What are the key directions in the genetics of attention deficit hyperactivity disorder?

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Purpose of review

The aim of this review is to describe the considerable advances in consolidating the empirical evidence on several key topics in the genetics of attention deficit hyperactivity disorder, namely the quantitative genetic studies of the nature of attention deficit hyperactivity disorder and its comorbidities, the molecular genetic studies that show modest but consistent effects of specific genotypes, and the growing recognition of genotype by environment interaction. Such interactions are studied to explain what happens when individuals with a susceptible genotype are exposed to a particular environment.

Recent findings

There have been a significant number of twin studies that have examined different models of the symptomatology of attention deficit hyperactivity disorder and how these symptoms are reported. Similarly, molecular genetic research is complicated by very different outcome measures, and study across the whole field is made more problematic by genotype by environment interaction effects. One of the most interesting areas of development is that of psychopharmacogenetics.

Summary

Two key developments have been integrative models of the genetics of attention deficit hyperactivity disorder and brain structure, which may have implications for future attention deficit hyperactivity disorder subtyping, and collaboration. This is not just within attention deficit hyperactivity disorder as in the IMAGE study, but also across disciplines.

Keywords

attention deficit hyperactivity disorder, comorbidity, family factors, genetics, subtyping

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Introduction

The high prevalence of attention deficit hyperactivity disorder (ADHD) [1] has long made it a focus of twin and family studies of its genetics [2]. The treatment of ADHD with stimulant medication has focused attention on dopamine, and there are now many molecular studies of candidate genes, as well as full-genome scans. DSM-IV never follows DNA, however, and there is ongoing debate as to genetically homogeneous subtypes of ADHD and to how genetics handles the two DSM-IV-defined dimensions of inattention and hyperactivity–impulsivity.

We have reviewed the recent literature to address two key questions. The first is, what are the twin and family studies telling us about the nature of ADHD, its subtypes and the sensitivity of different measures of assessing ADHD? In the end, even the most sophisticated genetic or imaging studies depends on the quality of ratings by informants (children, parents, and teachers). As ADHD rarely occurs by itself, do comorbid conditions give a clue as to its heterogeneity? Secondly, how do we make sense of the explosion of molecular genetic studies of ADHD, often with contradictory findings? Rather than summarizing all these, we have sought to identify what may be key differences between studies and their outcomes. Three offshoots have come from the molecular work: first, more discussion of endophenotypes and the concept that the brain measures are closer to the gene than behavioural ratings; second, the growing evidence for genotype by environment interaction ($G \times E$), so that genotypes are differentially sensitive to environmental effects; third, psychopharmacogenetics – that there are genetic differences in the response to medication for ADHD.

Our task has been made easier by two recent texts [3••,4••]. The former has six chapters covering all aspects of genetics with a strong emphasis on putative endophenotypes. The latter is more clinically focused but has a considerable amount of relevant material, especially on treatment issues.

Twin and family approaches to the nature of attention deficit hyperactivity disorder

There have been two recent twin studies, one in Australia [5•] and one in the Netherlands [6•], based on the SWAN scale (Strengths and Weaknesses of ADHD Symptoms and Normal Behavior). While the SWAN scale may seem less relevant to clinical populations, it is uniquely important for population-based samples as it recognizes that some children may perform above average. The scale not only covers the range from 'no symptoms' to 'severe impairment' but also allows for the possibility of children who do 'better than average' on symptoms of inattention and hyperactivity–impulsivity. While this does have some applicability to treatment programs that may seek to make children 'better' than average, its real role lies in the EDAC (Extremely Discordant and Concordant) approach to sibling studies, as it creates distinctions within the large group of children who are usually categorized as having no symptoms.

