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Insights into attention-deficit/hyperactivity disorder from recent genetic studies

Isabell Brikell^{1,2}, Christie Burton³, Nina Roth Mota⁴, Joanna Martin⁵

¹ Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

² National Centre for Register-based Research, Department of Economics and Business Economics, Aarhus University, Aarhus, Denmark

³ Neurosciences and Mental Health, Hospital for Sick Children, Toronto, Canada

⁴ Department of Human Genetics, Radboud University Medical Center, Donders Institute for Brain, Cognition and Behaviour, Nijmegen, The Netherlands

⁵ MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff, United Kingdom

Corresponding author: Dr Joanna Martin, MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Hadyr Ellis Building, Maindy Road, Cardiff CF24 4HQ. Email: martinjm1@cardiff.ac.uk

Abstract

Attention-deficit/hyperactivity disorder (ADHD) is a common and highly heritable neurodevelopmental disorder (NDD). In this narrative review, we summarize recent advances in quantitative and molecular genetic research from the last 5-10 years. Combined with large-scale international collaboration, these advances have resulted in fast-paced progress in understanding the etiology of ADHD and how genetic risk factors map on to clinical heterogeneity. Studies are converging on a number of key insights. First, ADHD is a highly polygenic NDD with a complex genetic architecture encompassing risk variants across the spectrum of allelic frequencies, which are implicated in neurobiological processes. Second, genetic studies strongly suggest that ADHD diagnosis shares a large proportion of genetic risks with continuously distributed traits of ADHD in the population, with shared genetic risks also seen across development and sex. Third, ADHD genetic risks are shared with those implicated in many other neurodevelopmental, psychiatric and somatic phenotypes. As sample sizes and the diversity of genetic studies continue to increase through international collaborative efforts, we anticipate further success with gene discovery, characterization of how the ADHD phenotype relates to other human traits and growing potential to use genomic risk factors for understanding clinical trajectories and for precision medicine approaches.

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder (NDD) (Polanczyk et al., 2007, 2014). While the exact causes of ADHD remain unclear, advances in quantitative and molecular genetic methods demonstrate that genetic factors play a crucial role in its etiology. In this narrative review, we briefly outline the clinical presentation and epidemiology of ADHD and summarize insights from recent genetic research, focusing on studies from the last 5-10 years, and particularly genome-wide association studies (GWAS) and downstream analyses. By highlighting converging evidence from twin and family studies with recent molecular genetic approaches, we illustrate how genetic risks contribute to the development of ADHD across different definitions, ages, sex, and comorbidities. Finally, we discuss implications and future directions, highlighting areas where further genetic research is needed.

Clinical diagnosis

ADHD is characterized by developmentally inappropriate symptoms of inattention and/or hyperactivity/impulsivity. Based on current diagnostic criteria using the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (APA, 2013), 6 inattention and/or 6 hyperactivity/impulsivity symptoms must be present for at least 6 months, before age 12, and impair function across multiple settings (e.g. home and school). The International Classification of Diseases (ICD-11) (WHO, 2018) includes the same symptoms and criteria, except that the number of symptoms and age-of-onset are not specified (Posner et al., 2020).

The first descriptions of clinically-significant attention deficits were published in the late 1700's (Martinez-Badía & Martinez-Raga, 2015). These early descriptions contain many features of ADHD (e.g., inattention, fidgeting), although hyperactivity first formally described in 1932 (Faraone et al., 2015; Lange et al., 2010). ADHD first appeared in DSM-II and ICD-9. Currently, DSM-5 (APA, 2013) and ICD-11 (Posner et al., 2020) recognize three presentations: predominantly hyperactive/impulsive, predominantly inattentive, and a combined presentation.

Both pharmacological and non-pharmacological treatments are used to manage ADHD. Pharmacological treatments can be categorized into stimulant (methylphenidate and amphetamine-derivatives) and non-stimulant (atomoxetine, guanfacine and clonidine) drugs, both of which increase extracellular catecholamines (Golmirzaei et al., 2016). Stimulants are typically the first-line recommended drug treatment and have been shown to be effective in children and adults across several meta-analyses (Faraone & Buitelaar, 2010; Moriyama et al., 2013). Non-stimulants are typically used when stimulants are ineffective, contra-indicated or have intolerable side-effects (Faraone et al., 2006). Non-pharmacological treatments include behavioural management, psychoeducation, neurocognitive and dietary interventions,

which have all shown promise in individual studies, but only modest effects in meta-analyses (Thapar & Cooper, 2016). The Multimodal Treatment of ADHD study (Disorder, 1999) found that methylphenidate, alone or with psychosocial treatment, was the most effective in reducing ADHD symptoms. For more detailed information about treatments, see (Faraone et al., 2015; Posner et al., 2020; Thapar & Cooper, 2016).

Epidemiology

ADHD is common worldwide, with meta-analyses reporting prevalence of 5-7% in children and adolescents (Polanczyk et al., 2007, 2014; Willcutt, 2012). Despite a public perception that ADHD is being increasingly diagnosed, a meta-analysis reported relatively stable prevalence estimates between 1985-2012 (Polanczyk et al., 2014). While prevalence estimates vary by geographic location, with the highest prevalence observed in North America, followed by Europe, meta-analyses suggest that much of this variability is due to differences in study characteristics, assessment tools, diagnostic criteria and availability of services (Polanczyk et al., 2007, 2014). The fact that ADHD is prevalent across the world reinforces why inclusion of genetic diversity, currently lacking in ADHD genetic research, is critical for equity in outcomes and progress.

