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ORIGINAL ARTICLE

Copy number variants and therapeutic response to antidepressant medication in major depressive disorder

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It would be beneficial to find genetic predictors of antidepressant response to help personalise treatment of major depressive disorder (MDD). Rare copy number variants (CNVs) have been implicated in several psychiatric disorders, including MDD, but their role in antidepressant response has yet to be investigated. CNV data were available for 1565 individuals with MDD from the NEWMEDS (Novel Methods leading to New Medications in Depression and Schizophrenia) consortium with prospective data on treatment outcome with either a serotonergic or noradrenergic antidepressant. No association was seen between the presence of CNV (rare or common), the overall number of CNVs or genomic CNV 'burden' and antidepressant response. Specific CNVs were nominally associated with antidepressant response, including 15q13.3 duplications and exonic *NRXN1* deletions. These were associated with poor response to antidepressants. Overall burden of CNVs is unlikely to contribute to personalising antidepressant treatment. Specific CNVs associated with antidepressant treatment require replication and further study to confirm their role in the therapeutic action of antidepressant.

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INTRODUCTION

Major depressive disorder (MDD) is a severely disabling disease affecting a large number of adults at some point in their lifetime. Antidepressants are most commonly used as the first line of treatment for MDD. However, individuals vary widely in their response to treatment, and currently, there is no way to predict an individual's response. Prediction of how an individual will respond to a specific treatment is needed to reduce the delay to alleviation of symptoms and the cost of treatment and disability. Although the existence of any single common genetic variant with a large enough effect to meaningfully predict antidepressant response is unlikely,[1–5] we have shown that antidepressant response is moderately heritable[6] and other forms of genetic variation remain to be investigated for a role in antidepressant response.

Copy number variants (CNVs) are submicroscopic deletions and duplications in genomic DNA that have been implicated in a variety of different psychiatric disorders, including schizophrenia, autism, attention deficit/hyperactivity disorder and MDD.[7–13] Individuals with MDD have been shown to have an increased burden of rare deletion CNVs compared with controls.[13] We hypothesise that rare deletion CNVs may also affect how individuals respond to treatment with antidepressants. To date, there is no published report on the relationship between CNVs and response to treatment with antidepressants. In this manuscript, we use information from Illumina genotyping arrays to assess the role of CNVs in response to treatment with antidepressants in individuals with MDD. We undertook a comprehensive approach to explore the role of CNVs in response to antidepressant treatment by assessing both global number and burden of CNVs as well as specific CNVs.

MATERIALS AND METHODS

Sample

The Novel Methods leading to New Medications in Depression and Schizophrenia (http://www.newmeds-europe.com) sample included 2146 treatment-seeking adults diagnosed with MDD according to DSM-IV/ICD-10 (Diagnostic and Statistical Manual of Mental Disorders/International Classification of Diseases, Tenth Revision), with prospective data on outcome of treatment with serotonin reuptake inhibitor (SRI) or

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norepinephrine reuptake inhibitor (NRI) antidepressants for up to 12 weeks.[1] This sample combined data from studies conducted by academic institutions (GENDEP, $n=868$; GENPOD, $n=601$; GODS, $n=131$)[2,14,15] and pharmaceutical industry members of the European Federation of Pharmaceutical Industries and Associations (Pfizer, $n=355$; GSK, $n=191$). Individuals were excluded if they had diagnoses of schizophrenia, schizoaffective disorder, bipolar disorder or current alcohol or drug dependence. Individuals were given either an antidepressant that acts primarily through blocking the reuptake of serotonin (selective SRI (SSRI): escitalopram, citalopram, paroxetine, sertraline, fluoxetine) or an antidepressant that acts primarily through blocking the reuptake of norepinephrine (NRI: nortriptyline, reboxetine).

Further information on the component studies can be found in Supplementary Materials.

Genotyping

All DNA samples were from venous blood. Information was available from 1166 samples genotyped on the Illumina 660W BeadChip and 746 samples genotyped on the Illumina 610Quad BeadChip (Illumina, San Diego, CA, USA), which have identical tag single-nucleotide polymorphism coverage. Raw Illumina data in the form of .idat files were imported into the GenomeStudio and processed according to Illumina's recommended guidelines to derive the log R ratio (LRR) and B allele frequency (BAF) for each marker within each sample. A consensus marker set between the Illumina arrays of 561 733 markers was used.

CNV calling

LRR and BAF data were processed with PennCNV[16] (version dated June 2011) and QuantiSNP[17] (version 2.3) using all markers and within-sample correction for waviness artefacts attributable to local GC content. The 'HD' prior parameter settings for LRR thresholds were used within the QuantiSNP analysis, as recommended by the author.

