Contribution of copy number variants on antipsychotic treatment response in Han Chinese patients with schizophrenia

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Summary

Background Response to antipsychotic drugs (APD) varies greatly among individuals and is affected by genetic factors. This study aims to demonstrate genome-wide associations between copy number variants (CNVs) and response to APD in patients with schizophrenia.

Methods A total of 3030 patients of Han Chinese ethnicity randomly received APD (aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone, haloperidol and perphenazine) treatment for six weeks. This study is a secondary data analysis. Percentage change on the Positive and Negative Syndrome Scale (PANSS) reduction was used to assess APD efficacy, and more than 50% change was considered as APD response. Associations between CNV burden, gene set, CNV loci and CNV break-point and APD efficacy were analysed.

Findings Higher CNV losses burden decreased the odds of 6-week APD response (*OR* = 0.66 [0.44, 0.98]). CNV losses in synaptic pathway involved in neurotransmitters were associated with 2-week PANSS reduction rate. CNV involved in sialylation (1p31.1 losses) and cellular metabolism (19q13.32 gains) associated with 6-week PANSS reduction rate at genome-wide significant level. Additional 36 CNVs associated with PANSS factors improvement. The *OR* of protective CNVs for 6-week APD response was 3.10 (95% *CI*: 1.33–7.19) and risk CNVs was 8.47 (95% *CI*: 1.92–37.43). CNV interacted with genetic risk score on APD efficacy (*Beta* = –1.53, *SE* = 0.66, *P* = 0.021). The area under curve to differ 6-week APD response attained 80.45% (95% *CI*: 78.07%–82.82%).

Interpretation Copy number variants contributed to poor APD efficacy and synaptic pathway involved in neurotransmitter was highlighted.

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Keywords: Schizophrenia; Antipsychotic treatment response; Copy number variants; Genome-wide association study; Drug target

Introduction

Schizophrenia (SCZ) is a complex disease with highly heterogeneous clinical phenotype including hallucinations, delusions, disorganised thinking and speech, reduced emotional expression, and cognitive deficits.[1] Antipsychotic drugs (APD) are the mainstay of treatment in

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Research in context

Evidence before this study

Treatment response in patients with schizophrenia varies significantly among individuals, with about 25% of patients showing good responses. Common genetic variants have a small impact on antipsychotic treatment response. By contrast, copy number variants (CNVs) can have a major impact on antipsychotics response, yet our understanding of their role remains limited. We searched PubMed with combinations of the search term "(drug effects OR drug therapy) AND schizophrenia AND (copy number variant OR CNV)", without restrictions on language of publication, for articles published before September 11, 2023. Our search identified 39 original articles. However, only Martin AK et al., Psychol Med 2016 assessed the rare CNV duplication burden in patients with treatment-resistant schizophrenia, and several studies assessed associations between candidate schizophrenia-associated CNVs, drug metabolism CNVs and antipsychotic treatment phenotypes (i.e., treatment-resistant, social function, and clozapine-associated neutropenia). No genome-wide significant CNV loci have been identified. Therefore, the rare CNV mechanism of antipsychotic treatment response needs further exploration. Using data from the Chinese Antipsychotics Pharmacogenomics Consortium, the largest genome-wide association study of treatment response to antipsychotics in schizophrenia so far, we have identified associations between antipsychotic treatment response and common genetic variants. The genome-wide CNV association study is reported in this study.

Added value of this study

Associations between CNV and antipsychotics efficacy were reported at four levels in samples of Asian ancestry. Increased global CNV losses burden related to poor antipsychotic efficacy, and synaptic pathway and xenobiotic metabolic pathway were highlighted. We identified 7 rare CNV loci associated with antipsychotic treatment efficacy, which are regulators between G-protein-coupled receptors activity or drug metabolism and antipsychotic response. The CNVs showed larger effects than common genetic variants on antipsychotic efficacy.

Implications of all the available evidence

Together with previous studies using candidate CNVs, our findings suggest that CNV have a significant impact on antipsychotics response and pharmacogenetics could guide individualised treatment of schizophrenia. Future research with larger samples and in different populations is needed before these results can be translated to clinical practice.

clinical management of schizophrenia. However, the APD response can vary significantly among individuals, and approximately 1/3 of individuals diagnosed with SCZ experience treatment-resistant psychotic symptoms.[2,3] Advances in common genetic variants have led to some progress in understanding the inter-individual variations in APD response, but the genetic rare, highly penetrant and deleterious risk variants have not been fully elucidated.

Studies on genomic copy number variants (CNVs) have established a role of rare genetic variants in the etiology of SCZ.[4] These findings on disease-associated CNVs identified significant risk for neurodevelopmental and psychiatric disorders[5–7] and an increased burden of CNVs in cases of SCZ.[8,9] The impact of CNVs on APD efficacy has also been noted, such as the genome-wide burden of CNVs,[10,11] schizophrenia risk CNVs[11–13] and CNVs in relation to cytochrome P450 genes,[14] which affect enzymatic activity and individual drug response. While some SCZ-associated CNVs (SCZ-CNVs, i.e., duplications of the 16p11.2 and 15q11.2-q13.1 regions, and deletions of the 22q11.2) have been reported to be enriched in treatment-resistance cases,[11,12] a major limitation is the inability to directly assess the association between unknown CNVs and APD efficacy.

In this study, we presented the genome-wide association analysis of CNVs in relation to APD efficacy in patients with SCZ of Han Chinese ancestry and assessed the impacts of previously implicated SCZ-CNVs and CNVs intersecting with APD target genes on treatment efficacy, using 6-week acute phase treatment data from a large randomised controlled trial. The interaction and joint effects between rare CNVs and common single nucleotide variations (SNVs) on APD treatment response were further explored.

Methods

Study design and participants

The Chinese Antipsychotics Pharmacogenomics Consortium (CAPOC) recruited 3030 patients with schizophrenia and randomly assigned participants to six groups to receive APD treatment for 6 weeks, from 2010 to 2012. Briefly, individuals of Han Chinese ancestry, had a diagnosis of schizophrenia based on the Structured Clinical Interview of DSM-IV, and scored more than 60 on the Positive and Negative Syndrome Scale (PANSS) scores, were recruited. Sex was self-reported by study participants and was not taken into consideration during the study design phase. Individuals were interviewed by a psychiatrist and PANSS scores were recorded at 0, 2, 4 and 6 weeks. Patients and psychiatrists were unmasked to assigned antipsychotics while the assessors were masked to the group assignments. Intervention procedure can be found in Supplementary Notes and basic information across six groups were listed in Supplementary Table S1. More details related to this trial can be found in

previously published pharmacogenomics genome-wide association study (GWAS).[15]

This study is a secondary data analysis. No significant difference on demographics was found between the sample used in the present study and the original whole sample (see Supplementary Table S2). Consistent with the pharmacogenomics GWAS study, we used percentage change on PANSS to assess APD treatment efficacy (higher scores suggesting higher improvement). The PANSS reduction rate was calculated according to the formula:

$$PANSS\ reduction\ rate = \frac{PANSS\ baseline\ score - PANSS\ endpoint\ score}{PANSS\ baseline\ score - 30} \times 100$$

PANSS reduction rate at 2 weeks and 6 weeks were both obtained. The 50% PANSS reduction rate at 6 weeks was used as a threshold to differ treatment response (TR) and non-treatment response (NTR). Considering the heterogeneous treatment efficacy across different symptoms, we also focused on the treatment improvement for five PANSS dimensions (positive symptom, negative symptom, cognition, depression, and excitement symptoms). PANSS factor reductions (PANSS baseline score - PANSS endpoint score) were calculated and higher scores suggested higher improvement.