ADHD is often persistent, with around 15% of affected children continuing to meet full diagnostic criteria by early adulthood and an additional 50-70% continuing to experience impairing symptoms (Faraone et al., 2006; Caye et al., 2016). Remittance of symptoms with age, particularly hyperactivity/impulsivity, is one reason for the lower prevalence of ADHD in adults, which is estimated at 2.5% (Michielsen et al., 2012; Simon et al., 2009). However, current prevalence is likely underestimated (Ginsberg et al., 2014), as ADHD in adults only recently became recognized (Asherson & Agnew-Blais, 2019; Franke et al., 2018). In childhood, ADHD is more common in males than females, with a 4:1 ratio observed in clinical studies, whereas sex differences in adults are minor (Faraone et al., 2015).

Observational studies have linked several potential risk factors to ADHD, including pre- and peri-natal factors, exposure to toxins and pollutants, dietary factors, and psychosocial adversities (Faraone et al., 2021). However, it remains unclear whether these factors are causal or may in part, or fully, be confounded by genetic factors. For example, smoking during pregnancy was postulated to be a causal risk factor for offspring ADHD, but family-based studies strongly suggest that the association is better explained by unmeasured familial confounding, where shared genetic factors increase both the risk of maternal smoking during pregnancy and offspring ADHD (Langley et al., 2012; Skoglund et al., 2014; Thapar et al., 2009). In contrast, putative risk factors such as low birth weight, low family income in early life, and severe psychosocial deprivation, show evidence of associations with ADHD even after

accounting for shared familial factors (Hultman et al., 2007; Larsson et al., 2014; Stevens et al., 2008).

ADHD is frequently comorbid with other psychiatric and somatic disorders throughout the lifespan, however the pattern of comorbidity changes across development (Franke et al., 2018). The most prevalent childhood-onset psychiatric comorbidities are other NDDs, such as autism spectrum disorders (ASD) and learning disorders, as well as externalizing conditions including oppositional defiant disorder (ODD) and conduct disorder (CD) (Franke et al., 2018; Giacobini et al., 2018; Taurines et al., 2010). Mood and anxiety disorders are common comorbidities across the lifespan, (Giacobini et al., 2018; Taurines et al., 2010) while substance use disorders (SUD) and personality disorders become more prevalent during adulthood (Franke et al., 2018; Taurines et al., 2010). A recent systematic review concluded that obesity, sleep disorders, and asthma are well-documented somatic comorbidities of ADHD in adulthood (Instanes et al., 2018). Current research also supports an increased risk of diabetes, hypertension, certain autoimmune and inflammatory disorders, infections, migraine, and epilepsy in children, adolescents and adults with ADHD (Akmatov et al., 2019; Bertelsen et al., 2016; Chen et al., 2018; Cortese et al., 2018; Hegvik et al., 2018; Nielsen et al., 2017; Salem et al., 2018). Increased mortality rates in ADHD have been reported in studies based on nation-wide register data in Denmark and Sweden. Although the observed absolute risk was small (0.3-0.5%), the relative risk of premature death in ADHD was found to be substantially higher than in the general population and appeared largely explained by unintentional injuries and suicide (Dalsgaard et al., 2015; Sun et al., 2019). Notably, treatment can reduce the risk of many negative outcomes associated with ADHD (Faraone et al., 2021).

Quantitative genetic studies of ADHD

Quantitative genetic research (e.g., family and twin studies) provides convincing evidence that genetic factors are important in ADHD (Faraone & Larsson, 2018). Early family studies found that first-degree relatives of children with ADHD had 4-to-5-fold higher risk of ADHD, compared to relatives of controls (Biederman et al., 1992; Faraone et al., 2000). Such findings were recently extended in a large population-based register study (N=1,656,943), showing that full-siblings of individuals with clinically-diagnosed ADHD had an 8-fold increased risk of ADHD. Notably, the risk of ADHD in monozygotic (MZ) twins was increased 70-fold, whereas the risk in dizygotic (DZ) twins was no higher than in full-siblings (Chen et al., 2017). The greatly increased ADHD risk in MZ twins, who are genetically identical, compared to DZ twins, who share on average 50% of their segregating genes, is a well-replicated finding. Meta-analyses of twin studies (with the largest including 75 studies and 166,826 twin pairs) converge on heritability (h^2) estimates of 70-80% and provide limited evidence for shared

family environmental contributions (Burt, 2009; Nikolas & Burt, 2010; Polderman et al., 2015). Meta-analyses also suggest that heritability is similar for inattentive and hyperactive/impulsive symptom dimensions, with 50-80% of genetic influences shared across dimensions. (Nikolas & Burt, 2010). Although family studies have found ADHD risk to be somewhat higher in relatives of females with ADHD, compared to relatives of affected males (Faraone et al., 2000; Martin et al., 2018; Taylor et al., 2016), more than two decades of twin studies have provided limited support for differential heritability of ADHD by sex (Polderman et al., 2015).

It should be noted that the majority of twin studies rely on North American and European samples. In a meta-analysis spanning 50 years of twin research (2,748 studies, 17,804 traits), less than 6% of studies were based on South American, African or Asian samples (Polderman et al., 2015). Thus, many conclusions from twin research may not extend to other populations. For example, a recent study of ADHD traits in Chinese adolescent twins found smaller genetic and larger shared environmental influences than previously reported in Western populations (Zheng et al., 2020), highlighting the necessity of collecting globally representative samples and suggesting that the contribution of environmental influences to ADHD may vary by societal/contextual factors.

