Original Article

Psychiatric gene discoveries shape evidence on ADHD’s biology

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A strong motivation for undertaking psychiatric gene discovery studies is to provide novel insights into unknown biology. Although attention-deficit hyperactivity disorder (ADHD) is highly heritable, and large, rare copy number variants (CNVs) contribute to risk, little is known about its pathogenesis and it remains commonly misunderstood. We assembled and pooled five ADHD and control CNV data sets from the United Kingdom, Ireland, United States of America, Northern Europe and Canada. Our aim was to test for enrichment of neurodevelopmental gene sets, implicated by recent exome-sequencing studies of (a) schizophrenia and (b) autism as a means of testing the hypothesis that common pathogenic mechanisms underlie ADHD and these other neurodevelopmental disorders. We also undertook hypothesis-free testing of all biological pathways. We observed significant enrichment of individual genes previously found to harbour schizophrenia de novo non-synonymous single-nucleotide variants (SNVs; P = 5.4 × 10−4) and targets of the Fragile X mental retardation protein (P = 0.0018). No enrichment was observed for activity-regulated cytoskeleton-associated protein (P = 0.23) or N-methyl-D-aspartate receptor (P = 0.74) post-synaptic signalling gene sets previously implicated in schizophrenia.

Enrichment of ADHD CNV hits for genes impacted by autism de novo SNVs (P = 0.019 for non-synonymous SNV genes) did not survive Bonferroni correction. Hypothesis-free testing yielded several highly significantly enriched biological pathways, including ion channel pathways. Enrichment findings were robust to multiple testing corrections and to sensitivity analyses that excluded the most significant sample. The findings reveal that CNVs in ADHD converge on biologically meaningful gene clusters, including ones now established as conferring risk of other neurodevelopmental disorders.

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INTRODUCTION

Attention-deficit hyperactivity disorder (ADHD), a childhood-onset neurodevelopmental disorder,1 is highly heritable.2,3 Despite this strongly consistent finding, some remain sceptical about the diagnosis of ADHD, the biological validity of such a construct, and its neurodevelopmental origins.4 Public misunderstanding is further fuelled by the relative scarcity of knowledge regarding its pathophysiology. The knowledge gap on pathophysiology is not straightforward to address given practical limitations to directly assess biological and molecular systems in those who are affected. Genetic findings offer one non-invasive approach to providing clues about the biology and pathogenesis of neuropsychiatric disorders.5–7

In the last 5 years, one class of genetic variant (large, rare chromosomal deletions and duplications (copy number variants; CNVs)) has been found to contribute to ADHD risk across multiple studies.8–12 Common genetic variants also contribute to ADHD when considered ‘en masse’ as a composite risk.13–19 One important observation from the original ADHD CNV studies was that the CNVs spanned chromosomal and gene regions that overlapped with schizophrenia and autism loci.9,11 Since then, exome-sequencing investigations of schizophrenia and autism have been published and have highlighted additional novel genomic regions that harbour neurodevelopmental disorder risk variants (single-nucleotide variants; SNVs).20–23 Exome-sequencing results for ADHD are awaited. Unlike CNVs, which generally span multiple genes, SNVs are located in individual genes and thus offer improved resolution for testing cross-disorder pathogenic mechanisms.

Schizophrenia and autism genetic findings have also indicated specific biological mechanisms; these involve targets of the Fragile X Mental Retardation protein (FMRP) in schizophrenia and autism24 and in schizophrenia, genes involved in glutamatergic post-synaptic processes: ARC (activity-regulated cytoskeleton-associated protein) and NMDAR (N-methyl-D-aspartate receptor) complexes.20,21,25 Additional pathways have been reported to be enriched for SNVs (for example, calcium channel complexes in

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and the deviations of the two models compared. If there is no enrichment of case CNVs hits on pathway genes, then the difference in deviations should be distributed asymptotically as a $\chi^2$ on one degree of freedom.29 CNV length was fitted in the model because long CNVs are more likely to hit any set of genes than small ones, and CNV length may differ systematically between cases and controls. The ‘number of genes hit outside a pathway’ was fitted to allow for case CNVs influencing disease status by hitting genes other than those in the pathway being tested. A binary variable (yes/no) is used for whether a CNV ‘hits gene(s) in a pathway’ rather than the number of genes in the pathway hit by the CNV (which is also a possibility) to allow for some pathways having several genes that are physically close together (thus, likely to be hit by the same CNV). The same analysis method was used to determine gene-specific enrichments, by defining the ‘pathway’ as the gene.

For all analyses, we tested pathways showing significant enrichment in the combined data set of five studies and then undertook tests of sensitivity by examining each of the five data sets separately and rerunning analysis after excluding the most significant single sample. Additional analyses were stratified by CNV type (deletions and duplications). As the number of duplications was greater than the number of deletions,10 we tested for differential strengths of enrichment by comparing case duplications to case deletions in the logistic regression framework described above.

