

Shared polygenic contribution between childhood attention-deficit hyperactivity disorder and adult schizophrenia†

Marian L. Hamshere, Evangelia Stergiakouli, Kate Langley, Joanna Martin, Peter Holmans, Lindsey Kent, Michael J. Owen, Michael Gill, Anita Thapar, Mick O'Donovan and Nick Craddock

Background

There is recent evidence of some degree of shared genetic susceptibility between adult schizophrenia and childhood attention-deficit hyperactivity disorder (ADHD) for rare chromosomal variants.

Aims

To determine whether there is overlap between common alleles conferring risk of schizophrenia in adults with those that do so for ADHD in children.

Method

We used recently published Psychiatric Genome-wide Association Study (GWAS) Consortium (PGC) adult schizophrenia data to define alleles over-represented in people with schizophrenia and tested whether those alleles were more common in 727 children with ADHD than in 2067 controls.

Results

Schizophrenia risk alleles discriminated ADHD cases from controls ($P=1.04 \times 10^{-4}$, $R^2=0.45\%$); stronger discrimination was given by alleles that were risk alleles for both adult schizophrenia and adult bipolar disorder (also derived from a PGC data-set) ($P=9.98 \times 10^{-6}$, $R^2=0.59\%$).

Conclusions

This increasing evidence for a small, but significant, shared genetic susceptibility between adult schizophrenia and childhood ADHD highlights the importance of research work across traditional diagnostic boundaries.

Declaration of interest

None.

Large-scale genetic association studies have identified replicable susceptibility alleles for some psychiatric phenotypes.¹ This includes both common and rare variants. A striking finding has been that susceptibility variants identified to date often confer susceptibility to more than one of the traditional clinical phenotypes, a finding that has the potential to increase understanding of the biological relationship between these traditional diagnostic categories.^{1–3} The focus of this study is childhood attention-deficit hyperactivity disorder (ADHD) and its potential genetic relationship to adult schizophrenia and bipolar disorder. There is evidence of some degree of shared genetic susceptibility between schizophrenia and childhood ADHD for rare chromosomal variants.⁴ In the present study, we have considered another possible source of genetic overlap, namely common single nucleotide polymorphisms (SNPs) and we have extended the analysis to consider bipolar disorder as well as schizophrenia. The only prior study that has started to examine this, selected six bipolar genetic risk variants and identified no strong association with ADHD or with scores on the Mood Disorder Questionnaire.⁵ Here, we have used a more powerful, genome-wide approach and examined whether, when they are considered *en masse* using polygenic score analysis,⁶ multiple schizophrenia⁷ and bipolar disorder⁸ common risk alleles contribute to ADHD risk.

Method

In general, we followed the polygenic score analysis approach described by the International Schizophrenia Consortium (ISC).⁶ The basic principle of that analysis was that a set of many alleles that discriminated case status in a 'discovery' schizophrenia case-control sample, also significantly discriminated case status in an independent 'target' schizophrenia case-control sample. We

used the published Psychiatric Genome-wide Association Study (GWAS) Consortium (PGC) data-sets (schizophrenia and bipolar disorder) as two separate discovery sets and our ADHD data as the target set.

Sample

Discovery data

We made use of the PGC schizophrenia⁷ and bipolar disorder⁸ case-control data-sets. The schizophrenia sample comprised 9394 cases and 12 462 controls analysed at 1 252 901 SNPs. The bipolar disorder sample comprised 7481 cases and 9250 controls analysed at 2 427 089 SNPs. These studies contain individuals of European origin collected across Europe, the USA, and Australia. We note that there are a number of control individuals that contribute to both the PGC schizophrenia and bipolar disorder samples, including the Wellcome Trust Case Control Consortium (WTCCC) – Phase 1 control sample.⁹