Estimates from twin studies are also moderated by factors such as age and assessment method (Freitag et al., 2010). For example, in contrast to the stable and high heritability of ADHD found in meta-analyses of twin studies across childhood and early adolescence (Bergen et al., 2007), considerably lower estimates (30-54%) have been reported in adults (Brikell et al., 2015; Dick et al., 2005; Ehringer et al., 2006). Such differences appear to be partly driven by rater effects, with studies relying on self-ratings or different raters within a twin pair showing lower heritability (30-40%), compared to studies relying on a single rater (Kan et al., 2013, 2014; Merwood et al., 2013). When estimated from multiple informants or clinical diagnoses the reported heritability of ADHD is high (70-80%), independent of age (Brikell et al., 2015). Measurement can also impact heritability estimates (Freitag et al., 2010). Most ADHD scales only assess the negative end of the ADHD symptom distribution, leading to potential contrast effects (i.e. exaggerated differences between twins) and skewed symptom distributions, which may artificially inflate heritability and hamper detection of shared environmental effects (Derks et al., 2004). Twin studies using scales that assess the full continuum of ADHD symptoms may be less affected by contrast effects, while the evidence for better capturing the shared environment is mixed (Ebejer et al., 2015; Hay et al., 2007; Peng et al., 2016; Polderman et al., 2007).

Notwithstanding these methodological considerations, a large body of twin research has informed our conceptualization of ADHD in numerous ways. Several twin studies suggest that the development of ADHD is influenced by both stable genetic factors and the emergence of

new genetic factors from childhood to adulthood (Chang et al., 2013; Kuntsi et al., 2005; Larsson et al., 2006; Rietveld et al., 2004). For example, a longitudinal assessment of 8,395 8-16 year old twins showed that while both baseline symptoms and the change in hyperactive/impulsive symptoms over time were largely explained by genetic factors (90% and 81% h^2 respectively), only 40% of the genetic factors were shared between the two timepoints (Pingault et al., 2015). Twin studies also provided early evidence that ADHD is best viewed as the extreme end of a continuum of traits in the general population, by showing evidence for a strong genetic link between ADHD symptoms above a diagnostic threshold and subthreshold symptoms in the general population (Larsson et al., 2012; Levy et al., 1997). Moreover, a recent study of nearly 28,000 twins estimated the genetic correlation (r_g) between clinically-diagnosed ADHD and parent-rated symptoms at 0.56 and reported that 89% of this association could be attributed to genetic factors (Taylor et al., 2019). Twin and family studies have also elucidated the etiology underlying several cognitive and neurobiological features associated with ADHD (for reviews on current understanding of the neurobiology of ADHD, see (Faraone et al., 2021; Miranda et al., 2020)). ADHD or ADHD traits share genetic factors with various executive functions such as reaction time variability and response inhibition (Crosbie et al., 2013; Kuntsi et al., 2010, 2014; Michelini et al., 2021; Tye et al., 2011) as well as brain-based electroencephalographic (EEG) measures (McLoughlin et al., 2014; Michelini et al., 2021; Tye et al., 2011, 2012, 2014). Also, there is some evidence that MZ twins discordant for ADHD show subtle differences in various brain metrics, including total caudate volume (Tistarelli et al., 2020) and that unaffected siblings of ADHD cases show structural brain differences intermediate to those observed in cases and controls (Bralten et al., 2016; Greven et al., 2015). Together these studies support the brain-based, neurodevelopmental etiology of ADHD and that genetic factors which underpin clinically relevant ADHD are largely the same as those influencing variation in ADHD population traits.

Twin and family studies have also unequivocally demonstrated that comorbidity in ADHD is partly explained by genetic factors shared with other disorders (see **Table 1**), as highlighted by recent reviews (Andersson et al., 2020; Tistarelli et al., 2020). Among childhood-onset disorders, most research has focused on ASD and ODD/CD, which both show considerable genetic overlap with ADHD (Andersson et al., 2020; Tistarelli et al., 2020). ODD/CD traits appear more strongly genetically correlated with hyperactivity/impulsivity (Hur, 2015; Wood et al., 2009), whereas learning difficulties appear more closely genetically linked with inattentive symptoms (Greven et al., 2011, 2014; Liu et al., 2019; Wadsworth et al., 2015). Twin studies of the association between ADHD with anxiety and depression indicate moderate genetic correlations reported as early as preschool (Chen et al., 2016; Cole et al., 2009; Michelini et al., 2015; Rydell et al., 2017). Among later onset comorbidities, quantitative genetic research

shows clear genetic links with substance misuse (Capusan et al., 2015; Derks et al., 2014; Edwards & Kendler, 2012; Skoglund et al., 2015). While there is less research for eating disorders, bipolar disorder and schizophrenia, available evidence does support a genetic overlap with ADHD (Capusan et al., 2017; Larsson et al., 2013; Song et al., 2015; Yao et al., 2019). In a meta-analysis of 31 independent twin studies, genetic correlations between ADHD and externalizing (0.49 [0.37–0.61]), internalizing (0.50 [0.39–0.69]), and neurodevelopmental (0.56 [0.47–0.66]) traits were of similar magnitude and largely consistent across age, measurement scales and raters (Andersson et al., 2020). Further, emerging evidence from multivariate twin and family studies suggests that ADHD loads strongly onto a general genetic psychopathology factor. After accounting for this general factor, ADHD remains genetically associated with a specific neurodevelopmental factor, while genetic links to externalizing and internalizing psychopathology are considerably attenuated, supporting the neurodevelopmental etiology of ADHD (Du Rietz et al., 2020; Lahey et al., 2011; Pettersson et al., 2013, 2015). Although twin and family studies addressing non-psychiatric comorbidity in ADHD are sparse, genetic correlations with somatic/neurological conditions such as asthma, epilepsy and obesity (twin $r_g=0.20-0.30$) are weaker than between ADHD and other psychiatric disorders (Brikell et al., 2018; Chen et al., 2019; Holmberg et al., 2015; Mogensen et al., 2011).

In summary, quantitative genetic studies have demonstrated that the heritability of ADHD is high and of similar magnitude across ADHD symptom dimensions, severity, sex and development, and that genetic liability for ADHD is shared with neurodevelopmental, psychiatric, and somatic comorbidities.