Yet the studies are not without an interesting problem and difference. The monozygotic (MZ) twin correlations are very similar in both studies but the dizygotic (DZ) ones are quite different. What helps to explain this is that both studies included additional data, collected at the same time. The Australian study included a conventional DSM-IV scale analogous to the disruptive behavior rating scale (DBRS) [7] while the Dutch study included the parental version of the Child Behavior Checklist (CBCL). There are clearly differences in how parents recognize differences between their DZ twin children on these scales. Children are perceived as more similar on the SWAN scale, reasonably similar on DSM-scales and very different on the CBCL, emphasizing the point made by Thapar *et al.* [8]. It is not just an issue of differences in heritability, but also one of clinical significance as parents report on their children's ADHD symptoms does partly depend on how the questions are phrased.

Furthermore, the Dutch group [9••] performed a genetic analysis of some 1000 twin pairs, where they had data at ages 7, 10 and 12 on the CBCL, as well as data on the widely used Conners Rating scale and also a DSM-IV interview, based on a translation of the Diagnostic Interview Schedule for Children (DISC). The phenotypic (observed) correlations between the three scales ranged from 0.44 to 0.77, and the cross-twin correlations were used to demonstrate a substantial genetic correlation between the measures. This was complicated, however, especially in the two younger (age 7 and 10) CBCL measures, by a very strong contrast (or genetic dominance) effect in the DZ twins, which was less on the 12-year-old CBCL and on the other two measures. Was this just associated with parents differentiating their DZ twins more at earlier ages?

Both the Australian and the Dutch studies analysed inattention and hyperactivity–impulsivity separately, but a very large sample of 6222 pairs from the UK Twins Early Development Study (TEDS) [10••] examined the overlap between the two dimensions. While the genetic overlap is significant, they raised the interesting question of symptom-specific genes. Others have sought to dissect ADHD and its genetics, based on patterns of comorbidity; for example, is there a unique subtype of ADHD associated with obsessive–compulsive disorder (OCD) [11] and is there a differential genetic association of ADHD with substance abuse compared specifically with alcohol dependence [12]?

The relationship of ADHD to conduct disorder has long been a matter of controversy, and a recent very complex statistical analysis has addressed the question of whether there really is a subtype of ADHD with conduct disorder, consistent with the ICD-10 perspective. Although based specifically on twins with learning disabilities, the answer is negative and it is much better to consider conduct disorder as a correlated risk factor, rather than ADHD with conduct disorder being a distinct disorder [13••].

Twins, and especially discordant MZ pairs, are an important means of studying environmental effects. In a study of 95 such pairs, discordant and concordant for ADHD from the Netherlands Twin Registry [14••], the affected twin was smaller at birth and was delayed in both physical and motor development. Such discordant MZ twins are rare and the researchers identified differences between families of the concordant and discordant pairs on a number of key environmental variables often associated with ADHD, such as maternal smoking.

Discordant DZ pairs are much more common and the Colorado Learning Disabilities Research Center twin study [15•] used this approach to study differences on 17 measures of neuropsychological functioning between the twin with ADHD, the unaffected co-twin and control twins. Even after taking into account the symptoms of ADHD in the unaffected twins from the discordant pairs, they performed significantly worse on most measures, especially those of executive functioning, processing speed and response variability. While such results could be used to argue for the value of these measures as endophenotypes, the authors make some useful caveats about how these results could and should be interpreted.

Molecular genetics

ADHD is a disease of complex inheritance, so rather than there being a 'gene for ADHD', the disorder is due to a combination of several genes with interactions between them and also with the environment. This complicates

molecular studies and all must be seen in light of their inability to account for all the possible genetic and environmental interactions that might be present. Thus it is not surprising that in a genome-wide scan of 5980 single nucleotide polymorphisms (SNPs) in 1187 individuals [16], no genes of large effect were found. Is the phenotype correct? The study by Jain and colleagues [17] does suggest that we may have to think about the specificity down to the level of ADHD with or without ODD, conduct disorder and alcohol dependence, even though this is not consistent with the twin data discussed earlier.

As the dopaminergic system is the target for several medications for ADHD, several genes in this system have been investigated for associations with this disorder.

