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Genome-wide association of copy number variants across six major psychiatric disorders reveals genotype-phenotype relationships of rare variants

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Genome-wide association of copy number variants across six major psychiatric disorders reveals genotype-phenotype relationships of rare variants

A Dissertation submitted in partial satisfaction of the requirements
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in

Bioinformatics and Systems Biology

by

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Professor Sandra Sanchez-Roige

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The Dissertation of Omar Shanta is approved, and it is acceptable in quality and form for publication on microfilm and electronically.

University of California San Diego

2023

DEDICATION

To my parents and family who always believed in me.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

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ABSTRACT OF THE DISSERTATION

Genome-wide association of copy number variants across six major psychiatric disorders reveals genotype-phenotype relationships of rare variants

by

Omar Shanta

Doctor of Philosophy in Bioinformatics and Systems Biology

University of California San Diego, 2023

Professor Jonathan Sebat, Chair

Rare copy number variants (CNVs) have been strongly implicated in autism (ASD) and schizophrenia (SCZ), but well-powered genome-wide studies of rare variants have not been carried out across multiple major psychiatric disorders. Here we perform a genome-wide association of CNVs across schizophrenia (SCZ), autism spectrum disorder (ASD), bipolar disorder (BD), major depressive disorder (MDD), post-traumatic stress disorder (PTSD),

attention-deficit/hyperactivity disorder (ADHD) and in the combined cross-disorder cohort (XD) (N=537,466).

CNV calling was performed using a consistent ensemble pipeline that enables the combining of datasets and disorders. CNV burden and CNV-GWAS were used to characterize genetic associations genome-wide. Associations were tested for deletion (DEL) and duplication (DUP) separately, controlling for ancestry, genotyping platform, and cohort.

CNV burden analysis revealed that rare CNVs contribute to all 6 disorders but with effects that differ by disorder. Genome-wide association analyses of CNV across disorders found 36 significant associations at 21 independent loci. For all disorders, alleles span the full range of frequencies, but disorders differ in their distribution of effect sizes. Effects were strongest for ASD and were invariably positive. Rare variants in SCZ, BD, and MDD were a mixture of positive and negative effects. Effect sizes in MDD were comparatively weak. Many CNVs were associated with multiple disorders but not to the same extent. Some were predominantly associated with ASD (15q11-13 Dup), some were most strongly associated with SCZ (16p11Dup, 22q11Del), and other CNVs were weakly associated with several disorders but reached genome-wide significance only in the combined XD cohort (ASTN2, DLG2). Without exception, all associations occurred in genomic regions that are prone to high rates of structural mutation. 15 were hot spots for non-allelic homologous recombination (NAHR) and 6 were in common fragile sites (CFS) where chromosome breakage occurs within large neural genes (ASTN2, DLG2, DLGAP2/CSMD1, IMMP2L, NRXN1, SHANK3). Several large neural genes also intersect with topologically associating domain (TAD) boundaries, but associations were driven by protein coding deletions, and were not attributable to non-coding variants. An enrichment of CNV associations near TAD boundaries in this case may not be attributable to

cis-regulatory effects of rare variants, but instead attributable to the intrinsic genomic instability of these regions that gives rise to deletions.

Genome-wide analysis of rare CNVs across major psychiatric disorders identifies many risk loci including both positive and negative associations and novel gene associations. A comparative analysis highlights considerable genetic overlap between disorders but also distinguishable differences in allelic architecture and considerable phenotypic specificity to CNV associations.

Chapter 1 Introduction

Previous studies have demonstrated a strong contribution of rare variants to psychiatric disorders. Rare CNVs have been associated with ASD (Sebat et al. 2007) and SCZ (Walsh et al. 2008) and specific CNVs show strong association with risk (Sanders et al. 2015; Walsh et al. 2008) with odds ratio of 5-50. Subsequent whole exome sequencing studies of ASD (Gilman et al. 2011; De Rubeis et al. 2014) and SCZ (Singh et al. 2022) have identified specific genes involved in synaptic function and genetic regulation of fetal brain development.

However, the relationship of specific CNVs or genes to psychiatric traits is poorly defined. Individual rare variants each show association with a variety of developmental and psychiatric disorders, consistent with rare variants having variable expressivity for psychiatric traits. It is also consistent with the clinical presentation of a rare variant being influenced by the genetic-modifying effects of other rare and common variants (Antaki et al. 2022). For any given CNV or gene mutation, it's main effects on psychiatric traits remain unclear. We do not know if there is discernible specificity to its genotype-phenotype relationships or if rare variants with large effects essentially have a very broad influence on the severity of all psychiatric disorders.

