Genetics of Attention-Deficit Hyperactivity Disorder

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Contents

Abstract Attention-Deficit Hyperactivity Disorder (ADHD) has long been recognized as being a highly heritable condition and our understanding of the genetic contributions to ADHD has grown over the past few decades. This chapter will discuss the studies that have examined its heritability and the efforts to identify specific genetic risk-variants at the molecular genetic level. We outline the various techniques that have been used to characterize genetic contributions to ADHD,

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describing what we have learnt so far, what there is still to learn and the methodologies that can be used to further our knowledge. In doing so we will discuss research into rare and common genetic variants, polygenic risk scores, and gene–environment interplay, while also describing what genetic studies have revealed about the biological processes involved in ADHD and what they have taught us about the overlap between ADHD and other psychiatric and somatic disorders. Finally, we will discuss the strengths and limitations of the current methodologies and clinical implications of genetic research to date.

Keywords ADHD · Copy number variant · Genome-wide association study · Heritability · Polygenic risk score

Abbreviations

ADHD	Attention-deficit hyperactivity disorder
ASD	Autism spectrum disorder
CNV	Copy number variant
DNA	Deoxyribonucleic acid
DSM-5	Diagnostic and statistical manual of psychiatric disorders – fifth edition
EAGLE	EArly genetics and life course epidemiology (consortium)
EWAS	Epigenome-wide association studies
GWAS	Genome-wide association studies
GWEIS	Genome-wide environmental investigation studies
GxE	Gene–environment interactions
ICD	International classification of diseases
ID	Intellectual disability
iPSYCH	Lundbeck Foundation Initiative for Integrative Psychiatric Research
MR	Mendelian randomization
mRNA	Messenger ribonucleic acid
PGC	Psychiatric genomics consortium
PRS	Polygenic risk score
rGE	Gene environment correlations
SNP	Single nucleotide polymorphism
VCFS	Velo-cardio-facial syndrome

1 Overview

Like many other psychiatric disorders, Attention-Deficit Hyperactivity Disorder (ADHD) is heterogeneous and multifactorial in origin with multiple genetic and environmental factors contributing to the disorder. This chapter will review the contribution of genetic risks to ADHD, including both what we already know and

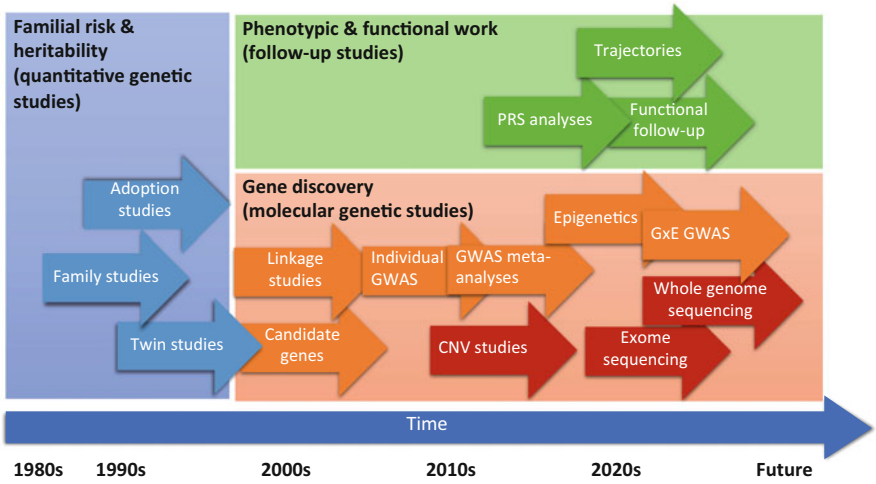

Fig. 1 A representation of an approximate timeline of genetic studies of ADHD. The left side of the arrows indicate the approximate time of the first studies that investigated ADHD genetics using the stated methods. The arrows indicate that these study types have continued to be used, or could return to use in future (e.g., candidate gene studies of specific identified genome-wide significant risk loci could be valuable in future). *GWAS* genome-wide association study, *CNV* copy number variant, *GxE* gene-by-environment interactions

the ways in which research is moving forward to identify additional genetic risks. We will briefly describe some of the different methodologies that are currently utilized to study the genetics of ADHD and highlight how these methods have helped our understanding of its etiology, as well as what our understanding of the genetics of ADHD indicates about the biological processes relevant to the disorder. Figure 1 describes the chronology of the different methodological techniques used in these investigations.

As has been highlighted throughout this book, ADHD is phenotypically heterogenous and this heterogeneity is also relevant to the genetics of ADHD. Thus, we will discuss not only our understanding of the genetics of ADHD, in general, but also how this may differ when looking across development into adulthood, the overlap with other psychiatric and somatic disorders as well as factors such as sex differences. Further, we shall briefly consider the interplay between genetic and environmental risks for ADHD and how these need to be considered together for a fuller understanding, before discussing the implications of our current knowledge of ADHD for clinical practice.

2 Conceptualizing ADHD as a Trait

For clinical purposes, it is helpful to view ADHD as a dichotomous yes/no diagnosis because clinical decisions, such as whether or not to initiate medication, are categorical. However, genetic findings converge with epidemiological evidence in suggesting that ADHD diagnosis lies at the extreme end of a population continuum or trait. Twin-studies show that there is no discontinuity in heritability along the ADHD continuum: i.e., heritability in those with high ADHD symptom scores appears to be the same as across the continuum of ADHD as a trait in the general population (Levy et al. 1997). However, one twin-study suggested that there may be discontinuity for those with extremely low ADHD scores (Greven et al. 2016), although further work is needed to confirm these results. Molecular genetic findings also support the idea that ADHD diagnosis lies at the extreme of a population continuum (Thapar 2018). ADHD polygenic risk-scores derived from ADHD case/control genome-wide association studies (GWAS; methods detailed later) are associated with ADHD trait scores in the general population (Taylor et al. 2019). The most recent, largest ADHD GWAS to date estimated the genetic correlation (r_g) between ADHD diagnosis and a meta-analysis of ADHD trait scores in the general population as 0.94 (Demontis et al. 2019), indicating that common genetic variants strongly overlap across these definitions of ADHD.