Target data

We interrogated genotype data from a UK/Irish ADHD GWAS.¹⁰ The sample comprises 727 children aged 4–18 years, recruited from UK community child psychiatry and paediatric clinics and from Dublin, Ireland. All children were White, of European origin and met research diagnostic criteria for DSM-III-R¹¹/DSM-IV¹² or ICD-10¹³ for ADHD or hyperkinetic disorder. Case exclusion criteria included bipolar disorder, schizophrenia, autism, epilepsy, intellectual disability (IQ <70) or any known major neurological or medical disorders. After complete description of the study to the participants, written informed consent was obtained. The ADHD GWAS sample also included 5081 UK controls from WTCCC.¹⁴ Genotyping for the ADHD cases was performed on the Illumina (San Diego, California, USA, www.illumina.com) Human 660W-Quad BeadChip, and genotyping for the controls

†See editorial, pp. 81–83, this issue.

was performed using the Illumina Human 1.2M BeadChip. The samples, quality control assessment and results of the primary ADHD GWAS are described in detail in a previous paper.¹⁰

Statistical analysis

Approximately half of the WTCCC2 control sample had been used in the primary bipolar disorder GWAS reported by WTCCC1⁹ and a schizophrenia GWAS reported by our own group,¹⁵ both of which contributed to the PGC studies of bipolar disorder and schizophrenia respectively. It was, therefore, necessary to remove those and any overlapping case individuals from our ADHD GWAS. First, we identified individuals that were included in the earlier studies (genotyped on Affymetrix GeneChip 500K Mapping Array; Santa Clara, California, USA, www.affymetrix.com) that were also present in the primary ADHD GWAS. To do this we used 71 565 SNPs that were common to the studies that had also passed our quality control procedures. These SNPs were used to estimate identity-by-descent statistics for all pair-wise combinations of individuals. Across the two data-sets, we identified 2474 related individuals in the control sample, of which 2452 were duplicates, and no related case individuals. The related controls comprised 13 parent-offspring pairs, 7 sibling pairs, and 2 half-sibling or avuncular pairs. The duplicates and close relatives were removed from the control set giving a sample of 2067 control and 727 case individuals for our analysis of ADHD cases *v.* controls. Similar quality control approaches have been applied to our ADHD,¹⁰ bipolar disorder⁹ and schizophrenia¹⁵ case and control samples to exclude overlapping and related individuals. Given that we have previously provided the results of the full ADHD GWAS elsewhere,¹⁰ we do not provide individual-level SNP results here.

We used PLINK (1.07) for manipulation of the genetic data and to produce polygenic scores. All statistical analyses were performed with R (2.11.1). Both PLINK and R were run on Linux (Fedora release 13, x86_64).

Polygenic analysis

We made comparisons between ADHD cases and controls to determine whether the schizophrenia and/or bipolar derived polygenic scores were significantly different. We first selected a set of SNPs in relative linkage equilibrium in our ADHD and control sample using a sliding window of 200 SNPs, moving it along the genome in steps of 5 SNPs and dropping a SNP when the pair-wise estimate of linkage disequilibrium (r^2) was greater than 0.2 (PLINK command: `-indep-pairwise 200 5 0.2`).¹⁶ From the results of the GWAS for each PGC sample, we identified for the selected SNPs their corresponding *P*-values, associated alleles, and the odds ratios (OR) for those alleles. Based on the result of both the ISC⁶ and PGC studies, our primary analyses are based on an 'association' threshold $P_T < 0.5$. Alleles that are more common in the cases for which the two-tailed *P*-values met the condition $P_T < 0.5$ are termed the 'score' alleles.⁶ For each individual in

the target data, we obtained the polygenic score for that individual which corresponds to the mean per-SNP product of the number of score alleles and the \log_e odds ratios.⁶ We employed logistic regression analysis to compare the polygenic scores in the target set (ADHD *v.* controls). As with our ADHD GWAS,¹⁰ to allow for population stratification within the sample, the regression analysis is performed conditional on two covariates (the first two principal components estimated from our GWAS data using EIGENSTRAT^{17,18} software designed for this purpose). For each analysis we report the *P*-value (two-tailed) and pseudo- R^2 , the latter being a measure of the estimated variability in case-control status explained. Analyses were performed separately for score alleles derived from schizophrenia and bipolar disorder data-sets.