Specific gene sets

**Genes selected by location.** Four sets of genes were defined: (a) non-synonymous and (b) loss-of-function de novo SNVs in schizophrenia were taken from the most recent published de novo exome-sequencing study of schizophrenia, which also catalogued and annotated all SNVs in previous studies in a consistent way.29 There were a total of 611 genes containing at least one non-synonymous de novo SNP, with 87 of these containing a de novo loss-of-function SNP. We also took sets of genes containing: (c) non-synonymous and (d) loss-of-function de novo SNVs from the two largest, recent exome-sequencing studies of autism.22,23 Combining the autism SNV sets from these studies, there were 2726 unique genes containing at least one non-synonymous de novo SNP, of which 538 contained a loss-of-function de novo SNP.

**Genes selected by function: FMRP targets, ARC and NMDAR.** Next, we examined a further three gene sets by function, selecting those implicated in schizophrenia and autism by CNV and more recent exome-sequencing studies. These were genes involved in FMRP targets (840 genes) as defined previously25 and the ARC (28 genes) and NMDAR (61 genes) complexes, as defined by Kirov et al.25 Bonferroni corrections were used to adjust for testing seven gene sets.

**Hypothesis-free analysis of all pathways.** This final analysis was undertaken using a large, unbiased, general set of pathways comprising:

- (a) Gene Ontology31 (http://www.geneontology.org/, accessed on July 2013)
- (b) KEGG23 (http://www.genome.jp/kegg/, accessed on June 2013)
- (c) PANTHER pathways version 3.1 (http://www.pantherdb.org/pathway/)
- (d) Mouse Genome Informatics database33 (http://www.informatics.jax.org/, accessed on August 2013)
- (e) BioCarta (http://www.biocarta.com, accessed on June 2013)
- (f) Reactome23 (http://www.reactome.org, accessed on June 2013)
- (g) NCI25 (http://pid.nci.nih.gov, accessed on June 2013)

Pathways containing between 3 and 1500 genes were used in the analysis (15 111 in total). To increase the accuracy of the asymptotic $P$-values described above and to reduce the chance of a small pathway being falsely declared to be enriched based on a few gene hits, analysis was restricted to pathways with at least 10 gene hits in the total sample (7034 in total). Correction for multiple testing of pathways was performed by calculating $q$-values.26

**RESULTS**

Table 1 shows the number of large, rare CNVs (>500 kb) for each of the previously published five case control samples and the total number of deletions and duplications. The rate and burden of CNVs for each sample have been published previously.9–11,26,37
Gene sets selected by location of schizophrenia and autism
de novo SNVs
The genes containing non-synonymous schizophrenia de novo SNVs were significantly enriched for case ADHD CNV hits \((P = 5.4 \times 10^{-4}\) for CNVs >500 kb, see Table 2), which is significant after Bonferroni correction. Findings remained significant even after the most significant single sample was removed from the analysis (Table 2). The significant enrichment was observed for duplications \((P = 5.6 \times 10^{-4}\) but not for deletions \((P = 0.37)\). However, there was no significant difference between ADHD duplication and deletions in terms of the rate of hits for genes previously found to carry non-synonymous schizophrenia SNVs \((P = 0.142)\). For sample-specific enrichments, see Supplementary Table 1, and see Supplementary Table 2 for gene-wide \(P\)-values. Restricting analysis to genes hit by loss-of-function de novo schizophrenia SNVs showed no significant enrichment for case CNV hits.

Table 2 shows a nominally significant enrichment of CNVs among autism de novo SNV genes (non-synonymous or loss-of-function), although these do not survive Bonferroni correction.

Gene sets selected by function
There was significant enrichment of ADHD case CNVs in FMRP targets \((P = 0.0018)\), which remained significant after Bonferroni correction (see Table 3 for details). The enrichments also remained significant when the most significant single sample was removed. Significant enrichment was observed for duplications \((P = 0.005)\) but not for deletions \((P = 0.18)\), although there was no significant difference between the rate of case duplication and deletion hits for FMRP target genes \((P = 0.247)\). See Supplementary Table 3 for sample-specific enrichments and Supplementary Table 4 for FMRP target genes that showed significant enrichment. There was no evidence of enrichment of ARC complex or NMDAR gene sets.