Due to variability between calling algorithms, we used two CNV calling algorithms (PennCNV and QuantiSNP) to minimise the number of false calls. A recent study showed the use of multiple calling algorithms increases the likelihood of validation by PCR to >95%.[18] CNV calls were merged between PennCNV and QuantiSNP. Specifically, a call or calls made by QuantiSNP or PennCNV were merged into a consensus call if within the same sample the calls overlapped. Only calls with overlap of >50% between the two regions were used for onward analysis. We excluded any call made with <10 consecutive markers, any CNV where 50% of the call covered a region within 500 kb of the telomere, centromere or immunoglobulin regions or a region where the marker density of the consensus marker set dropped below one marker in 200 000 bp, and any CNV <100 kb in size.

Sample and CNV quality control (QC)

Sample QC was performed using sample-wide metrics calculated by PennCNV. A sample was excluded from further analysis if any of the following criteria were met: (A) the s.d. of the LRR for autosomes was >0.25, (B) the s.d. for the BAF for autosomes was >0.04, (C) the drift of BAF values was >0.002, (D) the waviness factor was >0.04 or less than −0.04, (E) the genotype call rate was <98%, and (F) the logarithm of the total number of CNVs called by either algorithm before CNV call QC and after samples were excluded by steps A–E exceeded 3 s.ds. from the mean.

Only samples which passed QC for our whole-genome association study were considered for the analysis of CNVs. This ensured that individuals with ambiguous sex ($n=22$), abnormal heterozygosity ($n=16$), cryptic relatedness up to third-degree relatives by identity by descent ($n=20$) and non-European ethnicity admixture detected as outliers in an iterative EIGENSTRAT analysis of a linkage disequilibrium-pruned data set ($n=35$)[1] did not impact on the association results.

Definition of antidepressant response phenotype

We defined antidepressant response as a proportional reduction in symptoms over the course of treatment, consistent with previous reports.[1,2] Proportional improvement in depression severity was created for each component study based on the primary depression rating scale from baseline to the end of treatment, adjusted for age, sex and recruiting center. Depression severity was measured by one of the three primary rating scales (Montgomery–Åsberg Depression Rating Scale, Hamilton Rating Scale for Depression, Beck Depression Inventory).[19] The adjusted change score for each component study was *z*-transformed within each study to remove correlation between data origin and outcome and to eliminate study-specific effects.

Statistical analysis

Statistical analyses were done using PLINK[20] and STATA/SE 10.[21] PLINK was used to determine the number of CNVs and total size (kilobases) of CNVs for each individual. In addition to analysing the effect of all CNVs, we also separately examined the effects of common CNVs (found in >1% of individuals) and rare CNVs (found in <1% of individuals). Analyses were undertaken to investigate the effects of harbouring any CNVs and, more specifically, for the effect of deletion or duplication CNVs. CNVs were further annotated as to whether they covered gene-coding regions (genic) or exon-coding regions (exonic) as defined by RefSeq gene annotation coordinates obtainable from the UCSC genome browser (http://genome.ucsc.edu). Specific CNV regions were also analysed for their association with antidepressant response. For information about the number of individuals with a CNV in each of the categories examined, see Supplementary Materials.

CNV data were analysed using four linear regressions: (1) the entire sample, (2) only those individuals taking a SSRI, (3) only those individuals taking a NRI, and (4) differential response to treatment with either a SSRI or NRI (CNV × drug interaction). Analyses were co-varied for the s.d. of the log relative ratio and four principal components from the final iteration of the EIGENSTRAT analysis of linkage disequilibrium-pruned genetic data to minimise the influence of population stratification.

Analyses were also performed within each contributing sample and meta-analysed (see Supplementary Materials section 4).

Gene set analysis

Gene Ontology (GO) gene sets were taken from the gene2go file available from National Center for Biotechnology Information (NCBI) website. To maintain specificity, analysis was restricted to FAT terms for the categories biological process, molecular function and cellular component. FAT terms filter out very broad GO terms based on a measured specificity of each term. We consider a gene to be within a CNV region if their genomic coordinates overlapped (NCBI build 36). Enrichment of CNVs within a particular gene set was undertaken using a modified version of the methodology implemented in Kirov *et al.*[22] Briefly, two linear regression models were fitted and the change in deviance was compared between (1) and (2).

1. linear (antidepressant response) = CNV size + total number of genes intersected by a CNV outside the gene set + number of genes intersected by a CNV in the gene set.
2. linear (antidepressant response) = CNV size + total number of gene intersected by a CNV outside the gene set.