Ethics

The study was approved by the ethics committee of the Peking University Sixth Hospital and each participating site. The reference number was 2009-LUNSHEN-23 and approval date was April 21st, 2009. This study was registered at the Chinese Clinical Trial Registry (ChiCTR-TRC-10000934). The informed written consent was obtained for all included participants in accordance with the Declaration of Helsinki.

Data processing

Samples were genotyped with Illumina Human Omni ZhongHua-8 Beadchips (Illumina, San Diego, CA, USA). SNV quality control (QC) procedure and imputation can be found in the previously published manuscript,[15] and SNV-derived principal components (PCs) were performed. Samples with gender discordance were removed. CNVs were called with PennCNV and iPattern using all SNP array data, and CNVs detected by one method only were excluded. CNVs include both additional copies of sequence (gains or duplications) and losses of genetic material (losses or deletions). CNVs of opposite type across two methods were also excluded. Genotype data were obtained from 2714 individuals and 4810 CNV segments were called. To make our final data set of rare CNVs for all subsequent analysis, we filtered out variants that were present at >1% (50% reciprocal overlap) frequency, <30 kb and <10 probes in length. A total of 2039 individuals and 4206 segments passed CNV QC, including 2078 CNV losses and 2128 gains, and 2046 segments were overlapped with at least one coding exon. We further combined the GWAS QC procedure with CNV QC procedure, and a total of 1853 individuals and 4016 CNV segments were included in the CNV study. Details involved in the CNV calling and QC can be found in Supplementary Notes.

Statistics

CNV associations with APD efficacy were investigated at four levels: (i) genome-wide (ii) pathways, (iii) genes and (iv) CNV breakpoints. Analyses controlled for age, sex and top five PCs.

Genome-wide CNV carrier analyses for APD efficacy were performed partitioned by CNV type (losses or gains). CNVs overlapped with at least one gene coding exon were analysed as a subgroup that is more likely to exhibit functional significance. We further considered the CNV burden on APD efficacy and analyses were restricted to individuals with at least one rare CNV. Three distinct properties of CNV were measured to discern associations between CNV burden and APD efficacy: (i) kilobase (KB) burden of CNVs, (ii) number of genes affected by CNVs and (iii) number of CNV segments (NSEG). Genes were counted only if the CNV overlapped a coding exon. We also partitioned our burden analyses by CNV type (losses or gains) and CNV size measured by KB.

Gene sets that were suggested to be potentially involved in APD efficacy[8] were selected as candidate gene sets to assess the associations between concentration of CNVs and APD efficacy. These gene sets mainly represented: synaptic components, synaptic pathway, neuronal function, neuron projection, neurotransmission, nervous system development and xenobiotic metabolism. Additionally, an olfactory gene set was included as a negative control. For all gene-sets, gene identifiers in the primary source were mapped to Entrez-gene identifiers. Gene set was tested as a binary indicator representing whether the individual carried or not carried CNV-intersected genes within the specific gene set, using linear regression models. In addition to adjusting for the same covariates as those included in the CNV burden analysis, we further controlled for the total number of genes covered by CNVs per participant to account for signals that may arise due to the overall enrichment of CNV burden in patients with schizophrenia. *Benjamin-Hochberg* false discovery rate (*BH-FDR*) was performed separately across CNV type (gains or losses) and phenotypes.

Gene is used as a proxy to test associations between CNV loci and APD efficacy. Phenotypes of treatment efficacy including PANSS reduction rate and five PANSS factors at 2 weeks and 6 weeks were tested separately. CNVs were mapped to genes if they overlapped at least one exon. To correctly account for large

CNVs that affect multiple genes, adjacent genes were aggregated into a single locus if their copy number was highly correlated across individuals (more than 50% individual overlap). Multiple-testing thresholds for genome-wide significance were estimated from family-wise error rates (*FWER*) drawn from 1000 permutations. The criterion for genome-wide significance was a $FWER < 0.05$, and the criterion for suggestive evidence was a $BH\text{-}FDR < 0.05$.

Breakpoint-level association can provide a fine resolution for significant CNV loci. Tests for association were performed at each CNV breakpoint using the residuals of PANSS reduction rate at 6 weeks after controlling for covariates, with significance determined through 1 million permutations. Genome-wide significant threshold was estimated using the 5% *FWER* from 5000 permutations.

Associations between previously implicated CNVs, including SCZ-CNVs and CNVs intersected with APD target genes and metabolic genes, and APD response were also tested. CNV carrier analysis for any implicated CNV was performed using regression models, adjusting age, sex, top five PCs and the overall CNV burden. CNV association analysis for single CNV locus was further performed, and nominal significance level of lower than 0.05 was obtained from empirical *P* value (*EMP*) from 1000 permutations. We computed permutation-based *FDR* to control the false positive in multiple-testing for all implicated CNVs.

Finally, we evaluated the contribution of both SNVs and CNVs on APD efficacy. The area under the curve (AUC) was calculated to differ APD response. The significance level was set at $P < 0.05$. The flowchart is illustrated in Fig. 1. Details of statistical analysis are listed in Supplementary Notes.

Role of funders

The funders had no role in study design, data collection, data analyses, interpretation, or writing of report.

Results

Genome-wide analysis of CNV burden

At baseline, CNV gains carrier showed significantly negative association with PANSS score compared to CNV noncarriers, but no significant association between CNV burden and PANSS score was found (Supplementary Tables S3 and S4). We mainly focused on associations between CNV and APD treatment efficacy measured by PANSS reduction rate at 2 and 6 weeks. Compared to CNV noncarriers, carriers of copy number gains showed less PANSS reduction rate at 2 weeks (linear regression for NSEG: $\beta = -1.97$, $SE = 0.95$, $P = 0.038$, Table 1). The burden of CNVs on APD efficacy were further estimated. Measured by NSEG, total KB length, and genes affected by CNVs, and split by CNV type, we did not find significant overall CNV burden for APD efficacy. However, when considering only variants that overlap exons, we found higher copy number losses burden signal driven by NSEG significantly related to less PANSS reduction rate at 6 weeks (linear regression: $\beta = -5.73$, $SE = 2.64$, $P = 0.031$). Using 6-week TR/NTR as the treatment response phenotype, higher copy number losses burden driven by NSEG significantly decreased the odds of response to APD ($OR = 0.66$ [0.44, 0.98]). CNV carrier analysis and burden analysis performed for PANSS five factors can be found in Supplementary Tables S5–S7. CNV characteristics are shown in Supplementary Fig. S1. Additionally, CNV burden analysis partitioned by CNV KB size were also performed and gradient increases of effect sizes can be observed along with CNV size increased (Supplementary Figs. S2 and S3).

Gene set (pathway) carrier analysis

GO enrichment analysis were performed in CNVs overlap exons to display the concentration of CNVs among SCZ cases (Supplementary Fig. S4). A total of 21 gene sets were then evaluated in the gene set carrier analysis involved in APD efficacy (Supplementary Fig. S5 and Table S8). CNV losses at KEGG synaptic pathway (short name: Neurof_KeggSynaptic) was associated with PANSS reduction rate, positive symptom factor and cognitive factor reductions at 2 weeks (Fig. 2) after multiple correction of $BH\text{-}FDR < 10\%$. The KEGG synaptic pathway gene set mainly included genes involved in cholinergic synapse, glutamatergic synapse, dopaminergic synapse, GABAergic synapse, and serotonergic synapse. At the $BH\text{-}FDR < 10\%$ level, CNV losses at GO xenobiotic metabolism (short name: GO_Xenobio) was associated with depressive factor reduction, while CNV gains at Hallmark xenobiotic metabolism (short name: Hallmark_Xenobio) showed associations with cognitive factor reduction. None of the gene set passed the significance threshold for 6-week PANSS phenotypes.

