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ADHD genetic discoveries in the 21st century and their implications

Anita Thapar[1,2] MD PhD

1MRC Centre for Neuropsychiatric Genetics and Genomics, School of Medicine; Cardiff University
2 Division of Psychological Medicine and Clinical Neurosciences, School of Medicine, Cardiff University

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Abstract

Attention Deficit/Hyperactivity Disorder (ADHD) like all common medical conditions is explained by the contribution of multiple genes and environmental risk factors. Family and twin studies consistently have observed a prominent genetic contribution but it is only recently that technological advances now have enabled direct genetic investigations. In this article I selectively review genetic findings on ADHD over the last five years and focus on their implications for the conceptualization of ADHD and future clinical practice.

Recent, large-scale family studies and gene discoveries reveal the strong genetic overlaps between ADHD and Autism Spectrum Disorder, as well as Intellectual Disability. These findings highlight its neurodevelopmental nature. ADHD however shows substantial genetic correlations with a much broader group of neuropsychiatric disorders, especially major depressive disorder as well as with non-psychiatric characteristics. I discuss a few different explanations that might underlie these links. ADHD while usefully conceptualized as a disorder in clinical practice, is commonly viewed as a continuously distributed trait in the fields of developmental psychopathology and epidemiology. Recent genome-wide association study findings consistent with previous twin studies, highlight that ADHD appears to lie at the extreme of a continuously distributed dimension akin to hypertension and blood pressure. New genetic findings on developmental continuity and change are discussed and I emphasize the need for a developmental perspective to genetic studies. Finally, I consider potential future directions for scientists and the implications of new genetic findings for clinicians.

Introduction

The concept of Attention Deficit Hyperactivity Disorder (ADHD) as a clinical condition can be traced back to well before the last century (1). The view that such behaviors arose from early "brain damage" remained highly influential through much of the 20th century until the first wave of family and twin studies(2) indirectly revealed the contribution of genetic risk factors. During the 21st Century, technological advances and large-scale collaborative efforts have now enabled direct and successful genetic investigations into neuropsychiatric disorders, including ADHD (3).

ADHD, like all common medical conditions is not explained by genes alone; environmental risks also contribute (see elsewhere for a full discussion on environmental risk factors and designs to test causality (2)). In this article I selectively review genetic findings on ADHD over the last 5 years and focus on their implications for the conceptualization of ADHD and future clinical practice.

Investigating the neurodevelopmental nature of ADHD

Familial overlaps between ADHD and neurodevelopmental disorders: It has been known for decades that ADHD is familial and highly heritable (4) with heritability estimates of around 60-90%. Twin studies also have shown a strong genetic overlap with other child psychopathology; most prominently with behavioral problems such as conduct disorder (5). Indeed ADHD was considered primarily as an externalizing or behavioral problem (6). However more recent genetic studies have highlighted its neurodevelopmental nature (7). For example, national, registry-based family and twin studies have revealed a strong

familial and genetic overlap between ADHD and Autism Spectrum disorder (ASD). In one Swedish study (8) the monozygotic co-twins of those with ASD showed an increased risk of ADHD (OR = 17.77 95% CI 9.8-32.22) compared to dizygotic co-twins (OR=4.33 95% CI 3.21-5.86). These associations were most prominent for those with higher functioning ASD rather than low functioning ASD (with intellectual disability). Although the within-individual and within-family overlap of ADHD and ASD is now accepted, until the publication of DSM5, a diagnosis of ADHD in the presence of autism was disallowed.