One such gene is the dopamine transporter, *DAT1*, on chromosome 5. A recent study [18] confirmed the associations of two variable-number tandem repeats (VNTRs) in the 3′ untranslated region and intron 8 of the *DAT1* gene. Further study of the 3′ VNTR has shown that this gene may have a role in modulating the response to methylphenidate medication in ADHD patients [19]. In another study, an association was found with an SNP in the 5′ region [20]. The involvement of *DAT1* has further been confirmed in neuroimaging studies that show differences in imaging patterns between cases and controls [21].

In contrast, Shaw and colleagues [22•] found no association between *DAT1* and ADHD. The difference in results between these studies could be due to several factors. Variation in sample size results in differing power to detect true differences. Of the above studies, the samples range from 47 to 523 and so this may indeed be a contributing factor to the conflicting observations. In addition, the choice of sample will affect the outcome. Some are population-based while others are clinically referred where one would expect a higher prevalence of the disorder. Another factor is the difference in the question being considered by each study. Are they looking to associate the gene with ADHD, its severity, or the age of onset?

Another gene for which there have been many studies is the dopamine receptor D4, *DRD4*, on chromosome 11. An association exists between the SNP at rs7124601 and both inattentive and hyperactive–impulsive symptoms [23]. Another study by the same group [24] found no evidence of an association between ADHD and *DRD4*. This highlights the difficulty in interpreting results, as in the 2007 study they were looking for effects on age of onset while in the 2008 study they were looking for effects on ADHD symptomatology. Another group [22•] found an association for the 7-repeat allele of *DRD4* on ADHD. This group were looking at clinical outcome and cortical development so again they were asking a different question to both of the Lasky-Su studies. While the association of ADHD with IQ has long been recognized, a recent analysis from the IMAGE cohort has failed to replicate the connection with *DRD4* [25].

Are genes specific to ADHD or do they apply more generally to personality dimensions? This has long been an issue with *DRD4*, and a recent meta-analysis [26••] has confirmed there is an association with novelty-seeking and impulsivity but not the broader concept of extraversion.

Another dopaminergic gene under investigation, but less so than *DAT1* and *DRD4*, is the dopamine receptor D1, *DRD1*, on chromosome 5. This has been specifically associated with inattention problems [27] in a sample selected for reading problems. This study is very interesting given the long debate over the genetic association of reading and ADHD. Their results were specific to inattention and quite independent of reading disability. Again, there are studies that find no association [22•].

Moving away from the dopaminergic system, there are several other genes of interest. *SNAP-25*, on chromosome 20, is involved in presynaptic neurotransmitter release. A recent study found an association between two SNPs of this gene and ADHD [28]. Interestingly, they found the association was stronger in people with comorbid major depressive disorder. This highlights the importance both of sample selection and comorbidity in molecular studies of ADHD. If this group had screened out people with major depressive disorder, as many would, then their results would not have been so persuasive as the association with ADHD without major depressive disorder is weaker. Also, the observation that the association is stronger in people with the comorbid disorder shows that work on the interactions between the various genes involved with ADHD needs to be explored. While it is safe to say that no one gene causes ADHD, it may also be the case that no one gene causes only ADHD. This means that genes implicated in the commonly found comorbid disorders (such as *DRD1* for reading as noted above) should be explored to see whether they have any effect in ADHD when it is comorbid.

Other genes of interest include *MAOA* [29], *DBH*, *DRD2* [30] and *DRD5* [31] but rather than discussing these specific results, it is worth considering two more general issues.