3 Heritability of ADHD

For a number of decades there has been strong evidence from quantitative genetic studies, which study similarities between related individuals to infer genetic contributions, rather than directly assessing DNA at a molecular level, that ADHD is a highly familial and heritable disorder. As can be seen in Fig. 1, such insights were first observed using family studies, which compared the rates of ADHD between first-degree relatives of those with the disorder and unrelated controls. Family studies have demonstrated familial aggregation (running in families, possibly due to genetic factors, possibly due to shared environment) of ADHD with relative risks between 4.0 and 5.4% among first-degree relatives of those affected (Thapar et al. 2007). Adoption studies have shown that this familial transmission is explained predominantly by genetic factors, as adopted children are more similar to their biological parents, to whom they are genetically related but do not share a rearing environment, compared to their adoptive parents with whom they share an environment, but not genetics (Cantwell 1975; Cunningham et al. 1975; Sprich et al. 2000). Numerous twin-studies, which quantify the proportion of phenotypic variance attributable to genetic, shared, and non-shared environmental factors, have also confirmed a significant contribution of genetic factors to ADHD. Meta-analyses estimate heritability between 70 and 80% (Nikolas and Burt 2010), with the remaining variance explained mainly by non-shared environmental effects

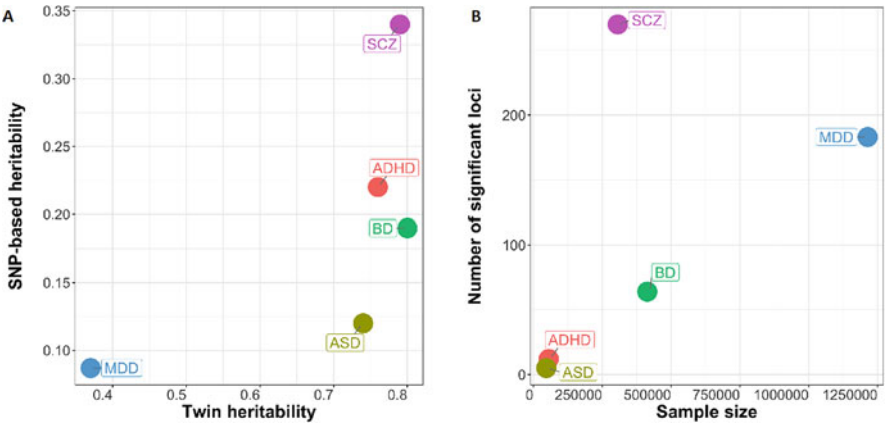

Fig. 2 A comparison of: (**a**) heritability estimates based on twin studies and genome-wide association studies (GWAS), as well as (**b**) the number of significant loci identified by GWAS, given available sample sizes, for ADHD, schizophrenia (SCZ), bipolar disorder (BD), major depressive disorder (MDD), and autism spectrum disorder (ASD). The twin heritability estimates are obtained from meta-analyses (references: Sullivan et al. 2000; Lee et al. 2019; McGuffin et al. 2003; Nikolas and Burt 2010; Tick et al. 2016; Hilker et al. 2018). The estimates of single nucleotide polymorphism (SNP)-based heritability and number of risk loci are obtained from the largest available GWAS for each study (references: Grove et al. 2019; Demontis et al. 2019; Levey et al. 2020; Mullins et al. 2020; Schizophrenia Working Group of the Psychiatric Genomics Consortium 2020)

(environmental factors that make twins more dissimilar, stochastic effects and error variance) and only a small proportion of the variance due to shared environmental factors (Nikolas and Burt 2010).

As illustrated in Fig. 2a, this demonstrates that ADHD has high heritability similar to other neurodevelopmental and psychiatric disorders, such as autism spectrum disorder (ASD), schizophrenia, and bipolar disorder, while being significantly more heritable than other more common mental health disorders, such as major depressive disorder. While these quantitative genetic methods are extremely useful for helping to understand the contribution of genetics at the population level and, as can be seen throughout this chapter, to help elucidate the genetic architecture around the phenotypic presentation of ADHD and its overlap with other disorders, they infer genetic (and environmental) contributions as a whole, rather than identifying specific risk-factors at the individual level. For such investigation, researchers have moved to using molecular genetic techniques. As can be seen in Fig. 1, such research has addressed two broad categories of genetic variants: rare variants (represented in red in Fig. 1) that have a frequency of $<1\%$ in the population and more common frequency variants (represented in orange). We will first discuss research which has looked at rare variants.

4 Rare Variants

There are numerous developmental syndromes that are caused by rare chromosomal mutations, such as aneuploidies and microdeletions. These are characterized by increased risk for a variety of health problems, in terms of neurodevelopment (e.g., intellectual disability (ID)), as well as general mental and physical health (e.g., congenital malformations and cardiac problems). Some of these rare chromosomal mutations are also associated with risk of ADHD and include, for example: Fragile X syndrome, Tuberous Sclerosis complex, Smith-Magenis syndrome, Velocardio-facial syndrome (VCFS), Prader-Willi syndrome, Turner syndrome, Klinefelter syndrome, and Williams-Beuren syndrome (Lo-Castro et al. 2011; Scerif and Baker 2015). In addition to these well-known rare syndromes, newer syndromes are being characterized (e.g., 16p11.2 duplication/deletion syndromes) and have also been linked to ADHD risk (Niarchou et al. 2019).