Power analysis

We aimed to determine whether the presence, number or burden of CNVs would predict response to antidepressant treatment in a clinically significant way. Simulations based on large antidepressant treatment trials have shown that a prediction is clinically significant if it explains at least 6.33% of the variance in treatment outcome.[23] Although it is vital for genetic predictors of antidepressant response to be translatable meaningfully into a clinical setting, results from other psychiatric disorder suggest more modest associations are more likely. We therefore also consider the power of the study to find an association that explains half (3.17%) and a quarter (1.58%) of what is clinically significant. Using the pwr package (Power analysis functions along the lines of Cohen[24]) in R,[25] we calculated the power of our four analyses (whole sample, serotonergic, noradrenergic and gene × drug interaction). All of our analyses had power >90% to detect a clinically significant finding at the alpha level of $P<0.05$. All analyses had an adequate statistical power (>80%) to detect a signal that explains only half (3.17%) of what would be clinically significant prediction. Three of our analyses (whole sample, serotonergic,and gene × drug interaction) had adequate statistical power (>80%) to detect a signal that explains a quarter (1.58%) of what would be clinically significant prediction, with the noradrenergic analysis having 53% power at this effect size. These power calculations consider each hypothesis separately.

RESULTS

In the combined sample, 1565 individuals passed QC for both the whole-genome association study and the CNV calls.

We found no association between the presence of any CNV, total number of CNVs or global CNV burden (total kb) and response to any antidepressant, serotonergic antidepressants, noradrenergic antidepressants or differential response to serotonergic and noradrenergic antidepressants (Supplementary Table S4). There was no relationship with rare or common CNVs or deletions or duplications.

We carried out additional analyses, restricted to CNVs which encompassed gene-coding regions (genic) or exon-coding regions (exonic), but we found no significant association between the presence of CNV, global number of CNVs or global CNV burden and antidepressant response, response to serotonergic antidepressants, response to noradrenergic antidepressants or differential response to serotonergic and noradrenergic antidepressants (Supplementary Tables S5 and S6). Furthermore, there was no association with genic or exonic rare or common CNVs or deletions or duplications.

Three thousand six hundred and twenty-three GO gene sets were assessed for enrichment of CNVs. No GO gene set remained significant after correction for multiple testing (false discovery rate <0.05). Nominally associated GO gene sets are reported in the Supplementary Materials.

Analysis of specific CNVs yielded several nominally significant ($P<0.05$) regions (Table 1). Ten CNV regions were nominally associated with response to any antidepressant. Of note, 11 individuals had a duplication at 15q13.3 encompassing *OTUD7A* and *CHRNA7* that resulted in poorer response to antidepressant treatment ($\beta=-0.871$; s.e. $=0.298$; $P=0.0035$). This CNV regions was independently associated with response to serotonergic antidepressants (eight individuals with duplication; $\beta=-0.716$; s.e. $=0.347$; $P=0.039$) and with response to noradrenergic antidepressants (three individuals with duplication; $\beta=-1.328$; s.e. $=0.578$; $P=0.021$). This region is highly polymorphic with numerous CNV events occurring in healthy controls (Database of Genomic Variants http://projects.tcag.ca/variation).

Two individuals had deletions in *NRXN1* resulting in poorer response to treatment ($\beta=-1.517$; s.e. $=0.697$; $P=0.030$). Both of these individuals were administered noradrenergic antidepressants. This CNV region was also associated with differential treatment response ($\beta=-0.744$; s.e. $=0.349$; $P=0.033$).

A full list of all nominally significant ($P<0.05$) specific CNV regions can be found in Table 1. UCSC browser illustrations for all nominally associated CNV regions can be found in Supplementary Materials section 5.

DISCUSSION

CNVs have been implicated in the aetiology of several psychiatric disorders, including major depression, where we have previously reported an overall excess of deletions affecting exons in cases compared with controls.[13] It is reasonable to hypothesise that CNVs might also influence the form or course of the illness, and this is the first investigation into the relationship between antidepressant response and CNVs. We took a comprehensive approach to explore the role of CNVs in response to antidepressant treatment by assessing both global number and burden of CNVs and considering possible roles of specific duplications, deletions, rare, common, genic and exonic CNVs. Although we found no association between global number and burden of CNVs and antidepressant response or an enrichment of CNVs affecting particular set of genes, we do observe a nominal association with burden of deletion CNVs from the meta-analysis undertaken in the noradrenergic antidepressant-only analysis (Supplementary