We interrogated the data further by creating polygenic scores based on simultaneous patterns of association in the PGC schizophrenia and bipolar disorder data-sets. Specifically, we were interested in testing the hypothesis that the set of alleles that showed evidence for association in both schizophrenia and bipolar disorder was the same set of alleles that was enriched for shared effects in ADHD risk. Alternative (non-null) hypotheses are that alleles that were relatively specific for one or the other disorder were enriched for those that confer risk of ADHD.

To examine these possibilities, we identified six sets of alleles. We first took the set of alleles at $P_T < 0.5$ in schizophrenia and divided them into those that did and those that did not also surpass $P_T < 0.5$ in bipolar disorder. Single nucleotide polymorphisms that surpassed $P_T < 0.5$ in both data-sets were further divided into two groups dependent on whether the allele that was over-represented in the bipolar disorder cases (compared with controls) was the same as the allele over-represented in the schizophrenia cases. These groups were then analysed separately. We note that, as expected given shared controls in the PGC schizophrenia and bipolar disorder GWAS data-sets, and also given the known overlap in polygenic risk between schizophrenia and bipolar disorder,⁶ if an SNP surpassed $P_T < 0.5$ in schizophrenia, it was slightly more likely also to do so for bipolar disorder than chance (Table 1). Moreover, for the same reasons, but most particularly because of the shared controls, where SNPs surpassed $P_T < 0.5$ for both schizophrenia and bipolar disorder, for most SNPs, the same allele was over-represented in both sets of cases compared with the controls. To help show the relationships between the six sets of SNPs, a graphical representation of the SNP selection is provided in the online supplement (online Fig. DS1).

Results

The polygenic score representing schizophrenia risk was significantly different between ADHD cases and controls, with higher scores observed in the ADHD cases (Table 1). Attention-deficit hyperactivity disorder cases also had a higher polygenic score representing

Table 1 Summary of results in the target sample comparing ADHD cases *v.* controls^a

Discovery sample	SNP selection criteria	SNPs, <i>n</i>	ADHD <i>v.</i> controls		
			<i>z</i> -statistic	R^2 , %	<i>P</i>
Bipolar disorder	Bipolar disorder $P < 0.5$	50 512	1.94	0.11	0.0519
Schizophrenia	Schizophrenia $P < 0.5$	48 494	3.88	0.45	1.04×10^{-4}
Schizophrenia	Schizophrenia $P < 0.5$ and bipolar disorder $P \geq 0.5$	22 595	1.63	0.080	0.102
Schizophrenia	Schizophrenia $P < 0.5$ and bipolar disorder $P < 0.5$	25 137	4.40	0.58	1.09×10^{-5}
Schizophrenia	Same direction of effect in schizophrenia and bipolar disorder	17 303	4.42	0.59	9.98×10^{-6}
Schizophrenia	Different direction of effect in schizophrenia and bipolar disorder	7834	1.21	0.044	0.225

ADHD, attention-deficit hyperactivity disorder; SNP, single nucleotide polymorphism.

a. In all analyses, the ADHD cases had more risk alleles than the controls. All *z*-statistics are distributed with one degree of freedom and all *P*-values are two-tailed.

bipolar disorder risk but the effect was weaker than that for the polygenic score representing schizophrenia as estimated by R^2 , and just failed to attain a conventional level of statistical significance. For both analyses, the magnitudes of these effects (as defined by R^2) were much smaller than the 6% or 3% observed when the discovery and target sets both comprise schizophrenia⁷ or both bipolar disorder⁸ data-sets respectively.