Beyond these specific syndromes, large rare deletions and duplications of segments of DNA, known as copy number variants (CNVs), have been found to be associated with risk of ADHD across many studies (Williams et al. 2010, 2012). In particular, CNVs spanning genomic regions that have previously been implicated in other neurodevelopmental and psychiatric disorders are associated with ADHD risk (Gudmundsson et al. 2019). Large, rare CNVs in other regions of the genome (i.e., those not robustly linked to neurodevelopmental disorders) are also associated with more broadly-defined, undiagnosed ADHD and other neurodevelopmental problems that are assessed using parental ratings (Martin et al. 2018a). Rare CNVs can be inherited from biological parents or occur de novo in the germline; the latter are on average more deleterious (Lionel et al. 2011; Martin et al. 2020).

Given the large sizes of CNV loci, which are often greater than 100,000 or even 500,000 base-pairs in length, these duplications or deletions can span dozens or even hundreds of genes, follow-up work is needed to identify the causal genes and understand the underlying biology. Several studies have conducted pathway or gene set analyses and determined that CNVs implicated in ADHD impact on biological pathways, including those related to ion channels, cholesterol metabolism, glutamate receptors, and central nervous system development (Elia et al. 2012; Thapar et al. 2016). Also, CNVs implicated in ADHD affect some of the same gene sets that have been implicated in ASD, as well as genes that have been implicated in schizophrenia (Martin et al. 2014a; Thapar et al. 2016).

CNVs that have been studied in relation to ADHD are generally very large (e.g. $>$500,000 or $>$1 million base pairs in length) structural variants. However, rare single-point mutations in protein coding regions of the genome, such as protein-truncating variants or damaging missense mutations, have also been implicated in ADHD, based on recent large exome sequencing studies (Ganna et al. 2018; Satterstrom et al. 2019). Because such exonic mutations are extremely rare, identifying specific genes that are robustly associated with ADHD is challenging, as larger sample sizes are needed to have sufficient statistical power. Collectively, the rare gene variants that have been implicated in ADHD are more common than in control

individuals and also overlap substantially with variants that have been implicated in ASD (Satterstrom et al. 2019). Although the costs of exome sequencing have decreased dramatically in recent years, there are currently few such large studies and no large whole genome sequencing studies (all the genome, not just the exome) of ADHD to date.

It is important to note that the etiology of ADHD is complex and that individuals with rare genetic syndromes, CNVs, or single-point mutations will not always manifest ADHD. Rare aneuploidies and CNVs have incomplete penetrance for a variety of phenotypes (Kirov et al. 2013). Evidently, other genetic or non-genetic factors also contribute to increasing or decreasing the risk of ADHD, in individuals with these rare mutations. To use psychosis as an example, although the 22q11 deletion of VCFS is a strong risk-factor for psychosis, a recent study of individuals with this deletion found that common genetic risk-factors linked to schizophrenia are also associated with increased risk of psychosis in the context of having this rare mutation (Davies et al. 2020). Thus, work integrating rare and common variant genetic risks will be needed to fully understand the impact of rare variants on individual risk of ADHD and heterogeneity in clinical phenotype.

5 Common Variants

Following early studies using candidate gene and linkage analysis approaches (see Fig. 1), hypothesis-free case-control GWAS have become the default genetic study design for assessing the contribution of genetic variants that occur commonly in the general population (typically defined as >1% minor allele frequency), known as single nucleotide polymorphisms (SNPs). Early GWAS analyses of ADHD (Lasky-Su et al. 2008; Neale et al. 2010; Stergiakouli et al. 2012; Yang et al. 2013) consisted of relatively small numbers of individuals with ADHD. These studies were underpowered to identify risk variants at conventional levels of genome-wide significance ($p < 5 \times 10^{-8}$) because they involve testing such a large number of SNPs but yielded important insights, which established that ADHD is characterized by a highly polygenic genetic architecture.

Through an international collaborative effort led by the Psychiatric Genomics Consortium (PGC) and the Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH), the first robustly associated SNPs increasing risk of ADHD have now been identified (Demontis et al. 2019). This largest GWAS to-date consisted of 20,183 individuals with ADHD and 35,191 comparison individuals and identified 12 genomic regions reaching statistical significance, with a total contribution from common risk-alleles to variance in ADHD (i.e., the SNP-based heritability or SNP-h^2) estimated at 21.6% (SE = 0.014) (see Fig. 2b for an illustration). Although the genome-wide significant loci may be individually important in providing clues to the location of the causal genetic risk variants and understanding the underlying biology of ADHD, it is clear that there is a large polygenic component to ADHD, with likely thousands of genes implicated in its

etiology, that are yet to be discovered. This is highlighted in Fig. 2: the currently identified genome-wide significant SNPs account for a small proportion of the heritability identified in twin-studies, something that is similar across disorders (see Fig. 2a), while the number of SNPs identified is small in comparison with discoveries for other psychiatric disorders, likely in part due to much smaller sample sizes (see Fig. 2b).

Secondary analyses based on the GWAS data investigating the functional (biological) role of implicated variants have further revealed that the polygenic signal of ADHD is enriched for regulatory elements that are specific to the central nervous system and also evolutionarily-constrained genomic regions (i.e., regions of particular importance to key biological functions in humans) (Demontis et al. 2019). The analyses also revealed little support for the most widely-studied candidate genes (e.g., dopaminergic genes), which had previously been defined in a hypothesis-driven way. As mentioned earlier (see Sect. 2), another key finding from this ADHD GWAS was the remarkably high genetic correlation between diagnosed ADHD and childhood population traits of ADHD, which was close to a correlation of one, replicating previous work by the EArly Genetics and Life course Epidemiology (EAGLE) consortium (Middeldorp et al. 2016). However, genetic correlation was lower with another definition of ADHD, one of self-reported diagnosis in individuals taking part in genetic testing by the personal genomics company 23andMe, with an estimated correlation of 0.65 (SE = 0.11). This is likely due to the heterogeneity of the ADHD phenotype self-reported by 23andMe participants, as well as ascertainment differences; for example, this is demonstrated by the dissimilar genetic correlation estimates between ADHD and educational attainment using the different definitions of ADHD (Demontis et al. 2019).