Gene-CNV association

To define specific loci that confer association with APD efficacy, we tested CNV association at the level of individual genes. For the primary APD efficacy phenotype of 6-week PANSS reduction rate, losses at 1p31.1 (*ST6GALNAC5,* linear regression: $\beta = -62.39$, $SD = 15.69$, $P = 7.26\text{e-}05$) and gains at 19q13.32 (*IGFL1/IGFL2,* linear regression: $\beta = -47.53$, $SD = 11.87$, $P = 6.55\text{e-}05$) attained genome-wide significance and both showed risk effects for treatment efficacy. Manhattan plots of the gene association analysis for CNV losses and CNV gains are shown in Fig. 3a–f. As far as the treatment response phenotype (TR/NTR) at 6 weeks, all 3 patients carrying losses at 1p31.1 were only identified in NTR group, and 5/6 patients carrying gains at 19q13.32 were identified in NTR group. Additional 5 loci attained genome-wide significance for PANSS

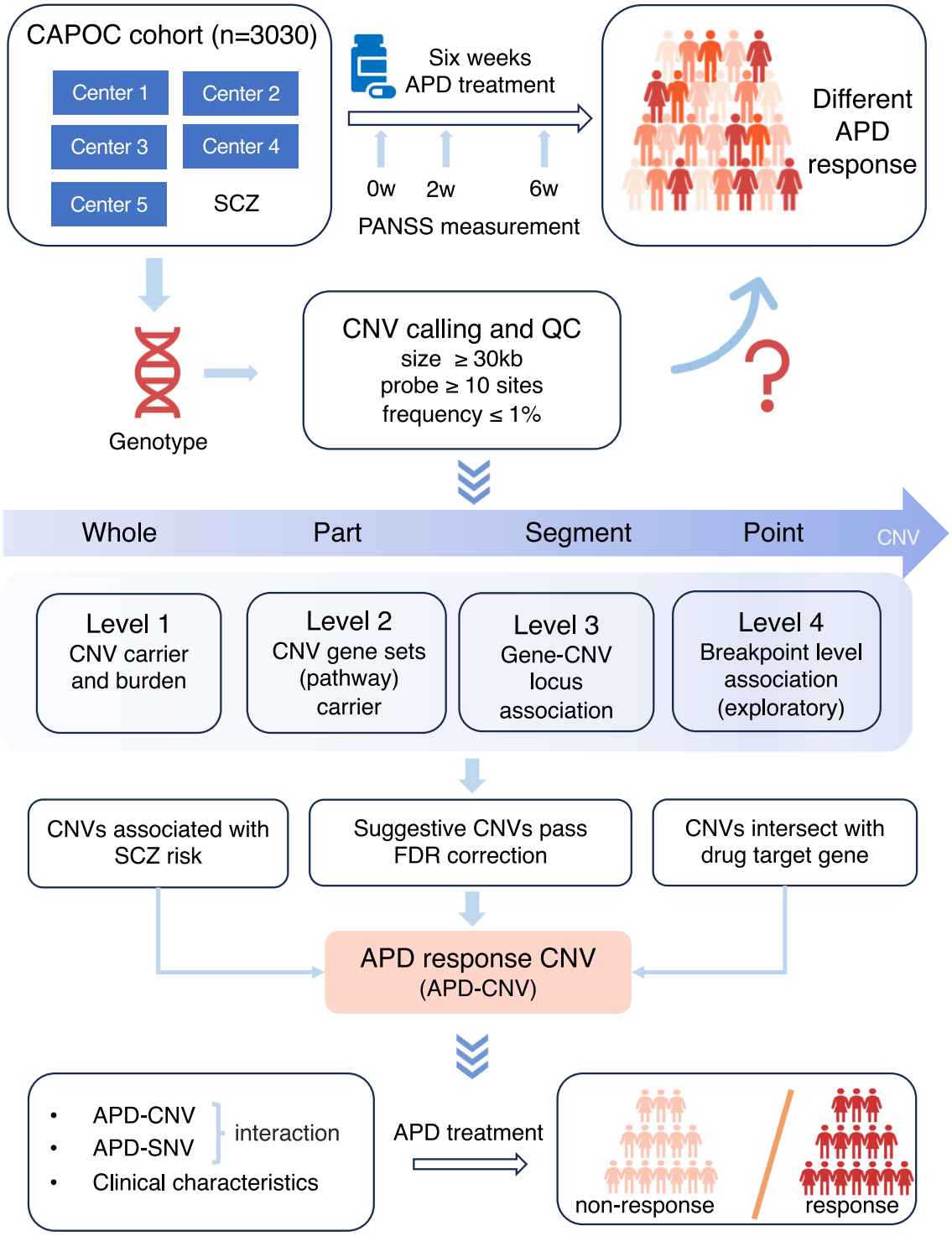


Fig. 1: Flowchart. CAPOC indicates The Chinese Antipsychotics Pharmacogenomics Consortium; SCZ indicates schizophrenia; APD indicates antipsychotic drug; CNV indicates copy number variants; QC indicates quality control; PANSS indicates the Positive and Negative Syndrome Scale; 2w indicates 2 weeks and 6w indicates 6 weeks; SNV indicates single nucleotide variation; APD-CNV indicates antipsychotic drug response associated copy number variants.

	CNV losses + gains				CNV losses				CNV gains			
	β	SE	t	*P*	β	SE	t	*P*	β	SE	t	*P*
CNV carrier analysis												
CNV non-carrier (ref., n = 991) vs CNV carrier (n = 2039)												
2-week	−2.05	0.89	−2.29	**0.022**	−1.81	0.96	−1.89	0.059	−1.97	0.95	−2.08	**0.038**
6-week	−1.29	1.31	−0.98	0.327	−0.73	1.38	−0.53	0.594	−1.37	1.36	−1.00	0.316
CNV non-carrier (ref., n = 991) vs Gene-mapped-CNV carrier (n = 1398)												
2-week	−2.04	0.95	−2.16	**0.031**	−1.31	1.12	−1.17	0.242	−2.23	1.02	−2.18	**0.030**
6-week	−0.77	1.37	−0.56	0.574	0.35	1.57	0.22	0.824	−1.19	1.47	−0.81	0.417
CNV burden analysis												
CNV burden analysis measured by NSEG												
2-week	0.04	0.36	0.11	0.912	−0.57	0.74	−0.77	0.442	−0.18	0.61	−0.30	0.766
6-week	−0.07	0.54	−0.14	0.892	−1.08	1.10	−0.98	0.327	−0.32	0.89	−0.36	0.718
Gene-mapped-CNV burden analysis measured by NSEG												
2-week	0.22	0.70	0.32	0.751	−3.32	1.91	−1.73	0.083	0.61	1.08	0.57	0.571
6-week	0.57	1.04	0.55	0.581	−5.73	2.64	−2.17	**0.031**	2.49	1.59	1.56	0.119

Note. Gene-mapped-CNV indicates copy number variants (CNVs) that overlap at least one coding exons. Bold value indicates $P < 0.05$. ref. = reference; NSEG = number of segments.