Recent genetic findings have also challenged the historical reticence about diagnosing ADHD in those with intellectual disability (ID) and about including those with lower IQ in genetic studies (9). It has always been recognized that ADHD is strongly associated with lower IQ and intellectual disability (10). Population-based twin studies of IQ and learning ability (e.g. reading) consistently showed that most of the correlation with ADHD symptoms was explained by shared heritability (10). Interestingly, even though the genetic overlaps between ID and autism (11) and between ID and schizophrenia are well recognized (12), investigations into the genetic links between ID and ADHD have been sparse. One recent registry-based, family study addressed this gap by examining ADHD diagnosis and intellectual disability (13). The authors found that most of the correlation between ADHD and ID liabilities was explained by genetic factors (estimate of 91%) except in the case of profound intellectual disability. Again these findings point to the neurodevelopmental nature of ADHD. These findings are important for scientists and clinicians. Historically, although those with lower IQ or ID have been excluded from studies of ADHD, this has not been the case for studies of schizophrenia or autism. This means that ADHD

research studies may not always have been fully representative of the clinic population.

Rare genetic mutations of strong effect: A number of rare Mendelian disorders and chromosomal anomalies are accompanied by ADHD as well as other neurodevelopmental and neuropsychiatric disorders. For example, ADHD is the most common neuropsychiatric disorder observed in 22q11.2 deletion syndrome (14) even though this syndrome is typically considered primarily as a psychosis risk factor. ADHD is also associated with Tuberous Sclerosis, Smith-Magenis Syndrome, Fragile X syndrome and Prader-Willi syndrome. These disorders however lead to a wide range of neurodevelopmental and neuropsychiatric phenotypes beyond ADHD, including ASD, anxiety, and depression and are often accompanied by intellectual disability and physical anomalies. That is, none of these genetic syndromes are ADHD-specific.

In the last decade, there have been growing efforts to identify novel, rare gene mutations that are associated with ADHD and other neuropsychiatric disorders through systematic investigations across the whole genome (3). One class of rare mutations, known as copy number variants (CNVs), that are chromosomal duplications and deletions, have been implicated in disorders that might be considered more neurodevelopmental in nature. These include intellectual disability, autism, schizophrenia and more recently Tourette's syndrome as well as ADHD (3,15). The genomic regions spanned by the ADHD-associated CNVs have been found to show significant overlap with CNVs involved in autism and schizophrenia highlighting the highly pleiotropic effect of CNVs.

The largest and only systematic investigation of another class of rare mutations in ADHD, rare exome sequence variants, comes from an as yet unpublished study of 3536 individuals with ADHD from the Danish iPSYCH register-based study (16). The investigators observed a similar burden of rare protein truncating variants (PTVs) in ADHD as was found in ASD and both neurodevelopmental groups were enriched for PTVs above the unaffected control rate (OR=1.24 for ADHD vs 0R= 1.23 for ASD). Intriguingly, the authors found that the genes affected by ADHD and ASD rare variants were indistinguishable.

Common gene variants of small effect size shared between ADHD and different neurodevelopmental disorders and traits: Very large sample sizes are required to detect individual common gene variants using genome-wide association study (GWAS) designs and until recently, these have been lacking for ADHD. However, the most recent ADHD GWAS included 20, 183 ADHD cases and 35, 191 controls and robustly implicated 12 independent genomic loci (18), including one containing the gene *FOXP2* that has previously been implicated in severe speech and language(17) problems. As none of the genome-wide significant loci contained any of the candidate genes previously implicated in ADHD (e.g. dopaminergic genes), this earlier literature is not discussed further. It is possible that evidence implicating some of these genes could emerge with larger GWAS.

Males are more commonly affected by ADHD and this is a characteristic feature of child neurodevelopmental disorders. Although previous studies based on siblings had suggested that females with ADHD may carry a higher burden of

ADHD genetic risk, and this would be a potential explanation for why males are more commonly affected (because females have to carry a greater burden of risk to manifest disorder), the latest GWAS findings did not show this (19).

Puzzlingly and in contrast to family and twin study findings, the international Psychiatric Genomics Consortium (PGC) cross-disorder study published in 2013 (20) found no genetic overlap between ADHD and ASD. In contrast, the more recent and much larger Danish nationwide iPSYCH GWAS of ASD observed a significant genetic correlation of 0.360 between ADHD and ASD (21). One possible explanation is that the 2013 PGC ASD sample was trio based (both parents and offspring) and might have included ascertainment biases, while the Danish sample was a nation-wide design based on all affected individuals (case-control). More importantly the new iPSYCH GWAS is very much larger and thus better powered.