Hypothesis-free analysis of all pathways
The most significantly enriched pathways are shown in Table 4, with those remaining significant in the sensitivity analysis highlighted in bold. As can be seen from the \(q\)-values, many of these were highly significant even after correction for multiple testing of pathways. Much of the enrichment appeared to come from duplications, with the exception of the ion channel pathways where enrichment was observed in both deletions and duplications but the strength of enrichment did not differ significantly for duplications and deletions (see Supplementary Table 5 for details). Ion channel pathways (ligand gated ion channel activity and ion gated channel activity), transmembrane transport and organonitrogen compound catabolic process were robust to sensitivity analysis (see Supplementary Table 6 for enrichment effect sizes and the number of gene hits for pathways listed in Table 4; see Supplementary Tables 7-9 for most significant ion channel pathway genes, organonitrogen compound catabolic process and carbohydrate derivative catabolic process genes and transmembrane transport genes).

### Table 1. Burden and type of CNVs >500 kb in cases and controls from each study

| CNV sample | CNVs | Number of CNVs | Number of deletions | Number of duplications |
|------------|------|----------------|---------------------|------------------------|
| ADHD cases | Controls | Ratio | \(P\) | ADHD cases | Controls | Ratio | \(P\) | ADHD cases | Controls | Ratio | \(P\) |
| Canada | | | | | | | | | | | | |
| N | 22 | 217 | 0.97 | 0.88 | 4 | 52 | 0.73 | 0.55 | 18 | 75 | 1.04 | 0.87 |
| Rate | 0.089 | 0.092 | | | 0.016 | 0.022 | | 0.073 | 0.070 | | |
| Cardiff | | | | | | | | | | | | |
| N | 65 | 78 | 1.45 | 0.021 | 13 | 13 | 1.74 | 0.15 | 52 | 65 | 1.39 | 0.066 |
| Rate | 0.108 | 0.074 | | | 0.022 | 0.012 | | 0.086 | 0.062 | | |
| CHOP | | | | | | | | | | | | |
| N | 220 | 382 | 2.33 | 4.7 \times 10^{-28} | 28 | 80 | 1.42 | 0.11 | 192 | 302 | 2.58 | 4.4 \times 10^{-29} |
| Rate | 0.217 | 0.093 | | | 0.028 | 0.019 | | 0.190 | 0.074 | | |
| IMAGE 2 (refs 10,16) | | | | | | | | | | | | |
| N | 89 | 191 | 1.28 | 0.042 | 22 | 47 | 1.29 | 0.32 | 67 | 144 | 1.28 | 0.084 |
| Rate | 0.122 | 0.095 | | | 0.030 | 0.023 | | 0.092 | 0.072 | | |
| PUWMa | | | | | | | | | | | | |
| N | 59 | 86 | 1.09 | 0.59 | 25 | 28 | 1.42 | 0.19 | 34 | 58 | 0.93 | 0.74 |
| Rate | 0.085 | 0.078 | | | 0.036 | 0.025 | | 0.049 | 0.053 | | |

**Abbreviations:** ADHD, attention-deficit hyperactivity disorder; CHOP, Children’s Hospital of Philadelphia; CNV, copy number variant; IMAGE, International Multi-Center ADHD Genetics; PUWMa, Pfizer-funded study from UCLA, Washington University and Massachusetts General Hospital; N: the number of CNVs observed in the sample; rate: the average number of CNVs per person.

### Table 2. Enrichment of ADHD case CNV hits in genes containing schizophrenia and autism de novo SNVs (non-synonymous and loss-of-function)

| Gene set | \#Genes | CNVs >500 kb |
|----------|--------|-------------|
| SCZ (NS) | 611 | 5.4 \times 10^{-4} |
| SCZ (LoF) | 87 | 0.33 |
| AUT (NS) | 2726 | 0.019 |
| AUT (LoF) | 538 | 0.026 |

**Abbreviations:** ADHD, attention-deficit hyperactivity disorder; AUT, autism; CNV, copy number variant; Del, deletion; Dup, duplication; LoF, loss of function; NS, non-synonymous; SCZ, schizophrenia; SNV, single-nucleotide variant. \(^a\)Number. \(^b\)\(P\)-value for pathway enrichment after omitting the most significant sample.

### Table 3. Enrichment of FMRP, ARC and NMDAR gene sets for ADHD case CNV hits

| Gene set | \# Genes | CNVs >500 kb |
|----------|--------|-------------|
| FMRP | 840 | 0.0018 |
| ARC | 28 | 0.23 |
| NMDAR | 61 | 0.74 |

**Abbreviations:** ADHD, attention-deficit hyperactivity disorder; ARC, activity-regulated cytoskeleton-associated protein; CNV, copy number variant; Del, deletion; Dup, duplication; LoF, loss of function; NS, non-synonymous; SCZ, schizophrenia; SNV, single-nucleotide variant. \(^a\)Number. \(^b\)\(P\)-value for pathway enrichment after omitting the most significant sample.
Secondary analyses of CNVs > 100 kb showed that observed pathways were generally significantly enriched in these analyses (results available from last author).