Molecular genetic studies of ADHD

Advances in genotyping technology in the past two decades have greatly improved our understanding of the genetic architecture of ADHD (i.e. the number, allele frequencies and locations of risk factors). Initial molecular genetic studies of ADHD focused on hypothesis-driven candidate genes and linkage approaches, with limited replication of results (Hawi et al., 2015), similarly to other psychiatric disorders (Sullivan, 2017). This literature and potential candidates that emerged (e.g. dopaminergic genes) has been extensively reviewed previously (e.g. (Faraone & Larsson, 2018; Thapar et al., 2007)) and this review focuses on more recent genome-wide studies. Initial ADHD GWAS (Neale et al., 2008, 2010; Stergiakouli et al., 2012) demonstrated important insights into the polygenic architecture of ADHD, but were underpowered to detect common risk variants at the established genome-wide significance level ($p < 5 \times 10^{-8}$). The first common genetic variants robustly associated with ADHD were recently identified through a large international collaborative effort led by the Psychiatric Genomics Consortium (PGC) and the Lundbeck Foundation Initiative for Integrative Psychiatric

Research (iPSYCH) (Demontis et al., 2019). This GWAS of 20,183 individuals with ADHD and 35,191 controls implicated variants in 12 independent regions across the genome, many of which are located in/near genes involved in neurodevelopmental processes (e.g. *DUSP6* and *FOXP2*); see **Figure 1**. There was little evidence to support a role for the most widely-studied candidate genes. These GWAS results showed partial replication (with significant sign concordance) using 3 different independent cohorts with self-reported ADHD or ADHD traits. Although the top loci each explained only a small proportion of phenotypic variance, the total estimated contribution from common risk alleles to variance in ADHD (i.e. the SNP-based heritability) was 21.6% (SE=0.014), indicating that with growing sample sizes additional common risk variants will be identified. Efforts are ongoing to increase the sample size for the next international GWAS meta-analysis to confirm these findings and discover more loci. Characterization of the genomic signal revealed that ADHD risk variants impact on regulatory elements specific to the central nervous system and located in evolutionarily-constrained genomic regions, i.e. genes that are particularly intolerant to loss-of-function mutations. Furthermore, ADHD genetic risk variants are shared with those implicated in lower total intracranial volume ($r_g=-0.23$, SE=0.06) (Klein et al., 2019), further supporting its classification as a brain-based disorder. Although the latest GWAS represents a significant advance in our understanding of ADHD common variant genetics, one important limitation is that 96% of the individuals included are of European ancestry and data are lacking for individuals from other ancestries (Demontis et al., 2019). The genetic correlation between ADHD in individuals of Han Chinese and European ancestries was previously estimated as 0.39 (SE=0.15) (Yang et al., 2013), suggesting that only a portion of common variants will extend to non-European ancestries.

Other recent GWAS, focusing on different definitions or groups of individuals with ADHD, demonstrate high genetic correlations between: a) ADHD in childhood and persistent ADHD in adulthood ($r_g=0.81$, SE=0.11) (Rovira et al., 2020), b) ADHD population traits and clinical diagnosis ($r_g=0.97$, SE=0.21) (Demontis et al., 2019), and c) ADHD in males and females ($r_g=1.22$, SE=0.13) (Martin et al., 2018). Notably, although very high, the genetic correlation between child and adult ADHD is not as high as across childhood ADHD cohorts (Rovira et al., 2020). Although the genetic correlation is also moderately high ($r_g=0.65$, SE=0.11) between clinically-diagnosed ADHD and self-reported ADHD in a population sample of adults taking part in personal genetic testing via 23andMe, there are also clearly phenotypic differences (e.g. in educational attainment) across these definitions of ADHD (Demontis et al., 2019).

Genetic correlations have also been seen with numerous additional phenotypes (see **Table 1**). Among psychiatric disorders, the strongest genetic correlations are with major depressive

disorder and ASD, with more modest genetic correlations with other disorders (e.g. schizophrenia and bipolar disorder) (Cross-Disorder Group of the PGC., 2019). Genomic SEM shows that ADHD clusters with ASD, as well as Tourette syndrome or aggression (Cross-Disorder Group of the PGC., 2019; Waldman et al., 2020). ADHD is also strongly genetic correlated with lower age at birth of first child ($r_g=-0.61$, $SE=0.04$), lower educational attainment ($r_g=-0.53$, $SE=0.03$), smoking ($r_g=0.48$, $SE=0.06$), insomnia ($r_g=0.42$, $SE=0.06$), and higher body mass index ($r_g=0.26$, $SE=0.03$) (Demontis et al., 2019). Recent studies also suggest that the dopaminergic system may be a shared mechanism underlying ADHD and obesity, sleep problems, asthma and migraine (Instanes et al., 2018; Mota et al., 2020).

Polygenic risk score (PRS) analyses have yielded significant insights into ADHD. Although PRS explain only a small proportion (~5.5%) of the phenotypic variance of ADHD case status (Demontis et al., 2019), they are a useful tool for hypothesis testing (e.g. testing association between individual genetic risk burden and clinical features, comorbidity, and long-term outcomes, as well as mediation or gene-by-environment interaction). In general, PRS studies support twin and genome-wide correlation analyses, demonstrating shared genetic risks across ADHD diagnosis and population traits, measured using different instruments, raters (parent- vs self-report) and at different ages (Burton et al., 2019; Groen-Blokhuis et al., 2014; Martin et al., 2014; Riglin et al., 2020; Ronald et al., 2021), as well as many other psychiatric and brain-based traits, including autistic symptoms, cognitive difficulties, depression, anxiety, risk-taking, alcohol use, and smoking (Du Rietz et al., 2018; Martin et al., 2018; Ronald et al., 2021). In the general population, ADHD-PRS capture a wide range of psychiatric outcomes, which can be partly summarized by a general factor of childhood psychopathology (Brikell et al., 2018; Riglin et al., 2019).