From the perspective of recent genetic discoveries, ADHD behaves as a typical neurodevelopmental disorder with a higher burden of rare mutations compared to controls and with genetic overlap with ASD and ID. However as we will discuss next, genetic overlap is extensive amongst different neuropsychiatric disorders, and the genetic links of ADHD are not restricted to a neurodevelopmental grouping.

Genetic overlap between ADHD and other neuropsychiatric disorders

One of the most striking findings to emerge from GWAS is the extensive genetic overlap for biomedical traits and disorders (22). ADHD GWAS findings are no

exception; ADHD showed significant positive genetic correlation with a wide range of neuropsychiatric disorders including schizophrenia, bipolar disorder, Tourette's syndrome, anxiety disorder and major depressive disorder and a significant negative genetic correlation with anorexia nervosa (18). ADHD also shows genetic overlap with some physical conditions (e.g. lung cancer, insomnia, migraine) as well as some social and environmental phenotypes (e.g. educational attainment, smoking behaviors)(18). It is clear therefore that ADHD does not show genetic overlap with neurodevelopmental disorders alone and that risk factors (e.g. gene or gene group or environmental risk such as smoking) for complex disorders including ADHD, do not necessarily provide a good means of defining diagnostic boundaries or meaningful groupings or making treatment decisions.

These recent GWAS findings of pleiotropy are not enormously surprising given that recent family and twin studies had also observed familial and genetic overlaps between ADHD and later-onset neuropsychiatric problems including schizophrenia, bipolar disorder(23), major depressive disorder (MDD) (24), as well as deliberate self-harm(25), completed suicide (25) and alcohol misuse(26). The observation of genetic overlap in itself is no longer a novel or clinically useful observation. Rather, we should be asking: what are the reasons that underlie these genetic correlations? For example, GWAS findings reveal that ADHD, typically an early-onset disorder, shows the strongest genetic correlation with major depressive disorder (rg=0.42). Is that because ADHD has an especially close biological relationship with depression? There is limited evidence to date to support this hypothesis. Does pleiotropy represent a causal

risk effect of ADHD on MDD? Consistent with this providing a partial explanation, some studies suggest that treatment of ADHD reduces the risk of future depression (27). However ADHD treatments are not effective for MDD. Another hypothesis is that a substantial proportion of those with recurrent MDD who are recruited into GWAS are misclassified and have undiagnosed ADHD or a history of ADHD but this seems unlikely to be a full explanation. These are all hypotheses that can be tested via epidemiological designs and novel genomic methods (e.g. Mendelian Randomization) to disaggregate pleiotropy among other designs (28).

Conceptualizing ADHD as a trait and category

From an epidemiological perspective, ADHD can be viewed as a trait as well as a category; higher scores are associated with adverse outcomes with no discontinuity at a specific cut-point(7). Although a diagnostic category for ADHD is helpful in clinical practice because many clinical decisions are categorical in nature (e.g. to use medication versus not), an understanding of its underlying structure can be informative for clinicians and patients as well as researchers. Twin studies suggested many years ago that ADHD appears to lie at the end of a continuum of genetic risk, with the same genetic risks contributing across the ADHD continuum in the population(2) with the possible exception of those scoring at the very low extreme end of the continuum(29). These findings, coupled with epidemiological studies, suggested that ADHD could be viewed as something akin to hypertension where the disorder lies at the extreme of a continuously distributed phenotype (i.e. blood pressure) that is present in the whole population.