Table 1: **CNV global carrier analysis and burden analysis for 2-week and 6-week PANSS reduction rate.**

factors improvement, including copy number gains at 5q23.1 (multigenic) and 16q21 (*CDH8*), and losses at 1p21.3 (*DPYD*), 5p13.2 (*NUP155/WDR70*) and 9p22.3(*SNAPC3*), are listed in Fig. 3g and Supplementary Figs. S6–S12. *BH-FDRs* also identified additional 31 suggestive loci (named FDR-CNVs) associated with PANSS factors reduction (Supplementary Tables S9 and S10). Partitioned by the effect directions (protection effect or risk effect, Supplementary Fig. S13), the *OR* of protective FDR-CNVs for TR attained 3.10 (95% *CI*: 1.33–7.19), and *OR* of risk FDR-CNVs for NTR attained 8.47 (95% *CI*: 1.92–37.43).

Values of DECIPHER Haploinsufficiency index (*HI*) less than 10% predict that a gene is more likely to exhibit haploinsufficiency.[16] Of the 23 suggestive CNV losses region, losses at 1p21.3 (*DPYD*, *HI* = 1.82%), 16q12.2 (*FTO*, *HI* = 1.4%), 3q26.31 (*NAALADL2*, *HI* = 9.95%), and Xq26.2 (*RAP2C*, *HI* = 9.2%) intersected with haploinsufficiency genes, but only *Xq26.2* covered the whole gene. The CNV losses at 1p21.3 (*DPYD*) in our sample covered several missense variants and the likely-pathogenic SNV (rs146170505),[17] resulting it a likely-pathogenic CNV. *DPYD* is one of the leading candidate schizophrenia susceptibility genes reported in both PGC2 and PGC3,[18,19] and is also a target gene of *MIR137*,[20] a significant etiological mechanism of SCZ that was addressed by PGC.[21] Gains at 16q21 (*CDH8*, *HI* = 3.45%) and 18q12.1 (*RNF138*, *HI* = 9.64%) also intersected with haploinsufficiency genes and covered the whole gene. The gnomAD assessed loss-of-function observed/expected upper bound fraction (LOEFU) for *CDH8* (intersect with16q21 gain) is 0.3, suggesting this region is at a high level of loss-of-function intolerance.[22] A recent CNV study found gain at 16q21 (chr16: 61,464,644–64,965,235) was a risk CNV for ASD.[23] The genomic region is different from our reported region, and the re-evaluation for this region in our sample failed to attain significance level of 0.05.

To explore the potential functions of the identified CNVs, the 12 genes that intersected with genome-wide significant CNV loci and clinical APD target genes were seeded to build a protein-interaction network in GeneMania.[24] As the network (Supplementary Fig. S14) showed, *ST6GALNAC5* was co-localized with *HTR2A*. *CDH8* was co-localized with *HTR2C* and *NUP155* was co-expressed with *HTR2C*. *DYPD* was mainly co-localized with *CYP2C19*, and co-expressed with *FMO* family, the family associated with drug metabolism. In addition, *AP3*S1 also co-expressed with *FMO5*.

Breakpoint-level CNV association

Manhattan plots for breakpoint–level association are shown in Supplementary Figs. S15 and S16. No independent CNV breakpoint surpass genome-wide significance. However, for CNV loci that is high diversity of alleles (which depends on the chip) at a single locus, the breakpoint–level association is able to delineate more details. For instance, the predominant peaks across breakpoints of CNV losses at 2p16.3, a hot CNV losses that enriched in schizophrenia cases, were observed in a transcriptional site of *NRXN1*, which is close to the base pairs identified in schizophrenia case–control study.[8] A snapshot of the visualization on 2p16.3 region from the UCSC Genome Browser and the breakpoint association results are list in Supplementary Fig. S17.

Previously implicated CNV association

We were interested in evaluating the effects of previously implicated CNVs on the APD treatment efficacy.

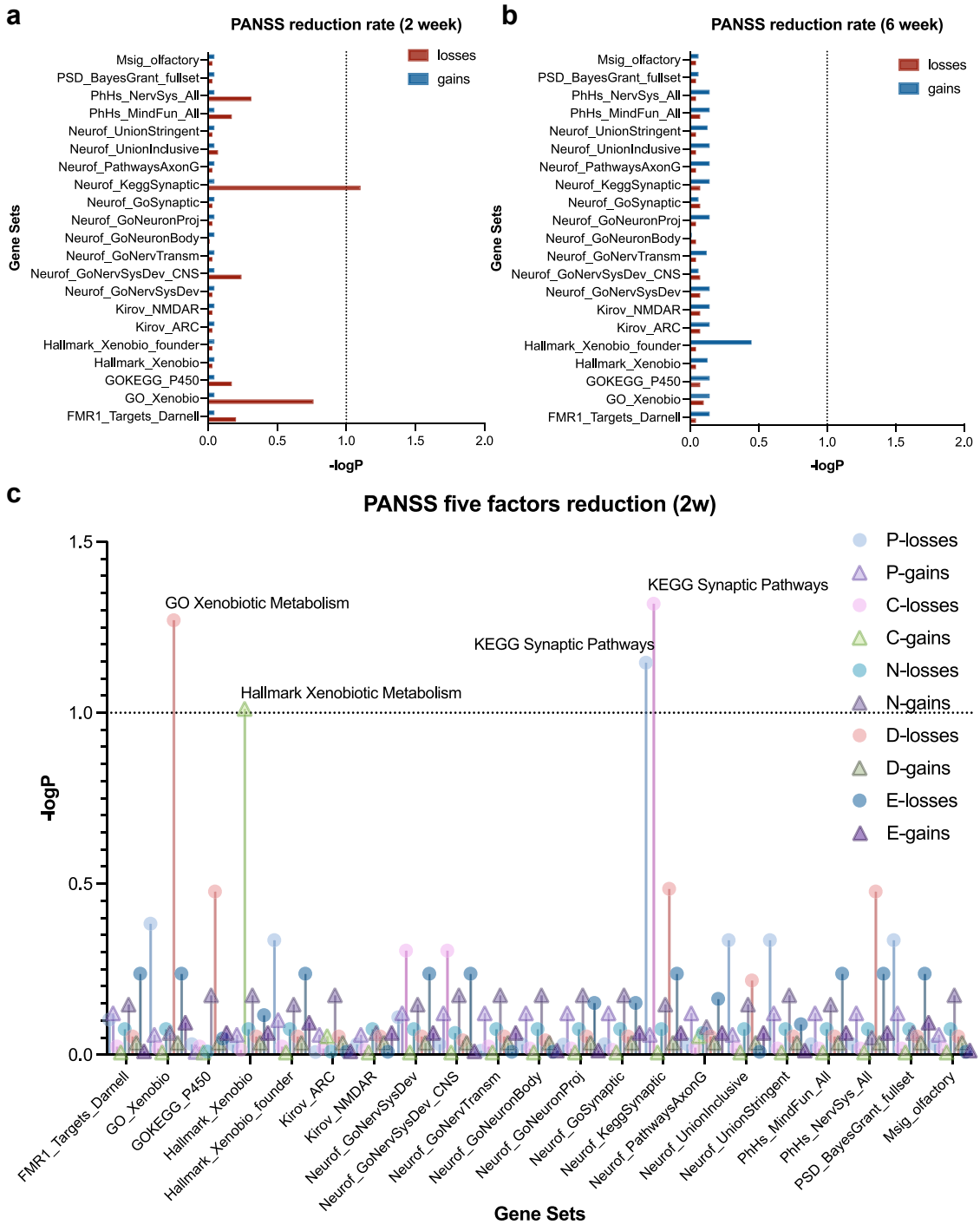
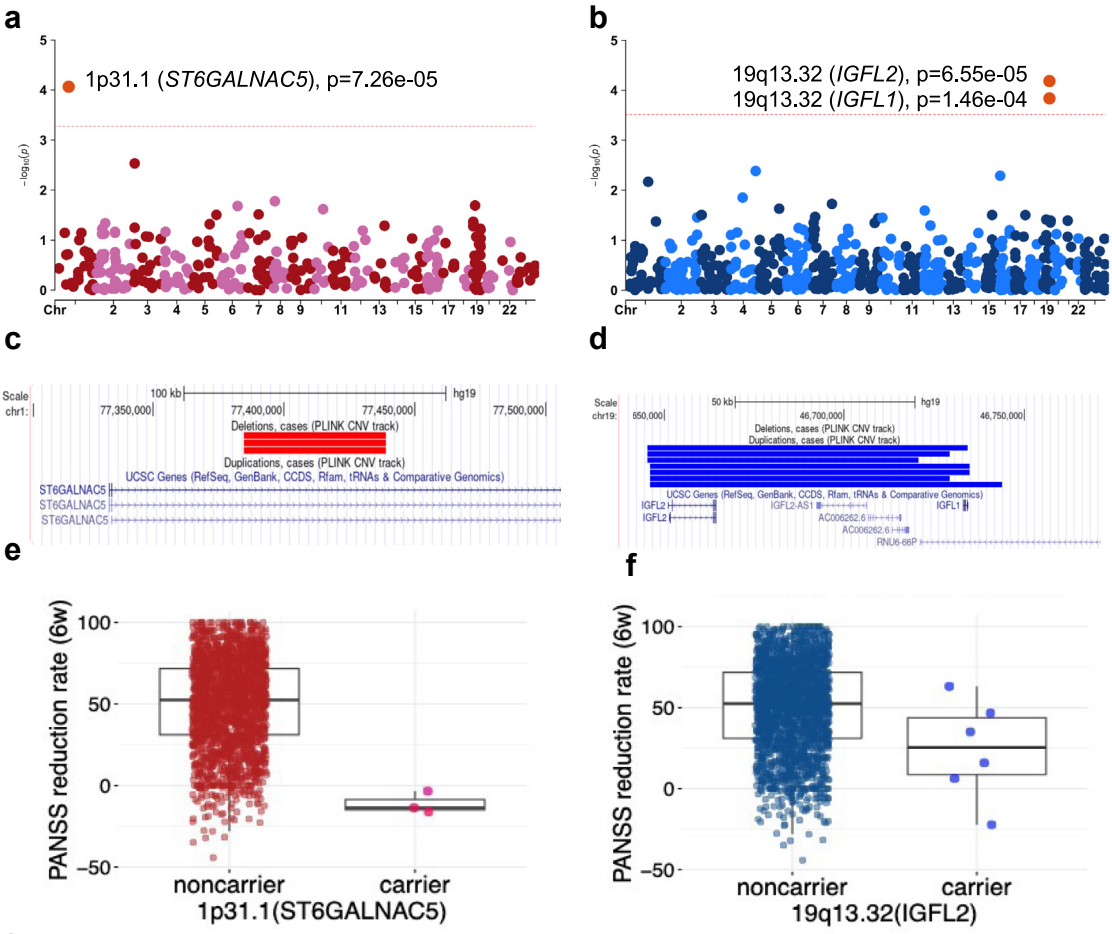