Studies have also examined the impact of ADHD-PRS on outcomes in clinical ADHD samples. Collectively, they suggest that PRS do not just capture risk for ADHD diagnosis but may also be a marker of phenotypic severity in individuals with ADHD, showing association with a wide range of comorbid phenotypes, including CD (Demontis et al., 2021; Hamshere et al., 2013), irritability/emotional dysregulation (Nigg et al., 2020; Riglin et al., 2017), severity of clinical profile (Vuijk et al., 2019), executive function difficulties (working memory, inhibitory control, response variability) (Chang et al., 2020; Nigg et al., 2018; Vainieri et al., 2021), and SUDs (i.e. alcohol and cannabis use disorders) (Wimberley et al., 2020). PRS studies also suggest that late-onset ADHD may differ in etiology from childhood-onset ADHD, but studies so far are inconclusive because of small sample sizes (Asherson & Agnew-Blais, 2019). The largest-to-date PRS study of sex differences found that males and females with ADHD do not differ significantly in terms of polygenic burden (Martin et al., 2018).

In addition to the role of common (>1% minor allele frequency) genetic risk variants in ADHD described above, rare variants (<1% frequency) also contribute to ADHD. Studies of rare chromosomal alterations indicate that ADHD is frequently associated with known genetic syndromes (e.g. 22q11.2 deletion syndrome and Williams syndrome) (Scerif & Baker, 2015). ADHD is also associated more generally with large, rare deletions or duplications of DNA, known as copy number variants (CNVs) (Williams et al., 2010, 2012), particularly those that have previously been implicated in other NDDs (Gudmundsson et al., 2019); see **Figure 1**. There is also preliminary evidence implicating *de novo* CNVs, i.e. variants not inherited from biological parents (Lionel et al., 2011; Martin et al., 2020). Evidence is currently mixed as to whether large, rare CNVs are associated with traits of ADHD in the general population (Guyatt et al., 2018; Martin et al., 2019). Results indicate that previously implicated neurodevelopmental CNVs are associated with diagnosed ADHD, whereas other large, rare CNV regions are implicated in more broadly-defined ADHD symptoms (Martin et al., 2019). Although the evidence collectively implicates these large structural variants in ADHD, further work is needed to uncover the specific genetic risks and biological mechanisms that are being disrupted. To this end, a recent paper integrated data from 11 published studies of CNVs in ADHD with existing biological databases and identified a credible list of 26 high confidence genes, enriched for expression in brain tissue and showing converging evidence from common variant analyses, which should be prioritized for further investigation (Harich et al., 2020).

A recent large exome sequencing study of 4,378 individuals with ADHD implicated rare protein-truncating variants intolerant to mutation as being important for ADHD, but without identifying specific genes or mutations (Satterstrom et al., 2019). Interestingly, this group of very rare variants was indistinguishable from variants implicated in ASD. Thus, evidence from quantitative genetics, together with common and rare variant studies, demonstrates that genetic risks implicated in ADHD are also implicated in other neurodevelopmental and psychiatric phenotypes. Large whole-genome sequencing studies of ADHD are currently lacking, but as samples grow, sequencing will enable examination of the role of structural variants that are not captured by microarrays (Troost et al., 2020), such as variable number tandem repeats (VNTRs), which have shown promise in candidate gene work (e.g. the DRD4 7-repeat) (Faraone et al., 2001; Li et al., 2006; Nikolaidis & Gray, 2010).

Implications & future directions

There is a high degree of convergence from quantitative and molecular genetic approaches, yielding important insights into ADHD. **Table 2** summarizes these robust findings based on large-scale studies, meta-analyses and reviews. The successes of ADHD genome-wide approaches in the last few years have paved the way for further discovery and understanding of the genetic architecture of ADHD, while validating its categorisation as a brain-based NDD.

Quantitative and molecular genetic research clearly demonstrates that ADHD diagnosis represents the extreme end of continuously distributed symptoms in the population. This poses a challenge for defining ADHD, with further work needed to determine how and when ADHD symptoms lead to impairment and the need for clinical intervention. However, this finding also highlights an opportunity to leverage already existing studies of ADHD symptoms in large population samples to understand the genetics of ADHD, with ongoing work to this end (e.g. EAGLE consortium (Middeldorp et al., 2016), Spit for Science (Burton et al., 2019)).

There are many unresolved issues in ADHD genetics that will require larger sample sizes. For example, do shared genetic risks between ADHD and comorbid conditions (**Table 1**) (Anttila et al., 2017; Demontis et al., 2019) result from shared phenotypic factors (e.g., cognitive deficits) and/or is an additional trait contributing to both phenotypes? Which (if any) specific genetic risk factors are unique to ADHD? Analyses of secondary phenotypes such as dimensional behavioural and cognitive traits may help answer some of these questions. Other unresolved issues include determining why males are more likely than females to be diagnosed with ADHD during childhood/adolescence, understanding the influence of genetic risks on persistence and remittance patterns and whether late-diagnosed ADHD is biologically the same condition as early-onset ADHD. Identifying causal risk factors for ADHD and establishing the mechanisms leading to negative outcomes has proven challenging and has primarily been done using twin and family data thus far. However, rapid advances in methods using measured genetic variants to evaluate causality (e.g. Mendelian randomization) (Davey Smith & Hemani, 2014) offer future research opportunities for ADHD. Mendelian randomization approaches have so far been used to study putative causal relationships between ADHD and phenotypes including SUD, depression, educational attainment, childhood obesity and coronary artery disease, with results supporting a potentially causal effect of ADHD genetic risk on these outcomes, with limited evidence for the reverse relationship (Leppert et al., 2019; Riglin et al., 2020; Treur et al., 2019). More work is also needed to clarify the role of environmental risk factors and gene-by-environment interactions in ADHD. This will be particularly important when genetic studies begin the much-needed inclusion of diverse ancestries in order to ensure equity of research outcomes and clinical benefit in ADHD, but also to improve prediction accuracy and understanding of biology (Peterson et al., 2019). Environmental variables will be particularly relevant in this context, given interplay of ethnocultural and environmental risk factors for mental health. Large-scale, well-powered gene-by-environment studies including genetically diverse samples will be an important step in identifying novel paths to prevention and treatment.