Further GWAS analyses using the primary ADHD sample have been performed to stratify the sample based on age and sex, yielding additional insights, which will be discussed later in this chapter. The high genetic correlations of different GWAS justify the prevalent approach of genomic discovery studies in terms of combining as many individuals as possible with a variety of definitions of ADHD, in order to maximize statistical power to facilitate identification of risk-variants (which is clearly necessary to identify genome-wide significant variants, see Fig. 2b). However, such an approach is a trade-off between the number of discovered risk-loci and specificity of those loci to a highly heterogeneous phenotype. Secondary analyses are then necessary to further characterize the impact of discovered genetic risks on specific clinical constructs.

6 Polygenic Risk Scores and Further Insights into Genetic Architecture

One highly versatile method, which can be used to follow up gene discovery studies (see Fig. 1) that has rapidly gained in popularity and has been applied widely in the context of ADHD, is polygenic risk-score (PRS) analysis. This method involves using the SNP effect-sizes obtained from an ADHD GWAS to calculate a genetic risk-score in an independent set of individuals. A variety of methods have been developed to determine how SNPs are selected and weighted to derive PRS (Wray et al. 2020). These scores can then be used to test hypotheses regarding shared genetic risks between ADHD and other phenotypes, compare polygenic burden in different groups, and also in more sophisticated ways (e.g., using mediation analyses, testing gene-by-environment interactions, or examining transmitted and non-transmitted risks across generations).

One of the main limitations of this method is that while the estimated SNP-h^2 of ADHD is 21.6%, PRS only capture a smaller proportion (~5.5%) of the phenotypic variance of ADHD diagnosis status (Demontis et al. 2019), so effect-sizes in secondary analyses tend to be relatively small. Another limitation is that PRS are sensitive to population ancestry and, given the predominantly European ancestry bias of the majority of GWAS analyses, PRS are not as powerful an analytic tool in individuals of non-European ancestries (Martin et al. 2019). These issues limit the current clinical applicability of PRS. However, with these caveats in mind, PRS have been successfully used to test numerous hypotheses, which can help to inform our understanding of ADHD nosology, heterogeneity, and developmental trajectories.

In line with twin-study findings and genetic correlation analyses from GWAS, PRS approaches have consistently demonstrated shared genetic effects between ADHD diagnosis and continuously distributed population traits of ADHD in a variety of samples, using various assessment tools, different informants (parent- and self-rated) and across many ages, including young adults (Groen-Blokhuis et al. 2014; Martin et al. 2014b; Brikell et al. 2018b; Burton et al. 2019; Riglin et al. 2020b). Shared genetic effects with a variety of phenotypes beyond ADHD have also been identified and will be discussed further in the next section.

PRS analyses can also be performed to examine other clinical features in the context of ADHD. Studies examining comorbid mental health problems have determined that a higher ADHD polygenic burden is associated with conduct disorder (Hamshere et al. 2013; Demontis et al. 2021), substance use disorders (such as cannabis and alcohol use: Wimberley et al. 2020), as well as irritability and emotional dysregulation (Riglin et al. 2017; Nigg et al. 2020). Several studies of cognition have also suggested that higher ADHD PRS are associated with more executive function difficulties, particularly in terms of inhibitory control and working memory (Nigg et al. 2018; Chang et al. 2020). On the whole, higher ADHD PRS are not just associated with risk of ADHD, but also appear to be associated with a greater mental health burden and poorer cognitive abilities in the context of having a diagnosis of ADHD.

PRS is a versatile analytic tool and can be used to address more complex hypotheses beyond group differences and univariate association. For example, it is possible to split the set of variants used to derive PRS into those that were transmitted from parents to children versus those that were not transmitted and to derive separate PRS for these sets of variants. Using this approach it appears that polygenic liability for ADHD that is transmitted from parents to children is associated with children's ADHD symptoms, but this is not true of non-transmitted PRS (de Zeeuw et al. 2020). Others have tested mediation models to determine whether ADHD PRS act on ADHD phenotypes via other measured phenotypes, such as working memory or neuroimaging measures (Nigg et al. 2018; Alemany et al. 2019). As the size and diversity of the discovery GWAS for ADHD and other phenotypes grow, PRS analyses will become more robust and better powered to test further hypotheses related to ADHD.

7 Genetic Discoveries and Insights into the Nature of ADHD

7.1 Developmental Change and Adult ADHD

ADHD symptom severity, especially hyperactivity-impulsivity, typically declines across adolescence and into adult life. However, most individuals with ADHD continue to show symptoms and impairment in adult life and a substantial proportion continue to meet full diagnostic criteria for ADHD (see Chapter "ADHD in children and adults: diagnosis and prognosis"). Longitudinal twin-studies have observed that genetic factors contribute to ADHD symptom persistence from childhood across adolescence (Pingault et al. 2015). More recent investigations have utilized ADHD PRS to examine developmental changes in ADHD symptom scores.