In the analyses based on the patterns of association in schizophrenia conditional on that in bipolar disorder, only the set of SNPs that surpassed $P_T < 0.5$ in both samples produced a significant score difference between ADHD cases and controls ($P = 1.09 \times 10^{-5}$). This effect appeared to be largely driven by the set of alleles with the same direction of effect in schizophrenia and bipolar disorder ($P = 9.98 \times 10^{-6}$). The scores derived from the set in which the alleles had opposite effects in schizophrenia than in bipolar disorder were not significantly different between ADHD cases and controls. Findings that were significant in Table 1 (plus the bipolar disorder analysis) are presented in online Fig. DS2 for a range of different significance thresholds. Consistent with the findings of the ISC, $P < 0.5$ gives most evidence for discrimination of ADHD cases from controls. Our significant results are maintained across the full range of thresholds.

For polygenic score analysis, the number of alleles used in the analysis can have a large effect on significance and the effect size estimated from R^2 . The number of alleles differed substantially between those that were in the same direction in schizophrenia and bipolar disorder ($n = 17\,303$) and those that were in opposite directions ($n = 7834$). We, therefore, undertook a simulation study to assess the impact of this variable on our evaluation of the contribution from alleles at SNPs surpassing $P_T < 0.5$ but for which the direction of association differed in schizophrenia and bipolar disorder. From the 25 137 SNPs surpassing $P_T < 0.5$ in both disorders (i.e. schizophrenia and bipolar disorder), we selected at random a subset of 7834 SNPs (i.e. the number that had been included in the analysis of SNPs showing different directions of effect), and the remaining subset of 17 303 SNPs (i.e. the number that had been included in the analysis of SNPs showing the same direction of effect), and performed polygenic score analysis on both sets of SNPs. The difference in R^2 was estimated from the two analyses. Repeating the procedure 10 000 times gave a distribution of difference in R^2 against which we could empirically evaluate whether our observation of a weaker result for the SNPs with opposite directions of effect simply reflects a smaller set of SNPs being used. In the simulated data, the probability of observing a difference in R^2 at least as large as that observed in the real data (i.e. observed difference in $R^2 = 0.55$) was 0.09 (i.e. in 900 out of 10 000 random SNP draws was a larger difference in R^2 detected than in the observed data). This does not allow us to reject the null hypothesis that there is no difference in the SNPs associated with schizophrenia and bipolar disorder at $P < 0.5$ with respect to the direction of effect. This in turn amounts to suggestive evidence ($P = 0.09$) that alleles that are over-represented in the cases in both schizophrenia and bipolar disorder GWAS data-sets proportionately capture more polygenic signal than those alleles that are more common in schizophrenia, but less common in bipolar disorder, when compared with controls.

Discussion

Aetiological overlaps between childhood-onset and major adult psychiatric disorders have, until relatively recently, been ignored in molecular genetic studies. Here, using a sample of 727 children and adolescents affected with ADHD and 2607 controls, we have

demonstrated significant evidence for an overlap in polygenic susceptibility to schizophrenia and ADHD. No significant evidence was observed for a similar overlap between polygenic susceptibility to bipolar disorder and ADHD, although the level of significance was suggestive, so a potential relationship may be detectable in future studies with larger samples. This is the first study of its kind to identify a SNP-based relationship between ADHD risk and that for either schizophrenia or bipolar disorder. In this study, the overlap between ADHD and schizophrenia appears stronger than it is between ADHD and bipolar disorder. However, this could, in part, be related to somewhat lower power (i.e. smaller sample size) of the PGC bipolar disorder sample than the PGC schizophrenia samples used in the discovery part of the analysis, although the differences in sample size are not marked. The estimated effect sizes of the schizophrenia and bipolar disorder polygenic risk scores we report here in our ADHD sample are smaller than those observed by the ISC when taking schizophrenia-defined score alleles and investigating these in individuals with schizophrenia or bipolar disorder compared with controls (2–3% and 1–2% respectively).⁶ The estimated effect sizes for bipolar disorder-defined score alleles in our ADHD *v.* control analysis are smaller than that observed when we reanalyse our data using the ISC schizophrenia data-set as discovery data (see the online supplement). As the ISC sample size (about 7000 individuals in total) is smaller than that of either the PGC schizophrenia or bipolar disorder sample, the discovery sample size cannot be a major factor driving the lower effect sizes seen here.