Emerging findings from studies of rare variants hold promise for future implementation of genetic testing for a subgroup of individuals with ADHD. Genetic testing is occasionally offered

to families with children who have severe intellectual disability or ASD. Given that some of the same rare CNV loci and genetic mutations have been implicated in ADHD (Gudmundsson et al., 2019; Satterstrom et al., 2019), genetic testing could offer insights and helpful clinical information to families with children with ADHD, if appropriately combined with genetic counselling. However, the complexity of ADHD etiology warrants caution in interpretation of genetic results. Also, given how common ADHD is, further research is needed to identify a subgroup of individuals who might benefit most from targeted genetic testing and counselling.

A major goal of genomic research is to understand the underlying biology of a disorder to develop new therapeutics and improve outcomes. Existing data points to possible biological mechanisms ([Faraone et al. 2015](#)) but large-scale GWAS and forthcoming whole-genome sequence data will undoubtedly aid in this endeavour. For example, the latest ADHD GWAS (Demontis et al., 2019) implicated *DUSP6*, a gene that may play a role in synaptic dopamine levels, which are targeted by stimulant medication; further investigation of this gene is therefore warranted. As more ADHD risk loci are discovered, methods will be required to parse out the functional variants in associated loci and functionally characterize their effects. Various types of quantitative trait loci (expression, protein, methylation) as well as gene expression data will be essential to these efforts (Breen et al., 2016). Capitalizing on approaches that can mine possible therapeutic targets from genome-wide data has already proved promising for ADHD (Hegvik et al., 2019). In addition to identifying novel targets for therapeutics, understanding the role of genetic variation in treatment response to current medications is urgently needed (Jensen et al., 2007). Thus far, pharmacogenomics of treatment response in ADHD have had little success and progress has been hampered by limited sample sizes. Only two small ($n < 200$) GWAS of methylphenidate response have been published so far (Mick et al., 2008; Payerols et al., 2018). There is preliminary evidence that ADHD-PRS may be associated with response to stimulant treatment (Zhong et al., 2020), however this needs replication. Given that ADHD medication treatment has been associated with positive effects across a range of outcomes (Chang et al., 2019), large-scale research efforts aimed at understanding the biological underpinnings of treatment efficacy and tolerance are urgently needed.

Conclusion

Following on from decades of quantitative and early molecular genetic (e.g. linkage) studies, recent advances in genotyping technology and bioinformatics methods have rapidly increased understanding of the genetic risk factors for ADHD in the last 5-10 years. In the near future, as larger and more diverse samples become available with the facilitation of large consortia like the PGC and growing national biobanks linked to health records, an increasing number of loci associated with ADHD will undoubtedly be detected. Implementation of state-of-the-art

bioinformatics will allow us to pinpoint causal variants and understand causal relationships between comorbid conditions and risk factors. These are necessary steps towards understanding the biology of ADHD and developing better interventions and treatments to improve the outcomes for individuals and their families.

Tables & Figures

Table 1: A summary of the evidence for shared genetics risks between ADHD and common comorbid psychiatric and neurodevelopmental phenotypes

Phenotype	Twin & family genetic research*	Molecular genetic research**
Anxiety disorders	Twin $r_g=0.45$ to 0.58^1	LDSC r_g not significantly different from zero after multiple testing correction ¹⁴
Autism spectrum disorder	Twin $r_g=0.59$ (0.49–0.69) ^{***2}	LDSC $r_g=0.37$ (0.05) ¹⁵ ; overlap of rare CNVs & PTVs ^{16,17}
Bipolar disorder	Twin $r_g=0.33$ (0.32-0.39) ³	LDSC $r_g=0.14$ (0.04) ¹⁵
Depression, major depressive disorder	Twin $r_g=0.34$ to 0.77^1	LDSC $r_g=0.44$ (0.03) ¹⁵
Eating disorders (ED)	Twin $r_g=0.14$ (0.0-0.22) with anorexia ⁴ Twin $r_g=0.28$ (0.20-0.3) with bulimia ⁴ Twin $r_g = 0.35$ (0.25-0.46) with binge eating disorder ⁵	LDSC $r_g=-0.26$ (0.06) with anorexia nervosa ¹⁵ ; ADHD-PRS positively associated with ED symptoms in children in the general population ¹⁸
Intellectual disability (ID)	91% of phenotypic correlation with ID due to shared genetic factors in quantitative genetic modelling of family data ⁶	LDSC $r_g=0.73$ (0.29) ¹⁹ ; overlap of rare CNVs ¹⁷
Language and learning difficulties	Twin $r_g=0.42$ (0.35-0.49) ^{***7} with reading difficulties ⁷ Twin $r_g=-0.41$ to -0.22 with maths ability ⁸	ADHD-PRS associated with lower language grades, difficulties with reading & spelling, and dyslexia ²⁰⁻²³
Motor difficulties, developmental coordination disorder (DCD), dyspraxia	Twin $r_g=0.99$ (0.69-1.00) with DCD ⁹	ADHD-PRS not associated with general neuromotor measures in infancy (except senses) ²⁴ ; Studies of DCD are lacking
Obsessive compulsive disorder (OCD)	Twin $r_g=0.24$ ¹⁰ Sibling $r_g= 0.63$ (SE=0.12) ¹¹ Heritable latent factor underlying ADHD, OCD, and tics ¹⁰	LDSC r_g not significantly different from zero after multiple testing correction ¹⁵
Oppositional defiant (ODD) and conduct disorder (CD), aggression	Twin $r_g=0.15$ to 0.76 with ODD ² Twin $r_g=0.17$ to 0.70 with CD ²	LDSC $r_g=0.74$ (0.18) between ADHD and childhood aggression ²⁵

