Shared biological risks that influence brain and behaviour

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Attention deficit hyperactivity disorder (ADHD) is a common childhood-onset neurodevelopmental disorder. Comorbidity with other neurodevelopmental conditions, learning problems and psychiatric disorders is high and ADHD symptoms themselves, particularly inattention, can also persist into adulthood. ADHD is indexed by high levels of functional impairment and adversely affects social relationships, academic achievements and employment record. Rates of substance misuse and smoking behaviours are elevated, contributing to the physical and mental health disadvantage of those with ADHD.

Although highly heritable, ADHD is aetiologically complex whereby the coaction and interaction of inherited and non-inherited factors likely play a role in its development, maintenance and adverse consequences. Indeed, no single causal risk factor, genetic or otherwise, has been identified to date as is the case for all common, complex disorders. The evidence suggests there is contribution from both common genetic variants of small effect size and rare variants (copy number variants) of larger effect size.[1] Such variants have been found to impact on similar biological pathways, interestingly including one related to nicotinic acetylcholine receptor signalling.[2 3] There is also growing evidence that ADHD inherited risks and associated gene variants have different phenotypic effects (pleiotropy). That is, the same set of genetic risks appears to influence ADHD, autism and other forms of developmental disorder/psychopathology and behaviour. A research question related to this observation is tackled by Thakur and colleagues.[4]

Their study sets out to examine genetic risks that may be shared between ADHD and the known comorbidity of smoking: a strategy which is attractive in view of ADHD being a risk factor for cigarette smoking and possible involvement of nicotinic acetylcholine receptor signalling. Also, it is a feasible approach given the genome-wide significant associations found in the large genome-wide meta-analyses of smoking behaviours.[5] Exploration of shared aetiologies to try and unravel the complex neurobiology of ADHD is currently topical: there is growing research into shared biological and cognitive risk mechanisms between ADHD and co-occurring conditions such as autism using genetic, cognitive and imaging designs.

Another dimension to the strategy of Thakur *et al*[4] is an interesting finding that the authors highlight: that ADHD has consistently been found to be associated with exposure to maternal smoking during pregnancy. This has been thought to be due to the causal risk effects of cigarette smoke on the developing foetus as there are biologically plausible mechanisms. The constituents of cigarette smoke can alter physiological processes which might in turn contribute to aberrant neurodevelopment in ADHD. However, research suggests that the association with maternal smoking during pregnancy may be due to the confounding effects of shared genetic liability between maternal smoking behaviour and offspring ADHD.[6]

The study by Thakur *et al*[4] benefits from a strong theoretical premise and hypothesis-driven approach and detailed neurocognitive profiling and rigorous phenotypic description with a dimensional and categorical approach. In summary, the research finds that of the five single nucleotide polymorphisms (SNPs) that were selected and considered to be significantly associated with smoking behaviour in the genome-wide meta-analysis, one, the C*allele of rs1329650 on 10q25 (which is associated with number of cigarettes smoked per day), is overtransmitted to the offspring with ADHD and is associated with several indices of phenotypic severity and neurocognitive dysfunction.

However, although the findings are potentially exciting, the authors are right to be tentative about their conclusions at this stage as there are certain cautions to be exercised when considering the implications. At a conceptual level, the SNPs found to reach genome-wide significance in the smoking meta-analysis have not been found to be associated with ADHD in either ADHD candidate gene meta-analyses or a meta-analysis of ADHD genome-wide association studies (GWAS). With small sample sizes (a limitation of all ADHD genetic studies to date) and the small effect sizes of individual gene variants, results can reflect Type 1 or Type 2 errors. Replication, as the authors state, is always necessary—especially as multiple outcomes were tested.

On the other hand, it is worth bearing in mind that studies investigating ADHD genetics to date have not had sample sizes comparable with those that have had success for other complex disorders, including psychiatric disorders. The meta-analysis of ADHD GWAS, which involves hypothesis-free testing of thousands of genetic variants, is almost certainly underpowered to detect effects. It may be that the common gene variants examined in the study by Thakur *et al* are found, in time, to be significant in subsequent GWAS or meta-analyses of larger ADHD samples. Such replications would lend greater weight to the results of this current investigation.