An observation that may help to provide insight into the genetic architecture of the relationship between the various disorders is the larger effect, as measured by R^2 for sets of SNPs that show similar directions of effect in schizophrenia and bipolar disorder. This observation needs to be treated with some caution because of the occurrence of some shared controls within the PGC schizophrenia and bipolar disorder data-sets that biases towards finding more shared susceptibility alleles than would be expected under the null hypothesis. Nonetheless, if this observation receives support in independent studies, it would suggest that not all schizophrenia susceptibility alleles are equivalent. They may reflect different phenotypic risk effects. Alternatively, given the overlap in schizophrenia and bipolar disorder, they may reflect the more ‘replicable’ or true alleles.

It is important to acknowledge that our findings do not distinguish between susceptibility alleles that may be (a) highly non-specific and span across multiple psychiatric conditions (not just schizophrenia and ADHD) and those that may be (b) relatively specific to schizophrenia and ADHD. Distinguishing between these possibilities will require studies that include a wider range of psychiatric phenotypes.

The links between ADHD, other early neurodevelopmental disorders (notably autism) and later-onset major psychiatric disorders are of growing interest. A subgroup of children with ADHD, but not a majority, develops later mood and bipolar affective disorder. The relationship with schizophrenia has been less well researched, although it is well recognised that a substantial proportion of those with schizophrenia and their offspring show early developmental problems that include attentional difficulties. Studies of ADHD in families in which a parent is affected with schizophrenia show that, in comparison with the offspring without ADHD, the offspring affected with ADHD experienced more neurological dysfunction,^{19,20} functional impairment,²⁰ psychotic-like symptoms²¹ and an increased risk of developing schizophrenia spectrum disorders.^{19,22} A history of DSM-IV childhood ADHD is also found to be more frequent in patients with schizophrenia spectrum disorders and in individuals at risk of developing these disorders than in the general population, although the reported

prevalence rate of ADHD varies widely, a likely consequence of sample characteristics.²³ Our results suggest that these observed links may in part follow from a shared genetic liability to ADHD and schizophrenia and that further investigation of whether they index specific neurodevelopmental impairments is needed.

Our observation of an overlap in genetic susceptibility for common variants in the current analysis is consistent with an observation of an overlap in genetic susceptibility between ADHD and schizophrenia for rare copy number variants (CNVs).⁴ In that study, based on a smaller sample of 366 ADHD case individuals (a subset of the sample presented here), we found that large (>500 kb), rare CNVs were significantly more common in cases than controls,⁴ and that CNVs identified in the ADHD cases were significantly enriched for loci previously reported in both autism ($P=0.0095$) and schizophrenia ($P=0.010$).⁴ We note that when excluding ADHD samples known to have large CNVs, our results are unchanged. Taken together with the current results, this is supportive evidence for an overlap in common, as well as rare, risk variants for ADHD and schizophrenia. We propose that in conjunction with the CNV data, this is suggestive evidence for the genetic architecture of ADHD being closer to schizophrenia than bipolar disorder.

As mentioned in the introduction, a striking finding from GWAS of psychiatric disorders has been the overlap in genetic association signals across different psychiatric disorders. An important goal of PGC, the international consortium for analysing psychiatric GWAS data, is to undertake systematic cross-disorder analyses using data-sets for schizophrenia, bipolar disorder, recurrent depression, autism and ADHD.³ The vast majority of the ADHD data that we report here are not included within the Cross Disorders Group (CDG) analyses (see online supplement for details). When the PGC CDG analyses are available it will be important to explore the similarities and differences between findings in the two data-sets.