DISCUSSION

In these analyses of ADHD case–control CNV data, the largest to date, we found highly significant enrichment of CNVs in many, although not all, hypothesised neurodevelopmental gene sets. Hypothesis-free testing revealed additional biological pathways enriched for CNVs in those with ADHD. Genes spanned by the ADHD CNVs were enriched for those that have recently been found to harbour schizophrenia-associated de novo SNVs. Previous work demonstrated overlap of ADHD CNVs with schizophrenia and autism CNVs; however, because we were now able to define our gene sets using SNVs, which impact on single genes rather than chromosomal regions encompassing multiple genes, the current findings more precisely suggest overlap at the level of genes. These findings therefore extend, refine and are independent of previous studies that suggest biological overlap across these clinically very different disorders.

The clinical co-morbidity and co-heritability of ADHD is much more strongly established with autism than with schizophrenia. Although previous studies, using some of the data sets in the present paper, found ADHD and autism overlap at the level of CNVs and CNV-associated biological pathways, we did not observe this extended to autism de novo SNV genes.

Targets of the FMRP have been implicated previously in both schizophrenia and autism. Complete expression failure of FMRP itself, which characterises Fragile X syndrome, is known to be associated with elevated rates of ADHD, autism and other neurodevelopmental disorders. Indeed, the majority of males with Fragile X syndrome show ADHD. Previous work has shown that the protein FMRP regulates activity of 842 biological targets and suggested that some of these likely underlie the manifestation of autistic features in Fragile X syndrome. Our findings show that genes encoding FMRP targets are also enriched in ADHD CNVs, which could help explain why children with Fragile X syndrome show such high rates of ADHD. The results suggest that FMRP-mediated biology may be relevant across multiple neuropsychiatric disorders that include ADHD, as well as autism and schizophrenia. Although a recent report suggests that what has been considered as the specific contribution of FMRP targets to the pathogenesis of autism might simply reflect involvement of long, highly brain-expressed genes, here large gene size is controlled for. Nevertheless, further work is needed to understand how FMRP is involved in the pathogenesis of different neurodevelopmental phenotypes, that is, ADHD, autism and schizophrenia, each of which has very different phenotype features and treatments.

Although schizophrenia and autism genetic findings have all strongly implicated the involvement of synaptic functions in pathogenesis, we did not observe that to be the case for ADHD. Nor did we replicate prior pathway analysis implicating neurite outgrowth at synapses in ADHD, although previous analyses have used SNP or candidate gene data or smaller data sets. We cannot be certain if this is a genuine point of difference or whether larger studies of ADHD, which consider additional types of mutations, for example, through exome sequencing, will yield a different pattern of findings.

The hypothesis-free analysis of all ADHD CNV pathways yielded strongly significant enrichment for multiple biological pathways. Many but not all of these were robust to analysis after excluding the most significant study. As expected for this final, hypothesis-free set of analyses, the significance of the enrichment was reduced by the removal of the most significant study, even when there was no significant difference in the strength of the enrichment between that study and the remainder of the sample, as was the case for most of the pathways highlighted here (see Supplementary Tables 1 for details). Thus, this analysis should be regarded as a sensitivity analysis testing the robustness of the finding. Nevertheless, the study demonstrates that most findings were robust to sensitivity testing, whereby we excluded the most significant sample, despite potential variation in case mix severity and ascertainment across research centres and concerns from some quarters about the validity of ADHD.

Although our study involves analysis of the largest ADHD CNV data set to date, there are several limitations. First, analyses of this type for any disorder are restricted by the quality of gene and pathway annotations and the fact that the same genes belong to multiple different functional gene sets. Second, genotyped ADHD
sample sizes have markedly lagged behind those of many other neurodevelopmental and psychiatric disorders and results of exome sequencing are awaited. Third, ADHD-associated CNVs do not capture all possible forms of genetic risk, or risk loci; however, previous findings from smaller, individual studies do suggest biological convergence of CNVs and common gene variants.\textsuperscript{7,17,42,44,45} However, the biology and validity of ADHD remain poorly understood and it is still widely considered to be primarily a catecholaminergic disorder.\textsuperscript{43} Findings from the present study highlight the consistent and robust neurodevelopmental nature of ADHD and provide novel insights about its biological underpinnings.

In conclusion, in an international, cross-centre analysis of ADHD CNV data, we find evidence of biological overlap with schizophrenia at multiple levels; previous findings of overlap with schizophrenia CNVs have now been extended to SNVs. Furthermore, FMRP target enrichment appears to characterise ADHD as well as schizophrenia and autism. Ion channel pathway involvement in ADHD was robust to type of CNV and across samples. The findings reveal that CNVs in children with ADHD, from across multiple centres, converge on biologically meaningful gene clusters that are now robustly established as involved in neurodevelopmental disorder risk.

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