Fig. 2: Gene set carrier analysis. Gene set tests were conducted in 16 gene sets for neuronal function, synaptic components, neurological and neuro-developmental phenotypes, 4 gene sets involved in xenobiotic metabolism, and 1 negative control gene set (Msig_olfactory), using 1853 individuals. (a,b) Gene set carrier analysis for PANSS reduction rate at 2 weeks (a) and at 6 weeks (b) partitioning by CNV type (gains and losses), the x axis is the –logP of the *BH-FDR P* values for gene sets, and significant line denotes the 10% *BH-FDR* threshold. CNV carriers of losses at Neurof_KeggSynaptic (KEGG Synaptic Pathways) gene set attained the *BH-FDR* threshold (P = 3.58e-03, P_{fdr} = 0.079). (c) Gene set carrier analysis for PANSS five factors reduction at 2 weeks. P: positive symptom factor, N: negative symptom factor, C: cognitive factor, D: depressive factor, E: excitement factor. The y axis is the –logP of the *BH-FDR P* values for gene sets, and significant line denotes the 10% *BH-FDR* threshold. The significant gene sets included: losses of KEGG Synaptic Pathways on cognition (P = 2.18e-03, P_{fdr} = 0.048), losses of GO Xenobiotic Metabolism on depression (P = 2.44e-03, P_{fdr} = 0.054), losses of KEGG Synaptic Pathways on positive symptoms (P = 3.24e-03, P_{fdr} = 0.071), and gains of Hallmark Xenobiotic Metabolism on cognition (P = 4.42e-03, P_{fdr} = 0.097).