GWAS findings have further added to this evidence. Two studies used an independent ADHD GWAS discovery dataset to generate ADHD polygenic risk scores (PRS), the relative burden of ADHD risk alleles carried by an individual, in population cohorts in the UK (30) and the Netherlands(31). Both found that ADHD PRS predicted ADHD trait levels in the general population. A third UK study(32) further observed that when PRS were derived for an ADHD trait measure in a population-based cohort, these predicted ADHD diagnosis in an independent patient sample. The most recent and largest ADHD GWAS (18) was able to go further by testing the genetic correlation between ADHD diagnosis and a large GWAS meta-analysis of ADHD trait measures in 17,666 European individuals from the EAGLE consortium(33). The findings are striking in that the investigators observe a genetic correlation of 0.94 between ADHD diagnosis in patients and ADHD traits in the population-based cohorts. Overall genetic findings converge in showing that ADHD diagnosis lies at the extreme of a quantitative trait.

However ADHD diagnosis genetic risk is not exclusively related to a single continuously distributed trait measure of ADHD. For example, one population-based cohort study(34) found that ADHD genetic risk scores predicted multiple childhood neurodevelopmental traits including social communication, cognitive ability/IQ, language and working memory although not emotion recognition. The findings on working memory recently have been replicated (35). Another study found ADHD genetic risk scores also predicted childhood irritability (36). These findings could simply reflect pleiotropy once again; with the same genes contributing to different childhood traits in the population. An alternative interpretation for the clinician and scientist is that a diagnosis of ADHD could be

conceptualized as the extreme of multiple liabilities or dimensions; this would be in keeping with the thinking of R-DoC.

Development and adult life

Although ADHD symptom levels typically decline with age, a proportion of individuals show persistently elevated symptoms or a continued diagnosis into adolescence or adult life(7). Longitudinal twin studies have all observed that ADHD persistence is associated with higher genetic loading; one study further suggested that ADHD trajectories through adolescence maybe explained by genetic liabilities that are independent of those that contribute to baseline symptom levels in childhood (37). A recent population-based, cohort investigation used ADHD GWAS findings to assess the contribution of ADHD common genetic variants to ADHD symptom trajectories between ages 4 and 17 years(38). ADHD PRS were significantly higher in children in the persistent trajectory than in those in a low symptom group (OR 1.31), an intermediate group (OR=1.22) and in a childhood-limited ADHD group (OR 1.27). Interestingly although the schizophrenia GWAS discovery sample is very much larger and more powerful than the ADHD GWAS, schizophrenia PRS and other neuropsychiatric PRS did not predict ADHD persistence. This highlights that there is a degree of specificity to genetic findings.

Other genetic studies that have assessed adult ADHD in individuals over the age of 18 years using cross-sectional designs also support the suggestion that persistent ADHD has higher genetic loading. For example, a recent family-Swedish registry-based family study observed a substantially higher relative risk

of clinically recognized ADHD in siblings of those who had ADHD at age 18 or older (Hazard Ratio HR 11.49) than siblings of those with ADHD at a younger age-below the age of 18 years (HR 4.68)(39).

However twin studies of adult ADHD repeatedly have yielded very low heritability estimates, in contrast to the consistently high heritability estimates observed in child twin studies. A Swedish registry study (40) however showed substantial heritability for ADHD across the life span including in adult life (h^2=0.72 95% CI 0.56-.84). Here, ADHD was defined using an ICD diagnosis or on the basis of prescribed ADHD medication. These findings suggest that with a clinician's diagnosis, where perhaps age of onset, symptom pervasiveness and impairment criteria are used rather than self-report questionnaire measures, the developmental differences in genetic architecture are not as pronounced at least in terms of twin study findings.

Although there are international efforts to assemble large adult ADHD datasets, so far GWAS have yet to yield genome-wide significant loci and rare variant studies(41,42) will also require much larger sample sizes before they can be used to further assess developmental differences in ADHD genetic architecture at a molecular level (see Franke et al(43) for an extensive review of adult ADHD genetics).