	Heritable latent factor underlying ADHD, ODD, and CD ¹²	
Schizophrenia	No twin studies: 1st degree relatives OR=1.17-2.22 2nd degree relatives OR=1.06-1.11 ¹³	LDSC $r_g=0.13$ (0.03) ¹⁵ ; overlap of rare CNVs ^{16,17}
Substance use disorders	Twin $r_g=0.33$ to 0.44 with alcohol dependence ²	LDSC $r_g=0.44$ (0.10) with alcohol dependence ²⁶
Tic disorders, Tourette syndrome	Twin $r_g= 1.00$ (0.63-1.00) ⁹ , 0.31 ¹⁰ Sibling $r_g= 0.26$ (SE=0.21) ¹¹	LDSC $r_g=0.27$ (0.06) ¹⁵

CNVs: copy number variants; LDSC: linkage disequilibrium score correlation; PRS: polygenic risk scores; r_g : twin or SNP-based genetic correlation; OR: odds ratio; SE: standard error; CIs: confidence intervals.

* A note about the evidence presented for twin/family genetic associations: results of genetic correlation are obtained from quantitative genetic modelling in twin- and/or extended family studies. Genetic correlations from published meta-analysis are presented preferentially, followed by ranges of estimates obtained from prior published reviews. Otherwise single study estimates are presented with 95%CIs/SE, where available. When no twin studies are available, associations from large-scale family co-aggregation studies including multiple relative types are presented.

** A note about the evidence presented for common variant associations: results of the largest available genetic correlation analyses using linkage disequilibrium score correlation (LDSC) are presented preferentially and where such analyses are not available, then available PRS results are summarized.

*** Meta-analytic estimate(95% CI), estimated in the cited study.

References:

- ¹ (Martin, Taylor, et al., 2018)
- ² (Andersson et al., 2020)
- ³ (Song et al., 2015)
- ⁴ (Yao et al., 2019)
- ⁵ (Capusan et al., 2017)
- ⁶ (Faraone et al., 2017)
- ⁷ (Daucourt et al., 2020)
- ⁸ (Greven et al., 2014)
- ⁹ (Lichtenstein et al., 2010)
- ¹⁰ (Pinto et al., 2016)
- ¹¹ (Mathews & Grados, 2011)
- ¹² (Tuvblad et al., 2009)
- ¹³ (Larsson et al., 2013)
- ¹⁴ (Purves et al., 2019)
- ¹⁵ (Cross-Disorder Group of the PGC., 2019)
- ¹⁶ (Williams et al., 2012)
- ¹⁷ (Gudmundsson et al., 2019)

- ¹⁸ (Yao et al., 2019)
- ¹⁹ (Niemi et al., 2018)
- ²⁰ (Rajagopal et al., 2020)
- ²¹ (Gialluisi et al., 2019)
- ²² (Verhoef et al., 2019)
- ²³ (Gialluisi et al., 2020)
- ²⁴ (Serdarevic et al., 2020)
- ²⁵ (Demontis et al., 2021)
- ²⁶ (Walters et al., 2018)

Table 2: A summary of robust converging findings from twin/family and molecular genetic ADHD research

Finding	Twin & family genetic evidence*	Molecular genetic evidence**
ADHD is highly heritable and polygenic	Twin-based $h^2 = 70-80\%$ ^{1,2,3}	Risk variants are distributed across the genome & allelic frequency. ¹⁷⁻¹⁹ Common variant SNP-based h^2 is 21.6% (SE=0.014). ¹⁷ Rare variants (CNVs & protein-truncating variants) are implicated. ^{18,19}
ADHD is a brain-based neurodevelopmental disorder	Strong twin/family r_g with other NDDs (e.g. ASD, ID, tics). ⁴ Twin r_g 0.30-0.80 with various EEG measures. ^{5,6,7} Some evidence that ADHD discordant twins show differences in caudate, right striatum and thalamus volume, and frontoparietal network activation. ⁸	ADHD risk SNPs and high confidence CNVs are expressed in central nervous system tissue. ^{17,20} Significant genetic correlation observed with intracranial volume ($r_g=-0.23$, SE=0.06). ²¹
Clinically diagnosed ADHD and population traits of ADHD share genetic risks	Strong genetic link between extreme and subthreshold variation in ADHD symptoms. ⁹ Twin $r_g = 0.56$ (0.53-0.59) between ICD-based ADHD and ADHD symptoms in the population. ¹⁰	Very high genetic correlation ($r_g=0.97$, SE=0.21) between diagnosed ADHD and ADHD population traits. ¹⁷ Rare CNVs are also associated with broadly-defined ADHD population traits. ²²
ADHD and comorbid conditions share genetic risks (see Table 1 for details)	Twin and family studies show significant genetic correlations across ADHD and numerous comorbid conditions, and the cross-disorder co-variance is often primarily attributable to a shared genetic factor. ^{4,9}	Significant genetic correlations or associations with PRS and rare variants for numerous disorders. ^{9,18}
Genetic factors are important for ADHD across development	h^2 in ADHD is high and stable across the lifespan. ¹¹ Age-to-age symptom stability is largely explained by genetic factors. ^{12,13}	High genetic correlation between ADHD in childhood and persistent ADHD in adulthood ($r_g=0.81$, SE=0.11). ²³