This interesting and novel study should be interpreted as preliminary evidence that the theoretical plausibility of shared inherited risks underlying ADHD and smoking behaviours could extend to detecting shared gene variants at a molecular level (see figure 1). Future research could perhaps consider replicating findings using case control designs as well as considering different ways of capturing smoking-associated genetic variation. It would also be interesting to investigate longitudinally the effects of smoking associated gene variants including the SNPs in this study, and to test whether they contribute to the known elevated risk of smoking behaviour in those with ADHD.

In summary, although the results of this exploratory study can only be considered as preliminary findings at present, this is an intriguing starting point from which to conduct further related

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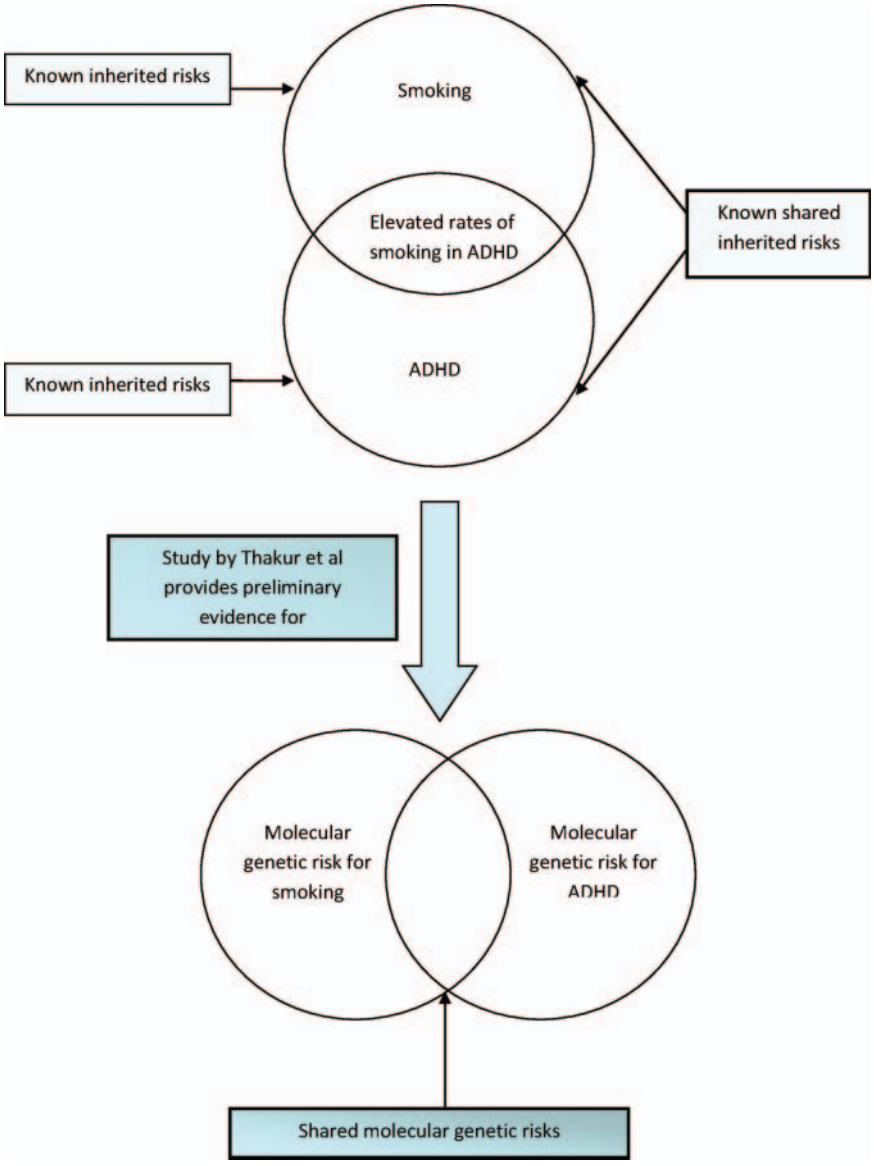

Figure 1 Illustration of shared genetic risks between attention deficit hyperactivity disorder (ADHD) and smoking.

analyses. Acknowledging that the same genetic risk variants can have different phenotypic effects could help inform discovery of risk variants for childhood developmental/psychiatric disorders for which it can be difficult to assemble very large sample sizes. Such efforts could help uncover novel biological risk pathways and contribute to explaining neurodevelopmental comorbidities.

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