Table 1. NEWMEDS CNV results for specific CNV regions

Analysis	*Cytoband*	*CNV location*	*No. people with CNV*	*Type of CNV*	*Genes within CNV region*	*Coefficient*	*s.e.*	P-*value*
Whole sample analysis	15q13.3	chr15:29,420,453-30,302,218	11	Duplication	OTUD7A, CHRNA7	−0.8707	0.2976	0.0035
	4q28.3	chr4:135,125,711-135,395,786	9	Deletion	PABPC4L	−0.8765	0.3289	0.0078
	6q12	chr6:67,008,989-67,558,222	2	Deletion		1.6804	0.6973	0.0160
	3q26.2	chr3:4,140,865-4,258,763	4	Deletion	SUMF1	−1.1359	0.4930	0.0213
	20p12.1-12.2	chr20:11,834,502-12,675,209	2	Duplication	BTBD3	−1.5844	0.6970	0.0231
	8p23.2	chr8:2,334,306-2,577,510	12	Duplication		−0.6319	0.2886	0.0287
	2p16.3	chr2:50,464,580-50,823,891	2	Deletion	NXRN1	−1.5167	0.6970	0.0297
	17q25.1	chr17:69,345,596-70,193,536	4	Duplication	RPL38, TTYH2, DNAI2, KIF19, BTBD17, GPR142, GPRC5C, CD300A, CD300LB, CD300C, CD300LD, c17orf77, CD300E, RAB37	1.0711	0.4931	0.0300
	18p11.32	chr18:1,708,332-1,915,686	10	Deletion		0.6233	0.3127	0.0464
	9p23	chr9: 11,772,345-12,296,626	17	Deletion		0.4773	0.2402	0.0470
Serotonergic analysis	4q28.3	chr4:135,141,815-135,395,786	5	Deletion	PABPC4L	−1.4332	0.4378	0.0011
	20p12.1-12.2	chr20:11,834,502-12,675,209	2	Duplication	BTBD3	−1.5552	0.6920	0.0248
	8p23.2	chr8:2,334,306-2,570,171	8	Duplication		−0.7651	0.3506	0.0293
	15q13.3	chr15:29,420,453-30,302,218	8	Duplication	OTUD7A, CHRNA7	−0.7159	0.3468	0.0392
Noradrenergic analysis	15q13.3	chr15:29,807,358-30,302,218	3	Duplication	OTUD7A, CHRNA7	−1.3278	0.5747	0.0212
	2p16.3	chr2:50,464,580-50,823,891	2	Deletion	NRXN1	−1.5237	0.7007	0.0300
CNV × drug interaction	15q13.2	chr15:28,723,577-28,893,977	11	Duplication	ARHGAP11B,	−1.4758	0.5982	0.0137
	3q23	chr3:143,305,311-143,554,622	6	Duplication	TFDP2, GK5, XRN1	−2.3818	1.0811	0.0277
	2p16.3	chr2:50,464,580-50,823,891	2	Deletion	NRXN1	−0.7444	0.3488	0.0329

Abbreviations: CNV, copy number variant; NEWMEDS, Novel Methods leading to New Medications in Depression and Schizophrenia. Regression coefficient is standardised and can be interpreted as a measure of effect size. Positive values of regression coefficient mean that carriers of the CNV had better treatment outcome. Negative values of regression coefficient mean that carriers had worse outcomes. Cytoband information and CNV locations are from the US National Center for Biotechnology Information (NCBI) Build 36 and University of California, Santa Cruz (UCSC) hg18.

Table S22–S24). This result is of particular interest when placed in context of the previous result for MDD suggesting an association between exonic deletion CNVs and MDD.[13]

However, we did see some nominally significant specific CNV regions associated with response to antidepressant treatment. Further investigations into the role of specific CNVs in antidepressant response are warranted as the results here are suggestive pending positive replication. If specific CNVs replicate as predictors of response to antidepressant treatment, they may serve as strong predictors in a relatively small fraction of individuals with MDD. A large number of such rare predictors would be required to meaningfully personalise treatment of MDD at a population level. However, there is also the potential that a rare mutation strongly associated with antidepressant response may point to a molecular mechanism that is relevant for a much larger proportion of patients.