A UK population-based longitudinal study of ADHD symptoms (Riglin et al. 2016) found that ADHD PRS were associated with a persistent ADHD trajectory. Those in the persistent ADHD symptom trajectory class showed a higher burden of ADHD PRS than the low symptom group. ADHD PRS also distinguished the group with persistent ADHD symptoms from those whose symptoms had remitted by adolescence. This finding has now been replicated in another UK population-based study (Agnew-Blais et al. 2021). However, larger studies are needed to confirm these results and further understand the genetic factors linked to age-of-onset, persistence of ADHD in clinical populations, and the developmental trajectory of ADHD.

Despite growing interest in adult neurodevelopmental disorders, there have been far fewer genetic studies of ADHD in adulthood than among children. Early family studies suggested a higher familial loading for adult ADHD than for childhood ADHD (Faraone 2004). A more recent Swedish registry study (Chen et al. 2017) investigated the risk of ADHD in siblings of those with ADHD. This study observed a much higher risk of ADHD diagnosis in siblings of those who had a recorded

diagnosis of ADHD at age 18 or older (hazard ratio 11.49) (considered to be persistent ADHD) than in siblings of those with ADHD recorded only before age 18 years (hazard ratio 4.68). It was puzzling that early twin-studies of adult ADHD showed much lower heritability estimates than those observed for childhood ADHD. However, this is likely explained by the change of informant from parent to self-reported ADHD. More recent studies suggest that when informants are combined, the heritability of adult ADHD is similar to that observed in childhood. The largest twin-study of adult ADHD (Larsson et al. 2014) utilized Swedish registry data where ADHD was defined using an ICD-10 diagnosis or prescribed medication. This study observed substantial heritability for ADHD across the life-span, with a heritability estimate of 72% in adulthood.

To date there has been no well-powered GWAS of adult ADHD. The largest study to date (6,532 adult ADHD cases and 15,874 controls) yielded no genome-wide significant loci (Rovira et al. 2020). However, the authors did show a substantial genetic correlation ($r_g = 0.81$, 95% CI: 0.64–0.97) between ADHD assessed in adults and children. As noted previously, a UK study examined ADHD PRS generated from childhood ADHD GWAS data in a population-based cohort where ADHD symptoms at age 25 years were rated by parent and self (Riglin et al. 2020b). ADHD PRS were associated with both parent and self-rated ADHD symptom scores at age 25, again suggesting that, for common variants, adult and childhood ADHD share an underlying genetic liability.

7.2 Sex Differences

It is well established that ADHD, like other neurodevelopmental disorders, shows sex differences, although it remains unknown why males are more commonly affected and the magnitude of this difference is greater in clinical than epidemiological samples. To date, genetic studies have not elucidated a clear-cut reason for this male bias. Twin-studies of ADHD have not demonstrated sex differences in genetic loading. However, some sibling studies of ADHD have observed that the siblings of females with ADHD may be at higher risk of ADHD than the siblings of affected males (Martin et al. 2018c; Taylor et al. 2019). This suggests that females with ADHD may require a higher burden of familial liability to manifest ADHD than males (also known as the female protective effect); this could help explain the sex difference in prevalence. However, molecular genetic studies have not shown the same sex difference. An investigation of sex differences using the largest ADHD GWAS to date observed a genetic correlation close to 1 between males and females (Martin et al. 2018c). Also, that same study found no sex differences in ADHD PRS (Martin et al. 2018c), contrary to earlier findings of a higher burden of ADHD PRS observed in females with ADHD (Hamshere et al. 2013) in a much smaller study. The findings thus far suggest that the sex difference in ADHD prevalence is not explained by differential effects of common genetic variants, although large-scale

ADHD genetic studies have yet to explore this issue through analyses of sex chromosomes and rare variants.

PRS-by-sex interaction analyses or direct comparison of genetic burden in males and females can also be used to test for sex differences in the context of another psychiatric disorder. For example, it has been observed that the association between ADHD, PRS, and substance misuse disorders in individuals with ADHD is higher in females compared to males (Wimberley et al. 2020). Also, in children with a diagnosis of anxiety and/or depression, ADHD PRS are higher in females compared to males (Martin et al. 2018b), although no sex differences in anxiety or depression PRS have been reported in children with ADHD (Martin et al. 2021). Given the male bias in prevalence of ADHD and sex differences in comorbidity patterns in children with ADHD, further PRS studies examining sex differences will yield additional insights. For example, Martin et al. (2021) found some preliminary evidence for stronger associations between anxiety PRS and anxiety symptoms in males with ADHD compared to females, but this finding requires further investigation.

7.3 Relationship and Genetic Overlap with Other Neurodevelopmental Disorders

The Diagnostic and Statistical Manual of Psychiatric Disorders (DSM-5: American Psychiatric Association 2013) now groups ADHD with other childhood-onset neurodevelopmental disorders, including ASD, ID, communication and motor difficulties, as well as tic disorders. These disorders have some common features: typically they onset early in development, show a steady clinical course over time, rather than relapses and remissions, and more commonly affect males (Thapar et al. 2017).

As discussed previously, twin-studies have shown that ADHD and other neurodevelopmental disorders, whether defined as traits or disorder, have a shared genetic etiology. The findings on overlap of ADHD and ASD are especially interesting given that it is only since the publication of DSM-5 and ICD-11 (the most recent editions), that ADHD can be co-diagnosed with ASD. The largest study based on Swedish registry data (Ghirardi et al. 2017) showed that monozygotic co-twins of individuals with ASD had much higher rates of ADHD (odds ratio = 17.77) than dizygotic co-twins of those with ASD (odds ratio = 4.33). Swedish registry data were also used to examine the overlap of ADHD and ID in another study (Faraone et al. 2017). The authors observed that most of the correlation between ADHD and ID was explained by genetic factors (91%) except for those with profound ID. Although ADHD shows substantial phenotypic and genetic overlaps with other neurodevelopmental disorders, ADHD with comorbidities including ASD or ID or Tourette syndrome have historically been excluded from GWAS. This means that affected individuals will not be represented in these studies.