Future directions

The 21st century has witnessed the discovery of ADHD-associated rare and common genetic variants and resolved that its genetic architecture involves a

spectrum of genetic variation in terms of frequencies and effect sizes. These discoveries are already providing a start-point to gaining insights into the underlying biology of ADHD (e.g.(44,45) and for assessing novel treatments (46)). However, much more work will be needed to investigate the functional impacts of associated genetic variants at the level of molecules, cells, neural systems and circuits, as well as on development. Another observation is that so far, the identified genetic variants only explain a relatively small fraction of the inferred heritability (h^2=-0.22)(18) of ADHD that has been inferred from traditional genetic designs. This suggests that continued collaborative and larger ADHD genetic discovery studies will be required in the future to detect additional genetic contributions together with robust epidemiological designs to identify causal environmental risk factors. Novel strategies may be needed to consider alternative plausible risk mechanisms that might manifest as heritability, for example parentally-provided early environments(47) including the prenatal environment. The literature review of the previous five years on ADHD genetics has shown the enormous advantage of genetically-informative and genotyped nationwide patient registries and these will continue to remain an invaluable resource for investigating many of the questions raised in this review.

Recent genetic discoveries highlight the strong overlap between ADHD, ASD and ID. Indeed, in terms of rare mutations ADHD and ASD seem virtually identical(16), so it is welcome that previous diagnostic exclusion criteria for ADHD in the presence of ASD have been removed from DSM-5. Yet the clinical features and treatments of these disorders are so different. What determines

these differences is another crucial next research question (Figure 1). Typically these are early onset disorders. One possible contribution to differences is variation in prenatal environmental exposures, another is background common genetic variants. For example, ADHD common genetic variant risk scores predict lower cognitive ability and educational attainment, whereas ASD common genetic variants predict higher cognition and attainment (48). Lessons from genetic discoveries on strong diagnostic overlaps are timely for clinicians and especially for service providers that tend to be diagnosis-specific (e.g. ASD only) especially given the historical reticence about diagnosing ADHD in the context of ASD or ID. This is beginning to be recognized. For example, in 2017 in Wales, a nation of 3 million, multi-disciplinary child neurodevelopmental clinics informed by recent findings have been established recently and have replaced ASD and ADHD-specific assessment pathways.

In the last five years, GWAS have shown genetic overlap across multiple disorders. ADHD shows extensive pleiotropy that is especially prominent with major depressive disorder but genetic risks also show some specificity as only ADHD PRS appear to predict ADHD persistence(38). In the next five years, efforts need to focus on disaggregating this pleiotropy and testing alternative hypotheses using methods that are able to distinguish causal relationships, different ADHD subtypes and misclassification from pleiotropy (e.g. using Mendelian randomization and other similar methods). This is important because the different explanations will have diverse clinical implications (Figure 1).

Genetic findings have confirmed the epidemiological view of ADHD as lying at the extreme of a continuum (or several continua) and have started to highlight the importance of adopting a developmental perspective(37,38). Funders and ethics bodies need to recognize that developmental studies require longitudinal follow up and that this is expensive and time consuming yet scientifically invaluable. In this regard, longitudinal, population cohort designs are attractive for developmentally-informative genetic studies because, unlike patient registry data, they involve trait-based assessments; however non-random attrition is a problem and those with severe illness (at the extremes of dimensions) are under-represented. If ADHD is a trait, akin to blood pressure, then public /population health-based samples and approaches can be integrated with traditional genetics research on patients. This is beginning to happen. The conceptualization of ADHD as both a trait and a disorder is relevant to clinicians in that most will recognize the somewhat arbitrary nature of the diagnostic cut-point and frequently encounter sub-threshold cases. The presence of an underlying continuum means issues such as defining the boundary for impairment and treatment are not straightforward. For example, the blood pressure cut-point for defining hypertension has changed over time, and hypertension guidelines in some countries adjust the cut-point depending on comorbid disease (e.g. chronic renal disease).