Specific CNVs of interest are those regions previously implicated in other psychiatric disorders. Individuals with a duplication event at 15q13.3 had a poorer response to antidepressant treatment. This association was significant in each drug class-specific analysis as well, representing a global effect of this particular CNV on response to treatment. Although this CNV falls outside of the region associated with Prader–Willi (15q11-13; OMIM #176270) and Angelman Syndrome (OMIM #105830), it is within a region associated with numerous psychiatric phenotypes, including schizophrenia, autism spectrum disorder and bipolar disorder.[26–32] However, those CNV events were deletions, whereas our association is with a duplication event. This region has also been associated with MDD with individuals with MDD having reduced frequency of 15q13.3 CNVs than control populations.[13] The entire region encompassed by our CNV is highly polymorphic with numerous CNV events occurring in healthy controls (Database of Genomic Variants http://projects.tcag.ca/variation). Furthermore, two individuals harboured deletions in *NRXN1* that also resulted in poorer response to treatment. These CNVs encompass a number of exons within the gene and exonic deletions within *NRXN1* previously being implicated in schizophrenia[29,33,34] and autism.[26] The association of these CNVs suggest some overlap with other psychiatric phenotypes and potentially overlapping genetic architecture. Furthermore, the CNVs implicated in other psychiatric phenotypes negatively impacted on an individuals' ability to respond to treatment.

Our study has several limitations that should be taken into consideration when interpreting these results. Our analysis classifies antidepressants into mechanism of action (serotonergic versus noradrenergic) and cannot inform about the role of CNVs for a specific drug. Although we performed a number of tests, we report here only the nominal *P*-values and do not undertake any statistical correction. Therefore the results need to be taken with caution. Furthermore, while we report a number of nominally significant associations with specific CNV regions, all of these regions had CNV events reported in healthy controls according to the Database of Genomic Variation (http://projects.tcag.ca/variation), a database of CNVs from over 40 studies reporting CNVs seen in only healthy control individuals. We obtained our large sample by bringing together numerous different studies, which differ by rating scale used and method to recruit subjects. We took these steps as we are interested in predictors of antidepressant response that generalise to most individuals with MDD. Furthermore, our studies focus only on individuals of Caucasian/European ancestry and monoaminergic antidepressants. Results in other population and/or in drugs whose mechanism of action is non-monoaminergic may yield different results.

CONCLUSIONS

We have investigated for the first time the role of CNVs in response to treatment with antidepressants. Although we find no association between antidepressant response for global number or burden of CNVs, we find nominally significant associations with specific CNVs. These specific CNV associations are of high interest, particularly those regions previously implicated in other psychiatric phenotypes. The results presented here require replication but suggest a potential role for rare variants in response to antidepressant treatment. Further investigation is warranted into the role of specific CNVs in antidepressant response as well as rare or personal single-nucleotide mutations.

CONFLICT OF INTEREST

NP received honoraria for participating in expert panels from pharmaceutical companies including Lundbeck. GB is a member of a national advisory board for Bristol-Myer Squibb and Pfizer and has received research funding from GlaxoSmith-Kline, Wyeth-Lederle, Bristol-Myers-Squibb and Sanofi Aventis. ED is a full-time employee of F. Hoffmann-La Roche. ED was full-time employee of Glaxo-Smith Kline when he undertook work on this study. JRW is a full-time employee of Pfizer. JRW was full-time employee of F. Hoffmann-La Roche when this work began. NH has participated in clinical trials sponsored by pharmaceutical companies, including GlaxoSmithKline and Lundbeck, and received honoraria for participating in expert panels from pharmaceutical companies, including Lundbeck. MO'D's department received £2000 in lieu of an honorarium to MO'D from Lilly as a result of his participation in sponsored symposia in 2012. Those symposia were unrelated to the contents of this manuscript. DS is a member of a national advisory boards for Astra-Zeneca, Bristol-Myers Squibb, Eli Lilly and Lundbeck. KJA has been on the Advisory Board for the Bristol-Myers Squibb and Otsuka Pharmaceuticals and in addition received consultancy fees, including payment for lectures and educational presentations, from the same company. She was previously a member of various advisory boards, receiving consultancy fees and honoraria, and has received research grants from various companies, including Lundbeck and GlaxoSmithKline. She currently holds an Alberta Centennial Addiction and Mental Health Research Chair, funded by the Government of Alberta. PMG and AF have previously received consultancy fees and honoraria for participating in expert panels from pharmaceutical companies, including Lundbeck and GlaxoSmithKline, but have had no such income in the past 3 years. SK has received research funding from AstraZeneca, Bristol-Myers Squibb and GlaxoSmithKline and has served as consultant and/or speaker for AstraZeneca, Bioline, BMS-Otsuka, Eli Lilly, Janssen, Lundbeck, Neuro-Search, Pfizer, Roche, Servier and Solvay Wyeth. All the other authors declare no conflict of interest.

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Supplementary Information accompanies the paper on the The Pharmacogenomics Journal website (http://www.nature.com/tpj)