Molecular genetic studies have supported the genetic overlap between ADHD and other neurodevelopmental disorders (Thapar 2018). The largest ADHD GWAS to date observed a significant genetic correlation of 0.36 between ADHD and ASD (Grove et al. 2017). The relationship between ADHD and other disorders has also been examined in a recent GWAS meta-analysis of eight psychiatric/neurodevelopmental disorders that investigated the relationships across different disorders (Cross-Disorder Group of the Psychiatric Genomics Consortium 2019). The authors found three factors that explained the relationship between different disorders, where the "neurodevelopmental" factor encompassed ADHD, ASD, and Tourette syndrome. Surprisingly, depression was also captured by this factor. These findings highlight again that while diagnostic categories may be useful for some clinical purposes they ought not to be reified.

As noted previously, rare genetic variant studies also highlight the overlap between ADHD and other neurodevelopmental disorders. Recent investigations of CNVs associated with ADHD show that these CNVs also contribute to other neurodevelopmental and psychiatric disorders including ASD and schizophrenia (Williams et al. 2010; Lionel et al. 2011; Gudmundsson et al. 2019). A large exome sequencing study of ADHD found that the genes implicated by rare protein-truncating variants were the same as those found in ASD (Satterstrom et al. 2018). Overall, family and twin-studies, as well as common and rare variant genetic studies, all converge on the conclusion that there is a significant degree of shared genetic risks contributing to a broad range of neurodevelopmental disorders, not ADHD alone.

7.4 Relationship and Genetic Overlap with Other Psychiatric and Somatic Disorders

It has become increasingly clear that ADHD shares genetic liability with a range of other phenotypes, including psychiatric and somatic health conditions that typically onset later in life, as well as other complex human traits measured in the general population. PRS studies that have examined shared genetic liability with ADHD are too numerous to summarize comprehensively and we refer readers to a recent systematic review on the topic (Ronald et al. 2021). Here we summarize several important emerging findings.

A systematic review of twin and family genetic correlations between ADHD and other psychiatric phenotypes estimated a moderate pooled genetic correlation ($r_g = 0.50$) across childhood and adulthood neurodevelopmental, internalizing phenotypes such as anxiety or depression and externalizing phenotypes such as disruptive behavior problems (Andersson et al. 2020). In GWAS, the genetic correlation with major depressive disorder ($r_g = 0.44$, SE = 0.03) is the strongest, with significant but smaller correlations seen for anxiety disorders, schizophrenia, and bipolar disorder, as well as a small negative genetic correlation observed for

anorexia nervosa, which implies that some of the underlying risk loci are the same, but acting in opposite directions (Lee et al. 2019; Demontis et al. 2019; Purves et al. 2019). Genetic correlations have also been observed with substance misuse disorders, including alcohol dependence, smoking, and cannabis use (Walters et al. 2018; Demontis et al. 2019; Johnson et al. 2020).

Given the vast shared risks across psychiatric phenotypes, it has been proposed that there is a large major component of shared liability, referred to as a general psychopathology factor, or the "p" factor. Twin-studies support this theory of a shared genetic factor underlying ADHD and other psychiatric phenotypes (Pettersson et al. 2013, 2015), with especially strong genetic correlations with neurodevelopmental disorders (Du Rietz et al. 2020). PRS studies find that part of the shared common variant risk across disorders can be attributed to such a general factor, but that there are also specific genetic effects for ADHD not captured by the general factor (Brikell et al. 2018b; Riglin et al. 2019).

ADHD also shares genetic liability with phenotypes beyond neurodevelopmental and psychiatric disorders, including somatic health conditions and other non-medical traits. Twin studies support shared liability with obesity, asthma, epilepsy, coronary artery disease, and lung cancer (Brikell et al. 2018a; Chen et al. 2019; Holmberg et al. 2015; Demontis et al. 2019). Common variant positive genetic correlations have been reported for phenotypes such as insomnia, neuroticism, obesity, body mass index, number of children born, and rheumatoid arthritis, with negative genetic correlations including educational attainment and cognition, subjective wellbeing, and age at birth of first child (Demontis et al. 2019).

Thus, there are vast shared genetic risks across ADHD and numerous health- and behavior-related phenotypes. This shared liability may help to explain the comorbidity between ADHD and mental health as well as somatic health conditions. The results are largely consistent across different methods, ages and samples, although there are also gaps in the evidence; larger studies are needed to obtain more precise estimates regarding the degree of shared genetic risks. Further work is then needed to understand the specific underlying genetic risks that are shared across ADHD and any given phenotype. Mendelian Randomization studies suggest that some of this genetic overlap could represent causal effects of ADHD on physical health conditions including coronary artery disease and obesity as well as depression (Leppert et al. 2020b; Riglin et al. 2020a, b).

8 Biological Insights

A major motivation for conducting genetic studies is to gain novel insights into the pathophysiology of ADHD and to pave the way for novel treatments. However, a major challenge is that any association between a genetic variant and ADHD represents only the first step because the associated variant is not necessarily causal. Further work is needed to identify which specific genes are indexed by the associated variant and then to assess what these genes do and to characterize the underlying

mechanisms. As genes are expressed as messenger ribonucleic acid (mRNA) in different tissues that subsequently lead to the assembly of amino acids to form different proteins (for further details, see State and Thapar 2015), understanding the biological pathways by which genes influence disorder is important. For disorders such as schizophrenia and autism (Giegling et al. 2017; Thapar and Rutter 2020), multiple genes that have achieved genome-wide significance have been implicated; here, researchers have now focused on investigating whether the different implicated genetic variants converge on the same gene expression and protein networks (depicted as functional follow-up studies in Fig. 1).