The first issue is the increasingly recognized one of genotype–environment interaction where some genotypes are more sensitive or susceptible to environmental insults (e.g. birth complications, family problems). Nigg *et al.* [32••] developed a unique approach where markers on three genes were used to identify those at high risk

and to examine this relationship with psychosocial adversity. Interestingly, the outcome measure was not ADHD but a neuropsychological task often associated with ADHD, namely the Stop measure of response inhibition. A more direct measure of G x E in ADHD has come from the Mannheim Study of Children at Risk [33] where those homozygous for the 10-repeat allele of the 40-bp VNTR polymorphism of *DAT1* and who had experienced psychosocial adversity were more likely to display both inattentive and hyperactive–impulsive symptoms. Prenatal smoking has long been identified as a risk factor for ADHD, and Missouri studies [34••,35] have indicated an association with *DRD4* and *DAT1*. It may be premature to label such studies under the term G × E. It may be G × G. Psychosocial adversity does reflect genotype as well as environment, and certainly pregnant women who smoke may well have a risk-taking personality.

One of the most exciting areas of molecular genetics is that of psychopharmacogenetics and whether people with particular genotypes are more or less responsive to medication. While this is an obvious possibility given stimulant medication and the involvement of the dopamine genes in ADHD, work is at an early stage. Two recent texts [36,37] summarize the newer initiatives, which are helpful though not as exciting as one might have hoped. The adrenergic alpha2A receptor gene [38] does influence the response of inattentive symptoms to methylphenidate, suggesting a role for the noradrenergic system. On the other hand, other work [39] has found no role for key dopaminergic and serotonergic genes in their methylphenidate response. To show how sensitive and perhaps how speculative the whole topic is, a recent Montreal clinical sample [19] showed some genotypic differences in parental report but not in teacher report. As new medications are becoming available for ADHD, this area is likely to develop. Already there is a report [40] of differences in response to atomoxetine between children polymorphic for the cytochrome P-450 2D6 enzyme pathway, in terms of side effects such as heart rate, diastolic blood pressure and tremor.

As noted above, molecular genetic studies have very different outcome measures and the new genetic studies of drug response are clearly emphasizing this.

Conclusion

The area of ADHD genetics is exploding and, like any explosion, things are scattered. To continue the analogy, there have been several efforts to pick up the pieces, with at least one bold attempt at synthesis [41••] of a range of areas from brain imaging to molecular genetics, with a consideration also of environmental influences, namely potential prenatal insults, on ADHD. Their concept of putative ADHD subtypes based on dopamine is worthy of discussion if not a likely basis for DSM-V! It is consistent with another review centered around dopamine [42]. Another integrative approach comes from a group very experienced in neuroimaging [43], to map the effects of ADHD genes and treatments on neurobiology.

While any unitary theory of all aspects of ADHD is unlikely, these are significant initiatives. We must not forget, however, that many of our genetic analyses are limited by the diagnostic systems, and the suggestion [23] of weighting symptoms to maximize associations with SNPs is interesting in terms of letting genetics drive diagnosis rather than the reverse.

An increasing theme in research reports is the need to collaborate to achieve sufficiently large samples. A good example is the IMAGE (International Multi-Centre ADHD Gene) study [44••], which involved many European countries. Apart from the question of ensuring comparability of ascertainment and diagnoses across measures, such countries do differ genetically and the problem of potential genetic stratification does arise. As well as collaborating geographically, there is also the possibility of collaborating across conditions with the new public–private partnership, the Genetic Association Information Network (GAIN) [45••], with the realization that genome-wide scans for ADHD may well be informative about other conditions and vice versa.

A final question is why is there such an interest in genetics? We conclude with two points from the last chapter of one of the recent texts [46]. First, finding that ADHD is largely genetic does not mean pathologizing the condition, and neither does it absolve teachers and other professionals from any responsibility for a 'medical' problem. Genetic studies are giving us much more insight into what ADHD is and its association with a myriad of comorbid conditions. Their second point is sufficiently controversial that it is best summarized by a quote:

> Earlier identification of children at risk is likely to become feasible – for instance by foetal DNA analysis. Whether this leads onto screening programs and early interventions will depend on many factors still to be researched – not only the positive and negative predictive value of screening tests, but the cost and effectiveness of interventions and their public acceptability. (p. 498)

Is this the ultimate goal of genetic studies of ADHD?

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 425–428).

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