Given recent genetic discoveries, what are the implications for genetic testing in ADHD? The implication for clinicians are two-fold. First, relatives of those with ADHD including their parents are at elevated risk of a range of different neurodevelopmental disorders (e.g. ADHD, ASD, learning difficulties) as well as

other neuropsychiatric illnesses (most commonly MDD) that could impact on assessment, treatment delivery or treatment effectiveness. At present, routine testing for rare mutations in ADHD is not recommended although guidelines for such testing in clinical settings have now expanded in many countries to include mild intellectual disability as well as ASD in the US. It was not long ago that mild intellectual disability was considered primarily socio-cultural in origin so this represents a substantial shift in international clinical practice. There is little empirical evidence to guide us as to what should happen for ADHD. A much older study showed that the rate of established syndromes was sufficiently rare in ADHD that genetic testing is not warranted in those without ID (49). However that study predates current methods for detecting genomic anomalies and a crucial issue is how severely neurodevelopmentally impaired the target patient group is, especially given that ADHD is relatively common. Whether genetic testing in clinical settings extends to neuropsychiatric disorders such as ADHD and schizophrenia remains to be seen but as costs diminish and more knowledge about the causality of different mutations is gained, in my view clinical practice is likely to change within the next decade. This could be sooner if some of these rare mutations are found to have treatment or prognostic implications or are medically actionable.

The clinical utility of common genetic risk variants is less certain because their predictive power is weak and risk effects are defined in relation to a population rather than an individual. It is possible in the future that combining information on common genetic risk scores and family history (50)could be helpful for stratifying patients for the purpose of treatment or prognosis; for example in identifying those who are at elevated risk of future psychosis or in guiding

treatment. At present however these remain the domain of research questions that need to be answered.

In summary, many novel genetic findings on ADHD have emerged and will continue to do so in the 21st century. Such discoveries are of interest and relevance in my view to a much broader scientific field including neuroscientists, developmental scientists and population epidemiologists, as well as clinicians because they contribute to our conceptualization of ADHD and can shape the next five years of research and clinical practice.

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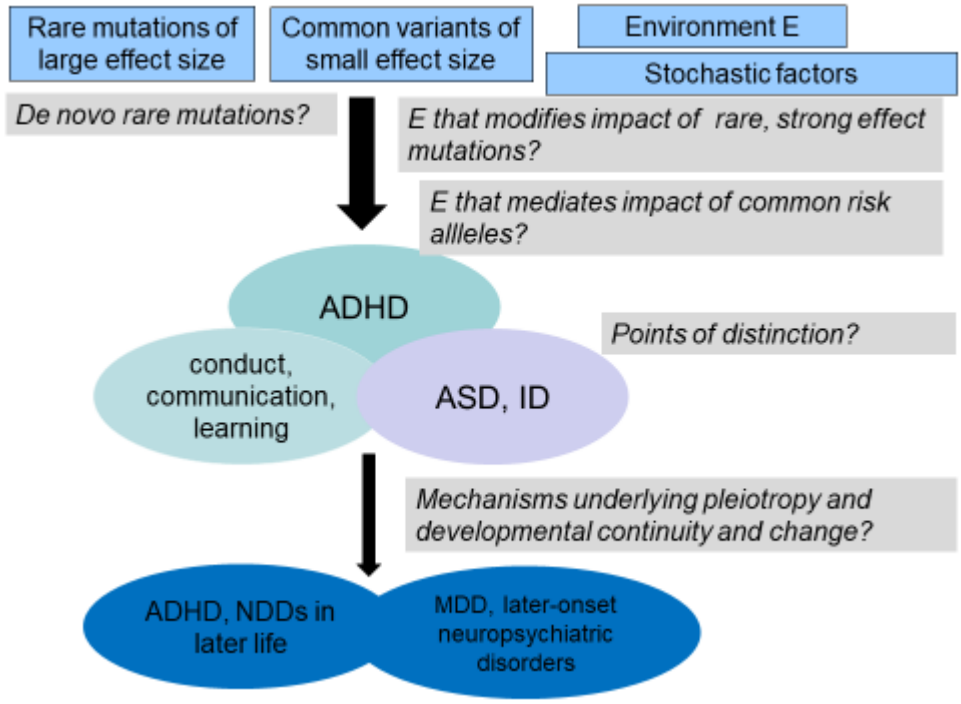
Figure 1

ADHD shows neurodevelopmental overlaps and pleiotropy: questions for the future



NDD: neurodevelopmental disorder