ADHD genetic risks are shared between males and females	Most twin and family studies do not find evidence for sex-specific genetic effects. ^{1,2,3}	Very high genetic correlation ($r_g=1.22$, $SE=0.13$) between male and female ADHD. ²⁴
Many 'environmental' risk factors for ADHD share genetic risks with ADHD	Association between smoking during pregnancy and offspring ADHD is genetically confounded. ^{14,15,16}	ADHD is genetically correlated with traits such as smoking ($r_g=0.48$, $SE=0.06$) and younger age at first birth of child ($r_g=-0.61$, $SE=0.04$). ¹⁷

Note: The studies highlighted in this table are based on large-scale data analyses, meta-analyses and other reviews, which collectively support this converging evidence from twin/family and molecular genetic studies. Although for some of these findings, individual studies may exist that do not support the finding, the majority of well-powered studies do converge to support the findings.

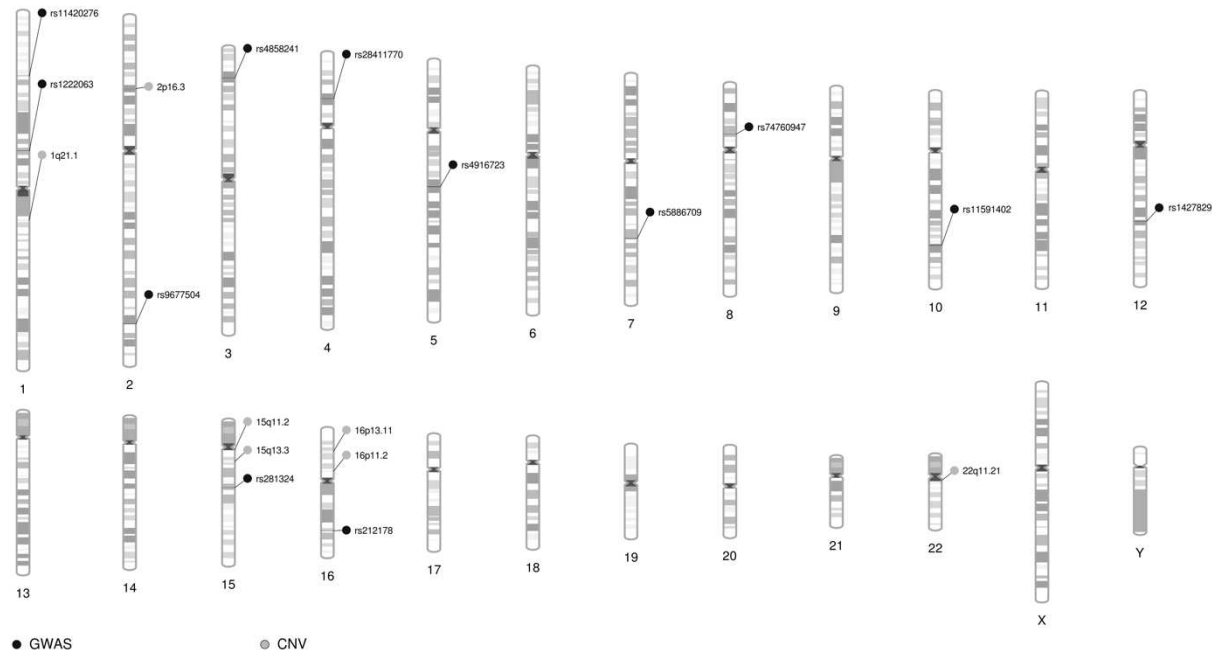
h^2 : twin or single nucleotide polymorphism (SNP)-based heritability; CNVs: copy number variants; PRS: polygenic risk scores; r_g : twin or SNP-based genetic correlation; ASD: autism spectrum disorder; EEG: electroencephalogram; ID: intellectual disability; NDDs: neurodevelopmental disorders.

References:

- ¹ (Faraone & Larsson, 2018)
- ² (Nikolas & Burt, 2010)
- ³ (Polderman et al., 2015)
- ⁴ (Andersson et al., 2020)
- ⁵ (McLoughlin et al., 2014)
- ⁶ (Tye et al., 2012)
- ⁷ (Tye et al., 2014)
- ⁸ (Tistarelli et al., 2020)
- ⁹ (Martin, Taylor, et al., 2018)
- ¹⁰ (Taylor et al., 2019)
- ¹¹ (Brikell et al., 2015)
- ¹² (Bergen et al., 2007)
- ¹³ (Chang et al., 2013)
- ¹⁴ (Thapar et al., 2009)
- ¹⁵ (Langley et al., 2012)
- ¹⁶ (Skoglund et al., 2014)
- ¹⁷ (Demontis et al., 2019)
- ¹⁸ (Gudmundsson et al., 2019)
- ¹⁹ (Satterstrom et al., 2019)
- ²⁰ (Harich et al., 2020)
- ²¹ (Klein et al., 2019)
- ²² (Martin et al., 2019)
- ²³ (Rovira et al., 2020)
- ²⁴ (Martin, Walters, et al., 2018)

Figure Legend

Figure 1: Locations of genomic loci robustly-associated with risk of ADHD diagnosis. GWAS: genome-wide association study; top variants from the largest ADHD GWAS (index SNPs are shown) from (Demontis et al., 2019). CNV: copy number variants implicated in ADHD, based on (Gudmundsson et al., 2019). Visualisation made using PhenoGram (Wolfe et al., 2013).



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Conflicts of Interest

All the authors report no conflicts of interest.

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