These approaches are being used in relation to ADHD genetic discoveries and will become more relevant as high confidence genes are identified. A growing number of bioinformatic resources enable scientists to infer indirectly the biological plausibility and function of an associated genetic variant. For example, it is possible to examine how genetic variants impact on diverse brain cell types, in different places across the brain and at different developmental periods, including prenatally. This is less costly and time-intensive than examining the function of genetic variants, one at a time, in model organisms and cellular models.

GWAS of common variants highlight that, individually, these each have a small effect-size and that tens of thousands of such variants likely contribute to ADHD risk. Typically, GWAS identify only regions of the genome that harbor potential risk-genes and, to date, ADHD GWAS have yet to provide definitive robust biological insights.

Rare variants are especially interesting from the perspective of offering insights into biology because they have larger effect-sizes than common variants. That is because damaging, larger effect-size mutations are rapidly removed from the population through natural selection and thus become rare. However, even for rare variant studies, association does not necessarily immediately reveal causal genes and biological processes. Rare variants can be inherited or be de novo in origin where the variant first arises in the parent germline (oocyte or spermatozoa) or later, after fertilization, when they are known as post-zygotic somatic variants (State and Thapar 2015; Lim et al. 2017). De novo variants are more likely to be causal and, for disorders such as schizophrenia and autism, there have been large-scale de novo CNV and sequencing efforts that are providing early biological insights into these disorders. Large de novo rare variant studies are lacking in ADHD, though as mentioned earlier, preliminary studies using whole exome sequencing in case-control studies are promising (Ganna et al. 2018; Satterstrom et al. 2019).

No genome-wide case-control CNV study to date has been large enough to implicate individual CNVs associated with ADHD risk (Thapar et al. 2016). One exception was a pooled analysis of duplications in the 15q13.3 region (on Chromosome 15) that encompasses the alpha-7 nicotinic acetylcholine receptor gene (CHRNA7) as well as other genes (Williams et al. 2012). The most comprehensive and recent investigation of published CNVs from 11 studies of ADHD identified 2,241 potential genes from these CNVs (Harich et al. 2020; Thapar 2020). This list was refined first by examining whether the CNVs in people with ADHD were likely to be in a position that disrupted genes. Then the authors used

bioinformatic data resources to examine the biological plausibility of these genes being related to ADHD; this included examining brain expression and cross-species data. Ultimately, this process yielded a final list of 26 high-confidence genes. This study highlights that a prohibitively large number of genomic loci can be refined to potentially causal genes by using bioinformatic approaches. However, there are drawbacks. For instance, among the included ADHD CNVs are those that are not genome-wide significant and all the published studies used different approaches to defining CNVs. Bioinformatic approaches are important but still inadequate. These genes will then need to be investigated in cellular systems and through backtranslation into animals to identify mechanisms.

9 Gene–Environment Interplay

To this point, this chapter has focused on the role of genetic factors in isolation. It is important to remember, however, that both genetic and environmental factors are relevant to the development and presentation of ADHD and that the interplay of these different factors is also of relevance. Some have argued that consideration of these interactions could also help account for some of the discrepancies between twin and SNP heritability estimates, as observed in Fig. 2a (Maher 2008).

One way in which genes and the environment work together is through gene-environment correlations (rGE). This is where an individual's genetic background shapes their environmental exposures. For example, individuals may actively seek out environments which match their genetic predispositions (active rGE) or evoke responses from others based on their disposition (evocative rGE). Developmentally, as parents provide both their child's genetic background and their rearing environment, this is also likely to result in an overlap between genetic and environmental exposures (passive rGE). There is evidence to suggest that the observed associations between ADHD and some putative environmental risk-factors may be the result of such correlations. For example, risks associated with parenting, including parent-child hostility, have been shown to be influenced by the child's behavior as well as their genetic liability for ADHD (Lifford et al. 2008; Harold et al. 2013). More recent PRS and Mendelian Randomization (MR) studies also suggest that ADHD genetic liability is associated with maltreatment and that this relationship may be causal (Leppert et al. 2020a; Warrier et al. 2021).

Genetic risk-factors are thought to account for the previously identified environmental risk-associations observed between maternal smoking during pregnancy and ADHD (Rice et al. 2018), highlighting the importance of taking into account potential genetic confounds when investigating environmental risk exposures. Genetically sensitive and natural experimental designs are needed to tease apart these relationships; it is important to remember the potential role of genetic factors when considering putative environmental risk factors and vice versa.

Gene–environment interactions (GxE), whereby genetic liability varies, depending upon environmental exposure, are also likely to be important in

understanding the etiology of ADHD. While of recognized importance, there are no robust GxE findings for ADHD using molecular genetic methods. This is partly due to the fact that identifying interaction effects is more difficult than identifying the main effects of genetic or environmental risks because even larger sample sizes than currently available are required. There were a number of GxE studies using a candidate gene approach, but as noted earlier, molecular genetic methods have moved away from this towards a whole genome approach while the role of previously suggested candidates has not been replicated using GWAS methods (Demontis et al. 2019).

Moving forward, researchers have started exploring ways to use GWAS data for GxE through Genome-wide Environmental Investigation Studies (GWEIS). These studies assess associations between environmental risks and SNPs across the genome, without requiring the main effects of potential risk genetic variants to be associated with the disorder at a genome-wide significant level. To date, there are no GWEIS studies in ADHD (and few for any psychiatric disorder) (Assary et al. 2018) and such methods are likely to be complex due to the issues of: small sample sizes; the fact that interactions can take many forms (each requiring different analytical approaches); and the multiple testing burden associated with genome-wide GxE analysis (Aschard et al. 2012). However, the recognized potential importance of GxE in our understanding of ADHD means that such studies are likely to be undertaken in the future.