Strengths and limitations

There are several strengths of this study including the systematic genome-wide approach, the large size of the training samples and the novelty of the analysis applied to ADHD and schizophrenia. It is, however, important to consider potential limitations. As with all large-scale genotyping approaches, there is the possibility that systematic bias may influence the results. Population stratification is a confounder that can cause bias in case-control studies. We do not believe that population stratification has resulted in the findings presented here. First, we take into account principal components of our genotype data to adjust for hidden stratification. Second, the ISC excluded population stratification as an explanation for the broad effects seen between cases and controls.⁶ Finally, it is highly unlikely that exactly the same stratification differences would occur between the case and comparison data-sets in both discovery and target samples.²⁴ We cannot exclude the possibility that genotyping platform has influenced our results. However, extensive quality control was performed for the PGC schizophrenia and bipolar disorder samples,^{7,8} and the target ADHD GWAS sample¹⁰ to ensure the genotypes for the case and control samples were comparable. A further potential source of bias is the theoretical possibility that by chance, or otherwise, our sample could have unusual phenotypic characteristics that increased the likelihood of a genetic similarity between ADHD and schizophrenia or bipolar disorder. Such an eventuality could, in principle, influence the statistical comparisons and/or limit the generalisability of findings to other samples. However, although noting that systematic phenotypic differences could occur, we are not aware

of such selection effects in our sample and have no reason to believe this affects our results or conclusions.

It is important to stress that the statistical significance seen in the comparisons we report are driven by large sample sizes, not large effect sizes. As in previous studies that use the polygenic score approach,^{6–8,24–26} the proportion of variance explained is negligible (<1% of the variance in the present study). However, we should note that the underlying variance being captured indirectly may be considerably greater. Indeed, in the ISC study,⁶ although R^2 was about 3%, the true total underlying variation in liability estimated by the polygenic model was approximately 33%, a conclusion broadly supported by similar analyses of the PGC data,^{7,8} and by an analysis of the PGC data using an entirely different approach.²⁷ As an increasing proportion of the common genetic variation is accurately captured through increased sample sizes, it can be expected that much more of the variance attributable to the polygenic contributions, unique and shared across disorders, will be explained. This approach may therefore become an increasingly useful research tool for probing the relationships between disorders, and even potentially a useful clinical tool.⁶

In summary, we provide evidence that common genetic variation contributes to risk for ADHD. ‘Risk’ alleles from schizophrenia in particular, and also bipolar disorder to some extent, are found to differentiate ADHD cases from control individuals. Our results indicate the need for further studies of the genetic relationship between ADHD and adult mood and psychotic disorders.

Marian L. Hamshere, PhD, **Evangelia Stergiakouli**, PhD, **Kate Langley**, PhD, **Joanna Martin**, BSc, **Peter Holmans**, PhD, Institute of Psychological Medicine and Clinical Neurosciences, MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University School of Medicine, Cardiff, UK; **Lindsey Kent**, MRCPsych, PhD, Bute Medical School, University of St Andrews, Fife, UK; **Michael J. Owen**, FRCPsych, PhD, Institute of Psychological Medicine and Clinical Neurosciences, MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University School of Medicine, Cardiff, UK; **Michael Gill**, MD, Department of Psychiatry, Trinity Centre for Health Sciences, Dublin, Ireland; **Anita Thapar**, FRCPsych, PhD, **Mick O'Donovan**, FRCPsych, PhD, **Nick Craddock**, FRCPsych, PhD, Institute of Psychological Medicine and Clinical Neurosciences, MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University School of Medicine, Cardiff, UK

Correspondence: Professor N. Craddock, Institute of Psychological Medicine and Clinical Neurosciences, MRC Centre for Neuropsychiatric Genetics and Genomics, School of Medicine, Cardiff University, Heath Park, Cardiff CF14 4XN, UK. Email: CraddockN@cardiff.ac.uk

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