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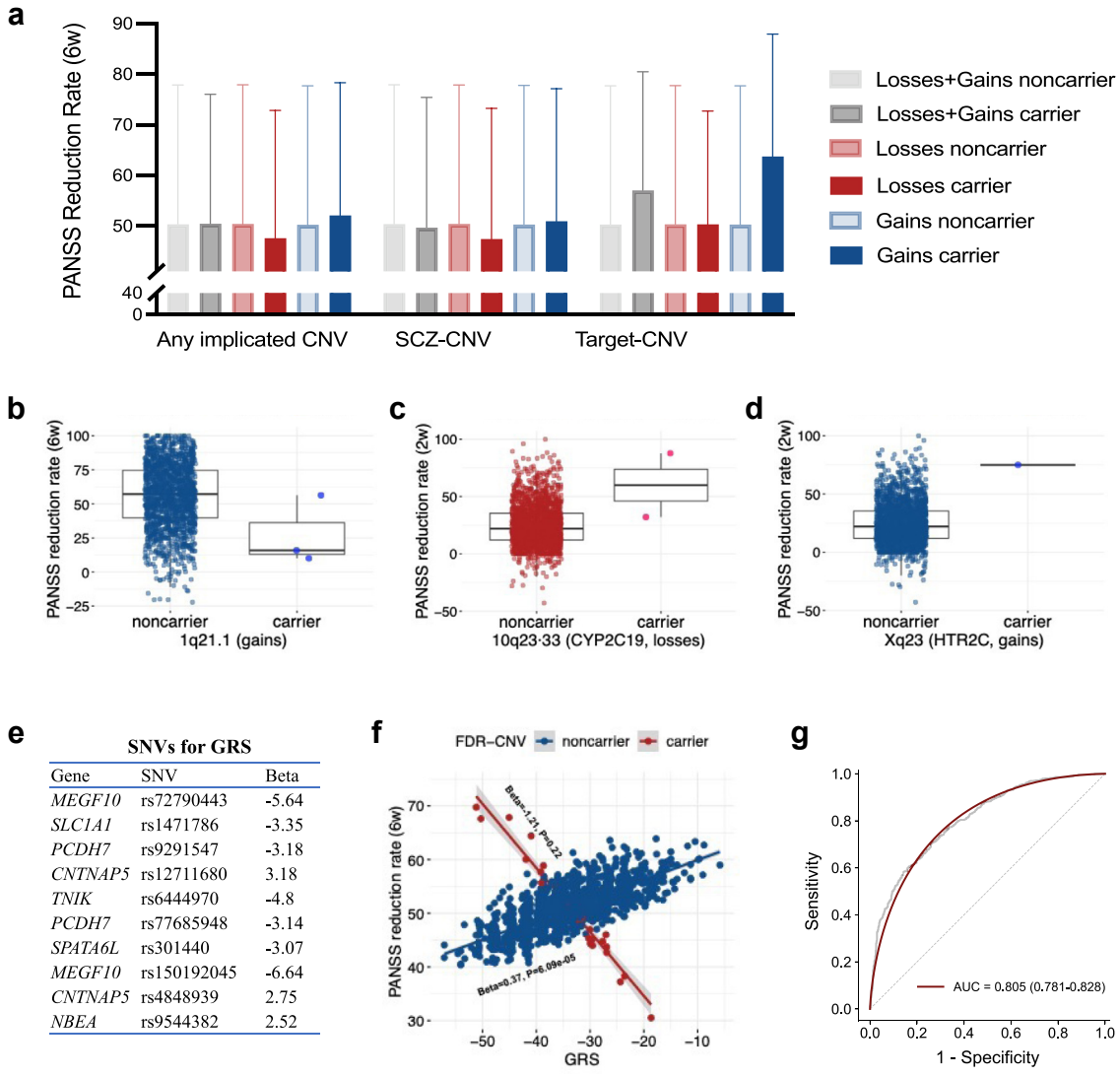
Locus	Type	CHR	BP1	BP2	Gene	Size (kb)	Direction	Phenotype	Beta	*SE*	*P* value	*BH-FDR*	*FWER*	Count
1p21.3	losses	1	98156892	98204094	*DPYD*	47.2	risk	2w Depression red.	-8.66	1.39	5.37×10^{-10}	1.78×10^{-7}	Yes	1
1p31.1	losses	1	77384769	77438811	*ST6GALNAC5*	54.04	risk	6w PANSS red. rate	-62.39	15.69	7.26×10^{-5}	2.55×10^{-2}	Yes	3
5p13.2	losses	5	37333727	37567851	*NUP155,WDR70*	79.49	protective	2w Cognition red.	8.93	1.75	3.49×10^{-7}	1.17×10^{-4}	Yes	1
9p22.3	losses	9	15393381	15431326	*SNAPC3*	38.85	protective	2w Negative red.	23.62	2.99	4.92×10^{-15}	1.64×10^{-12}	Yes	1
5q23.1	gains	5	115233116	115627570	*ARL14EPL, LVRN, AP3S1, COMMD10*	394.45	protective	2w Negative red.	23.62	2.99	4.92×10^{-15}	2.62×10^{-12}	Yes	1
16q21	gains	16	61042822	62378896	*CDH8*	384.83	protective	6w Cognition red.	14.39	3.18	6.34×10^{-6}	3.20×10^{-3}	Yes	1
19q13.32	gains	19	46645309	46743958	*IGFL2*	75.36-97.86	risk	6w PANSS red. rate	-47.53	11.87	6.55×10^{-5}	3.02×10^{-2}	Yes	6
					IGFL1	88.80-97.86	risk	6w Excitement red.	-12.26	3.04	5.93×10^{-5}	2.74×10^{-2}	Yes	4

Fig. 3: Gene-based CNV association analysis. (a,b) Manhattan plots displaying the -log10 *P* value for CNV losses (a, red) and CNV gains (b, blue) in the gene-based test for PANSS reduction rate at 6 weeks. *P* value cutoffs corresponding to *FWER* < 0.05 are highlighted in red dashed line and the cutoffs are 4.64e-04 (a) and 3.04e-04 (b), respectively. Loci significant after multiple test correction are labeled. In gene-based CNV association analysis, *IGFL1* and *IGFL2* were merged into 19q13.32 locus, and the minimum *P* value from *IGFL2* was selected to represent the region *P* value. (c,d) CNV tracks display losses at 1p31.1 (*ST6GALNAC5*, c) and gains at 19q13.32 (*IGFL2*/*IGFL1*, d) detected in our sample from the UCSC Genome Browser on Human (hg19). (e,f) The boxplots displaying the difference on 6-week PANSS reduction rate between 1p31.1 (e) and 19q13.32 (f) CNV carriers and noncarriers, and one sample carrying 19q13.32 gain is missed in scatter due to missing on phenotypes. (g) Tables for all CNV loci attained genome-wide significant threshold in gene-CNV association analysis for PANSS reduction rates and PANSS factor reductions at 2 weeks and 6 weeks. CNV indicates copy number variants, *FWER* indicates family-wise error rates, PANSS indicates Positive and Negative Syndrome Scale, and "red." indicates "reduction".

We focused on 32 SCZ-CNVs including 15 CNV losses and 17 CNV gains as previous study suggested,[8] and 24 of them were extracted from our sample (Supplementary Table S11). From the perspectives of pharmacogenomics, CNVs that intersected with at least one exon of atypical APD target genes and drug metabolism genes were considered as Target-CNVs,[25,26] resulting in 10 Target-CNVs extracted with 3 CNV losses and 7 CNV gains (Supplementary Table S12). The CNV count is illustrated in Supplementary Fig. S18.

Although CNV carrier of gains at Target-CNV reported more 6-week PANSS reduction rate, we did not find statistically significant difference on PANSS reduction rates at 2 weeks and 6 weeks between CNV carriers for any implicated CNV, SCZ-CNV or Target-CNV, than those noncarriers (Fig. 4a and Supplementary Table S13),



e

SNVs for GRS

Gene	SNV	Beta
MEGF10	rs72790443	-5.64
SLC1A1	rs1471786	-3.35
PCDH7	rs9291547	-3.18
CNTNAP5	rs12711680	3.18
TNIK	rs6444970	-4.8
PCDH7	rs77685948	-3.14
SPATA6L	rs301440	-3.07
MEGF10	rs150192045	-6.64
CNTNAP5	rs4848939	2.75
NBEA	rs9544382	2.52

Fig. 4: Effects of previously implicated CNVs and joint effects of CNVs and SNVs on APD response. (a) Between-group comparisons on 6-week Positive and Negative Syndrome Scale (PANSS) reduction rate between previously implicated copy number variants (CNVs) carriers and noncarriers partitioned by CNV type. Any previously implicated CNV, schizophrenia-associated CNV (SCZ-CNV), and antipsychotic drug target gene-intersected CNV (Target-CNV) were showed. Error bar indicates standard deviation. No significant difference was found. (b–d) Boxplots on PANSS reduction rate between carriers of nominally significant Target-CNV and those noncarriers, (b) shows gains at 1q21.1 (P = 0.031), (c) shows losses at 10q23.33 intersected with *CYP2C19* (P = 0.003), and (d) shows gains at Xq23 intersected with *HTR2C* (P = 0.010). (e) Top single nucleotide variations (SNVs) to calculate genetic risk score (GRS); (f) Significant interactive effects on 6-week PANSS reduction rate between CNVs passed FDR correction (FDR-CNV) and GRS ($P_{interaction}$ = 0.021). (g) Receiver operating curve for antipsychotic drug (APD) treatment response at 6 weeks, the area under curve (AUC) was 0.805 (95% *CI*: 0.781–0.828).