A further way in which researchers can investigate the interplay between genes and the environment is by studying epigenetic effects. Epigenetics is the study of factors which alter the expression of genetic factors (rather than changing the DNA sequence itself), including how environmental factors may lead to such changes. While there are few studies investigating epigenetics in ADHD to date, there are many challenges. That is because like GWAS, epigenome-wide association studies (EWAS) require very large samples that are not available currently. Also, association findings can arise as a result of confounders and reverse causation. To date some studies of ADHD have investigated DNA methylation as one marker of epigenetic variation. DNA methylation is a process whereby methylation of specific DNA loci can alter gene expression. For example, Mooney et al. (2020) performed an EWAS comparing DNA methylation markers between those with ADHD and controls. While no genome-wide significant findings were found, there were some promising indications that methylation variants were associated with both ADHD status and ADHD PRS. This finding requires replication, before attempting to identify which environmental factors may contribute to this altered methylation. For example, some smaller studies have looked at how gene expression (mostly through methylation) is associated with environmental exposure to factors such as pre-natal diet or toxins (Rijlaarsdam et al. 2017; Gervin et al. 2017). However these need to be regarded with caution at present given the caveats to epigenetic studies in humans.

10 Clinical Implications and Genetic Testing

As more ADHD risk genes are identified, what are the implications for clinicians? First, there are immediate implications for clinical practice. We already know that ADHD runs in families and is highly heritable. We also know that ADHD genetic risk-factors cross diagnostic boundaries. That means that the clinician needs to be vigilant to the possibility that any siblings and parents of the index child may also have ADHD, or a different neurodevelopmental disorder, and are at higher risk for depression and other psychiatric disorders. That is important insofar as if multiple family members are affected it could impact on household and family stress and so could affect assessment, compliance with clinic attendance and the success of clinical interventions. A second issue is the provision of information in clinics. Families often wish to know about the etiology of ADHD and its biology. Thus clinicians will need to be up-to-date on scientific progress and require skills in communicating the complexities of genetics. They will also need to ensure sufficient provision of genetic counselling to support families with the information they receive (Wilkins et al. 2016; Wolfe et al. 2018).

The next issue is whether genetic testing is warranted? Although rare variants associated with ADHD have large effect-sizes, routine genetic testing for those with ADHD is not currently recommended. However, recommendations may well change in the future. Guidelines in many countries now include genetic testing for those with mild ID and, in the USA, for those with autism. Currently, there is no empirical evidence to provide guidance on how clinically useful genetic testing in ADHD might be because a study in routine clinical practice has not been undertaken although it is possible, as costs decline and more knowledge about causality of specific variants is gained, that testing is introduced, especially if the variants have implications for treatment, prognosis or are potentially medically actionable. However, as we have highlighted, the genetics of ADHD, like other neurodevelopmental and psychiatric disorders, are complex. The effects of any identified larger effect variant will depend on other background genetic factors and non-genetic influences too. Also, the effects of any variant are probabilistic and, we know, likely pleiotropic. For these reasons, genetic counselling is important so that families understand what testing involves and what any findings could mean (Austin 2020). Future studies need to evaluate the potential benefits and risks of providing genetic feedback.

At present the clinical utility of common genetic variants is even less certain. The predictive power of ADHD and psychiatric PRS is weak. However, it is possible that more powerful PRS, generated from much larger GWAS, could contribute to clinical decision making, especially when combined with family history and clinical variables (Murray et al. 2020). For example, a higher rate of vigilance at follow-up may be warranted if a child with ADHD, who presents with first episode depression, has a family history and elevated genetic loading for bipolar disorder. One important consideration is that the population used to derive the risk predictors, including PRS, needs to be similar to the target population (e.g., ethnicity, specialist clinic

versus primary care). A serious concern among geneticists is that most of the world's GWAS focus primarily on individuals of European descent and are therefore less effective in PRS studies of non-European diverse ancestries (Martin et al. 2019). Thus, to enable equal health gains across different populations, it is essential that large-scale genetics research is conducted on diverse groups.

11 Summary

As summarized in Fig. 1, this chapter has highlighted the journey of ADHD genetic research, from the recognition and quantification of heritability estimates to identifying specific common and rare risk-variants for the disorder. However, there is still a long road ahead in such endeavors and, as seen in Fig. 2, our understanding is not as advanced as for some other psychiatric disorders. As can be seen in Fig. 2b, part of the reason for this is that sample sizes for studies of ADHD and other childhood-onset conditions, such as ASD, are much smaller than for schizophrenia, bipolar disorder, and major depressive disorder. As can be seen in the figure, there is a clear correlation between sample size and identification of genome-wide significant SNP associations highlighting the need for much larger studies for ADHD and other neurodevelopmental disorders. Large trio-based samples for investigating de novo rare mutations are also lacking. However samples with detailed clinical information will also be required if these findings are to be translated into clinical benefits.

It will also be important to consider the interplay between genetic and environmental factors, especially as our understanding of those genetic risks increases. However, this identification of genetic risks is only one step on the journey to understanding the etiology of ADHD; understanding the varied effects of such risks on the heterogenous phenotype of ADHD across the lifespan, as well as the biological processes that underpin ADHD, will also be of great importance. While we have some insights already using twin-studies, PRS, and some investigations into the biological underpinnings of ADHD, much more research is needed, including approaches that use newer techniques such as exome and whole genome sequencing. All these studies require extremely large ADHD samples. The study of the genetics of ADHD is therefore at an exciting stage where further developments are both likely and eagerly anticipated and, as our knowledge increases, we can hopefully reach the stage of utilizing molecular genetic knowledge in clinical practice.

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