genetics of ADHD to come from several fields of study. Our knowledge of rare variants should increase dramatically as we learn more about CNVs and as reports from exome, full genome and targeted sequencing studies unfold. With the discovery of genome-wide significant common variants, we look forward to studies that discover the functional variants responsible for these findings. With the discovery of these functional variants, we will learn more about the mechanisms whereby genetic risk variants increase the risk for ADHD.

Accumulating evidence from family, twin, and molecular genetic studies suggests that the disorder we know as

ADHD is the extreme of a dimensional trait in the population. The dimensional nature of ADHD has wide-ranging implications. If we view ADHD as analogous to cholesterol levels, then diagnostic approaches should focus on defining the full continuum of “ADHD-traits” along with clinically meaningful thresholds for defining who does and does not need treatment and who has clinically subthreshold traits that call for careful monitoring. The dimensional nature of ADHD should also shift the debate about the increases in ADHD's prevalence in recent years. Instead of assuming that misdiagnoses are the main explanation for the increased prevalence, perhaps researchers should explore to what extent the threshold for diagnosis has decreased over time and whether changes in the threshold are clinically sensible or not. A shift from categorical to dimensional constructs harmonizes with the Research Domain Criteria (RDoC) initiative of the National Institute of Mental Health [152]. RDoC seeks to define and validate dimensional constructs mediating psychopathology along with the neurobiological underpinnings of these constructs.

Unraveling the genetics of ADHD will be challenging. Technological advances are moving at a rapid pace. The next decade of work should give us more accurate measures of brain structure and function along with much more genomic, transcriptomic and epigenomic data. These advances will set the stage for breakthroughs in our understanding of the etiology of ADHD and in our ability to diagnose and treat the disorder.

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Compliance with ethical standards

Conflict of interest In the past year, SVF received income, potential income, travel expenses continuing education support and/or research support from Lundbeck, KenPharm, Rhodes, Arbor, Ironshore, Shire, Akili Interactive Labs, CogCubed, Alcobra, VAYA, Sunovion, Genomind, and NeuroLifeSciences. With his institution, he has US patent US20130217707 A1 for the use of sodium–hydrogen exchange inhibitors in the treatment of ADHD. HL has served as a speaker for Eli-Lilly and Shire and has received research grants from Shire.

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