respectively. And no significant enrich was found for any implicated CNV, SCZ-CNV or Target-CNV in TR group (Supplementary Table S14). Of the 24 SCZ-CNV loci, copy number gains at 1q21.1 showed risk effect on PANSS reduction rate at 6 weeks at nominal significance level of $EMP < 0.05$ (linear regression: $\beta = -29.54$, $SE = 13.76$, $P = 0.031$). Of the 10 Target-CNV loci, losses at 10q23.33 (*CYP2C19*, linear regression: $\beta = 39.49$, $SE = 12.59$, $P = 0.003$) and gains at Xq23 (*HTR2C*, linear regression: $\beta = 49.12$, $SE = 17.79$, $P = 0.010$) showed nominal protection effects for 2-week PANSS reduction rate. Boxplots are illustrated in Fig. 4b–d. But no variant passed permutation-based *FDR* correction in association analysis of single CNV locus. Additional losses at 1q21.1 (*FMO5*), 9p24.2, 16p11.2 and17p12, and gains at 5q12.3 (*HTR1A*), 9q34.3 and16p13.11 and passed nominal significance level of $EMP < 0.05$ for PANSS factors reduction. Details can be found in Supplementary Table S15. Combining effects of significantly implicated CNVs and suggestive FDR-CNVs identified in the genome-wide association analysis, a total of 45 CNVs collectively account for 4.50% of the variance (R^2) for 6-week PANSS reduction rate.

Joint effects of CNV and SNV

Contribution of both SNVs and CNVs on APD treatment efficacy was explored jointly. Ten SNVs (Fig. 4e) that related to APD efficacy identified in our previous GWAS study were selected to calculate genetic risk score (GRS).[15] The effect size of single CNV locus for 6-week PANSS reduction rate was 4.48 to 24.76 times than that of single SNV. GRS significantly related to 6-week PANSS reduction rate (linear regression: $\beta = 0.35$, $SE = 0.09$, $P = 1.63e\text{-}04$), and showed interaction effects with any FDR-CNV carrier ($P_{interaction} = 0.021$, Fig. 4f). In details, the effect of GRS can be observed in noncarriers of FDR-CNV, but cannot be observed in carriers of FDR-CNV. Combining with FDR-CNVs, GRS, top five PCs, clinical characteristics and early response at 2 weeks, the AUC to differ TR from NTR attained 80.45% (95% *CI*: 78.07%–82.82%, Fig. 4g).

Discussion

Antipsychotic treatment effectiveness varies greatly among individuals. Our study provides support for the significant contribution of CNV to the observed differences in individuals responses to antipsychotic treatment. In general, higher copy number losses burden was related to poor response to APDs. The CNV losses related to synaptic pathway and xenobiotic metabolic process contributed to APD response at early phase. We identified several CNV loci, including those involved in sialylation (1p31.1 losses), cellular metabolism (19q13.32 gains), pyrimidine base degradation (1p21.3 losses), calcium-dependent cell–cell adhesion (16q21 gains), nucleocytoplasmic transport (5p13.2 losses), vesicle-mediated transport (5q23.1 gains), and RNA polymerase II regulatory (9p22.3 losses), which were significantly associated with APD efficacy at the genome-wide level. These CNVs are implicated in G-protein-coupled receptors (GPCR) activity and drug metabolism. Furthermore, CNVs exhibited a greater impact than and interacted with SNVs in influencing APD efficacy, and are promising in guiding gene-oriented treatment.

Limited research has been conducted thus far regarding the association between SCZ-CNVs and the efficacy of APD. Kushima et al. found that patients with SCZ carrying clinically significant neurodevelopmental CNVs exhibited a higher likelihood of treatment resistance concerning improvement in social/occupational functioning compared to non-carriers ($OR = 2.79$).[9] A recent investigation into treatment-resistant SCZ identified a potentially elevated prevalence of SCZ-CNVs in the treatment-resistant sample compared to previously reported SCZ cases not specifically selected for treatment resistance.[12] In our sample, although we did not observe a significant enrichment of SCZ-CNVs in the NTR group compared to the TR group, we did identify several significant associations at individual CNV loci. Distinct from Kushima's study,[9] we utilised different tools to measure APD efficacy. And Martilias's study recruited patients with treatment resistance based on more stringent criteria (i.e., prolonged illness duration and changes in medication treatment), whereas our focus was on APD efficacy during the acute phase. The heterogeneous nature of the phenotypes in our sample may have limited our ability to replicate previous findings.

Our study supports the important role of neurotransmitters in the antipsychotic treatment when viewed through the lens of CNVs. Copy number losses burden decreased the antipsychotic treatment efficacy. The enrichment results showed that the genes affected by CNV losses were mostly enriched in pathways related to dopamine uptake involved in synaptic transmission, catecholamine uptake involved in synaptic transmission, and glutathione metabolic process, underscoring the potential function of neurotransmitters. By testing the associations between candidate gene sets and antipsychotic efficacy, the synaptic gene set, encompassing multiple neurotransmitters, emerged as particularly significant. In agreement with our findings, analysis of CNV models has revealed that synaptic properties are often impacted.[27] Synaptic modulators are likely to play a key role and could pave the way for improved treatment of schizophrenia.

The identification of 7 new loci associated with APD response was a significant advance of our study. CNV rescue strategies offer a distinct perspective that can inform and inspire the development of innovative therapeutics for schizophrenia. After identifying key genes with critical roles, new drugs can be designed to

replicate the beneficial effects observed in gene restoration approaches. CNV genes can be further annotated according to their potential for being drug targets.

The protein encoded by *ST6GALNAC5* (1p31.1) predominantly catalyses the biosynthesis of ganglioside GD1α from GM1b in the brain to modulate cell–cell interactions, and participated in the sialylation of glycoproteins or glycosphingolipids, which are important in neuronal development, nerve repair, immunological processes, tumour development and regulation of hormone sensitivity.[28,29] For antipsychotic treatment, alterations in N-glycans on serum glycoproteins have been detected after 6 weeks of olanzapine treatment alone.[30] Studies have demonstrated that olanzapine or chlorpromazine can elevate levels of polysialylated NCAM in the prefrontal cortex of healthy adult rodents, indicating that these drugs could potentially influence the localisation or recycling of this polysialylated protein.[31,32] Even though relatively limited understanding of glycosylation in the nervous system has been proposed, the association between ganglioside and APD efficacy may be attributed to the modulation of GPCR function by sphingolipids,[33,34] as demonstrated by interacts between GM1 and HT1AR at sphingolipid binding domain.[35] Losses at 1p31.1 may damage the stability of the membrane lipid and influence the GPCR activity. There has been compelling argument from observational studies of plasma, CSF and postmortem brain samples suggesting that abnormal glycosylation plays a role in the underlying pathophysiology of schizophrenia.[36] GWAS study involved in depression, cognition and memory also identified genome-wide significant variants in *ST6GALNAC5*.[37] Another study uncovered the important roles of ST6GALNAC family in leading glycosylation alterations across different brain regions in patients with Alzheimer's disease, showing reduced expression level of *ST6GALNAC5* in medial temporal cortex.[38] Pharmacological function of this CNV needs to be further investigated in order to provide a promising therapeutic strategy in 1p13.1.

The 19q13.32 covers the genes *IGFL2* and *IGFL1*, and *IGFL2-AS1*, a long non-coding RNA (lncRNA) that negatively regulates *IGFL1* expression.[39] IGFL is a family of secreted proteins and could act as secreted growth regulators, playing critical roles in cellular energy metabolism and in growth and development, especially prenatal growth.[40] The mRNA expression pattern of *IGFL* genes supports that the *IGFL* are expressed in fetal epithelial tissues where growth and differentiation tend to be high.[40] Previous studies have reported higher levels of *IGFL2-AS1* transcript in several types of cancer, and found important roles of cell proliferation, migration, and epithelial–mesenchymal transition in cancer.[41] However, few evidence of involvement in the metabolism was found.

Notably, the 1p21.3 losses, located within *DPYD*, a haploinsufficiency gene encoding the catabolic enzyme dihydropyrimidine dehydrogenase (DPD), hold significance. *DPYD* stands out as a prominent candidate in schizophrenia susceptibility, as reported in previous studies.[18–20] What garners our attention, however, is the CNV's impact on the efficacy of antipsychotic treatment. *DPYD* has been utilised to tailor dosages for fluoropyrimidine therapy in patients with cancer, with its metabolic activity toward fluoropyrimidine serving as the primary consideration.[42] Moreover, associations with *DPYD* variants have been identified in studies involving anticoagulants or antipsychotic drugs.[43] Through integration within the protein-interaction network, encompassing the clustering with *CYP2C19* and the *FMO* family, *DPYD* emerges as a pivotal player in the drug metabolism pathway.

In our study, three CNV gains around 120 kb at distal 1q21.1, locating in exon cluster region, confer risk for APD efficacy. The findings are consistent with the risk effect of 1q21.1 gains on schizophrenia and global developmental delay.[44] However, even though six deletions were also enriched in this region, no significant effect was found on any dimension of APD efficacy. The deletion of 2p16.3 is a hot spot that contributes to schizophrenia, especially in the region covering *NRXN1*.[45] In our sample, individuals with deletions in 2p16.3 were more resistant to APD response in negative symptoms than noncarriers. While the recurrent deletions/duplications at 22q11.2 represent a clinically relevant cause of schizophrenia,[46] we found a marginal risk effect of duplications at 22q11.21 on APD efficacy in cognition symptom.

A strength of our study lies in the opportunity it provides to evaluate the combined influence of common SNVs and rare CNV on the efficacy of APD. It is imperative to acknowledge the considerable impact of CNVs and the potential bias that may arise when assessing SNVs in isolation. Notable, in our sample, it has been estimated that approximately 20.8% of the total variation (around 6 million) in response to antipsychotics can be attributed to common SNVs across the genome.[15] Conversely, while rare CNVs were less numerous, with only 45 loci identified, they nonetheless contributed to 4.5% of the total variation. This significant effect size holds promise for advancing therapeutic efficacy and realizing economic benefits in drug target research based on CNV in the future. Moreover, on conjunction with the identification of common SNVs, rare variants such as CNVs emerge as genuine causal factors triggering response to antipsychotic treatments, rendering them significant candidates for genetic mechanism. Modelling the structure and function of relevant CNV in the context of antipsychotic efficacy represents an important opportunity to identify new therapeutics and promote gene-oriented APD treatment.

Strengths

The strengths of our study primarily lie in our ability to identify associations between rare CNVs and

antipsychotic efficacy at a genome-wide level, as well as explore the interactive effects of common and rare genetic variants. Schizophrenia is a complex and severe neuropsychiatric disorder in need of novel therapeutic insights. Our study has uncovered a significant burden of CNVs on antipsychotic treatment efficacy, further supporting the important roles of neurotransmitters in schizophrenia treatment. We pinpointed seven CNV loci associated with GPCR activity and drug metabolism, pivotal factors in determining responses to antipsychotic treatment. Despite their rarity, CNVs pose considerable risks. The discovery of protective CNV loci presents promising avenues for enhancing the effectiveness of antipsychotic treatment, while the recognition of risk CNV loci underscores the importance of alternative therapeutic strategies. Overall, our findings offer an opportunity for a personalised approach addressing both common and rare genetic vulnerabilities. Further research is warranted to validate these findings in larger cohorts and diverse populations, thereby advancing the application of personalised medicine in schizophrenia treatment.

Limitations

Several limitations have to be addressed. Associations between CNV and antipsychotic treatment efficacy may be obscured by treatment-related variables (i.e., long duration, several episodes) and external environmental factors. Evaluating these associations in a more homogeneous sample (e.g., first-episode drug-naïve individuals) could offer insight into such relationships. A limitation is the CNV cannot be validated due to the low frequency in populations. We focused primarily on the CNV signal mapped on exons where findings are more likely to be biologically interpretable and potentially clinically relevant than that from noncoding variants, but other important regulatory features may be ignored in the discovery phase. Limited by the CNV calling method using SNP array data, some small CNVs may be undetected. For example, the most important liver enzymes involved in APD metabolism are the P450 enzymes *CYP2D6, CYP3A4, CYP2C19* and *CYP1A2*. The length for these genes is around 4–27 kb except *CYP2C19* (92.8 kb), making them unlikely to be mapped within CNVs meeting our QC process. No CNV was identified overlapping with genes in the dopaminergic system, glutamatergic system, histaminergic system, or neurotrophic factors either. Moreover, phenotype associated with CNVs is nonspecific and SCZ-CNVs may also be correlated with ASD, developmental delay and intellectual disability, which may complicate the elucidation of the association between CNVs and APD response. Apart from the covariates included in our models, other potential factors, such as smoking, duration of illness, duration of treatment, baseline weight, antipsychotics, and concomitant therapy, should be analysed in future studies. The association between CNV and APD efficacy especially deserves to be analysed in patients with antipsychotics of different pharmacological mechanism. Furthermore, although our findings provide new insights into the APD treatment efficacy, the susceptible CNV loci were identified in participants of Han Chinese ancestry. These identified regions might not be associated with treatment response in other ethnic groups. Limited by the few studies involved in APD treatment response, we cannot calculate the genome-wide GRS for APD response. Of the interactive effects, we found that the effects of GRS may disappear when CNVs exist. However, we cannot exclude the insignificance might be caused by the low statistical power in CNV carriers. The limited number of CNV segments surrounding the schizophrenia risk genes identified in GWAS constrained our ability to thoroughly explore the interactive effects between CNVs and SNVs.

Contributors

HH and WY were co-primary investigators. DZ, HH and WY designed the study, acquired funding, and contributed to interpretation of data. YS, HH and WY wrote the first draft of the article. CNV calling was carried out by YS, QF, YC and HH. YS, YZ, ZL, YL, MY, and WB did the statistical analyses, data validation and interpretation of data. ZK, XF, GZ, JS, YY and LG were responsible for phenotype cleaning, preparation of the tables and figures, and provided further data interpretation. YS and YZ have accessed and verified the underlying data. All authors contributed to drafting the work or critically revising it for important intellectual content, and made substantial contributions to the concept and design of the study and data acquisition, analysis, and interpretation. All authors read and approved the final version of the manuscript.

Data sharing statement

Constrained by the local law on the management of human genetic resources and the requirements of the research project, the sharing of genetic data was restricted from public access. The data that support the findings of this study are available from the corresponding author, WY, upon reasonable request with proposal. All requests must be approved by the relevant ethics boards and data custodians.

Computer code relating to this study includes:

PennCNV v1.0.5: https://penncnv.openbioinformatics.org/en/latest/.

iPattern v0.582: https://www.tcag.ca/tools/index.html.

Plink-1.07-x86_64: https://zzz.bwh.harvard.edu/plink/.

Most custom scripts used in the production and/or analysis are publicly available via GitHub: https://github.com/QidiFeng/cnv_calling_QC_association/tree/main.

Declaration of interests

The authors declare no conflict of interest.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ebiom.2024.105195.

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