Well-powered studies across a range of psychiatric disorders are required to address this question. GWAS is being applied on large scales to characterize common variant influence on psychiatric and other complex traits. Cross disorder SNP GWAS has shown evidence of genetic risk factors being shared across psychiatric disorders (Cross-Disorder Group of the PGC et al. 2013). In addition to SNPs, relatively large (>10 kb) DNA copy number variants, both common and rare, are readily detectable using SNP genotyping arrays (Sebat et al. 2004). This has enabled very large-scale studies of the effects of rare CNVs on human disease and complex traits (Marshall et al. 2017).

We aggregated microarray intensity files from GWAS datasets of six psychiatric disorders to obtain rare CNV calls for 537,466 individuals including controls (N=413,560) and cases of schizophrenia (SCZ, N=31,673), autism spectrum disorder (ASD, N=13,208), bipolar disorder (BD, N=23,891), major depressive disorder (N=38,323), post-traumatic stress disorder (PTSD, N=13,794), and attention deficit/hyperactivity disorder (ADHD, N=3,523). CNVs were called using a centralized pipeline for systematic CNV calling across genotyping platforms and cohorts, and QC filtering of variants was performed with special consideration for genotyping platform differences in CNV calls. Statistical association tests were performed for rare deletions and duplications (occurring in < 1% of subjects) within individual cohorts as well as in the combined cases referred to as the cross-disorder (XD) cohort.

Chapter 2 Methods

Data Collection

The CNV subgroup of the Psychiatric Genomics Consortium (PGC) works in collaboration with principal investigators from many labs to obtain large sample sizes of microarray data and analyze them using a centralized pipeline for direct comparison between datasets and disorders. We were able to acquire a total of 537,466 samples that included data from 6 disorders (Table 1). These samples ranged across 14 platforms and 4 genome builds. All data was lifted over to GRCH38 for analysis. Samples were genotyped on either Illumina or Affymetrix array. Data from Illumina was collected as either raw intensity data (IDAT) files or final report files while data from Affymetrix was collected as CEL files.

Table 1: Sample sizes used for all six disorders
Samples for each disorder were matched by platform using a common set of controls across disorders. Samples were matched by genotyping platform and control samples were removed for individual disorders if there were no corresponding cases for the platform. EUR ASD contains family information while the rest of the disorders are case/control datasets.

Disorder	Cases	Controls	Total Samples
EUR ASD	13,208	23,340	36,548
EUR ADHD	3,523	51,651	55,174
EUR SCZ	31,673	353,930	385,603
EUR PTSD	13,794	329,257	343,051
EUR MDD	38,323	371,892	410,215
EUR BD	23,891	369,060	392,951
EUR XD	123,906	413,560	537,466

Copy number variant calling

For samples that were provided as IDAT files, the Illumina command line version of Genome Studio was used in conjunction with platform-specific manifest and cluster files to produce genotype call (GTC) files. Relevant features were extracted from GTC files to obtain final

report files with probes, genotypes, Log R Ratio, and B Allele Frequency for each sample. The genome builds across all platforms contained hg17, hg18, hg19, and hg38. The probe positions of samples that were not in hg38 were converted to hg38 using the LiftOver tool. Samples within each platform were grouped according to plate IDs to create batches. CNVs were called using two methods for Illumina/PsychChip arrays: PennCNV and iPattern, 4 methods for Affy6 arrays: PennCNV, iPattern, CScore, and Birdsuite, 2 methods for Affy Axiom arrays: PennCNV and QuantiSNP, and 2 methods for Affy5/500K arrays: PennCNV and Birdsuite. CNVs that were present in at least 2 callers were kept.

Quality control for CNVs

Quality control (QC) starts at the sample level and follows the same pipeline as the last SCZ CNV GWAS (Marshall et al. 2017). For Illumina arrays, Log R Ratio standard deviation (LRRSD), B Allele Frequency standard deviation (BAFSD), and waviness (GCWF) were extracted from PennCNV log files. Samples were retained if each of the measures were within 3 SD of the median. Affymetrix arrays used MAPD and waviness-sd parameters from affy power tools. Large CNVs that were fragmented were merged. The proportion of the chromosome that was tagged as a CNV was calculated and samples were excluded if >10% of the chromosome was marked as a CNV region to filter possible aneuploidies. CNV QC included the removal of CNVs spanning the centromere or telomere (100kb from end of chromosome), CNVs with >50% overlap with segmental duplications, immunoglobulin, or T cell receptor. Rare CNVs were identified by removing CNVs with >1% frequency within-platform or across all platforms. CNVs < 5kb in length or contained < 5 probes were excluded.

Filtering methods to remove spurious associations

CNVs that were found in only 1 platform or 1 dataset were causing spurious associations in the analysis, so 2 additional filters were applied systematically across deletions and duplications separately. CNV frequency was calculated within-platform and within-dataset as shown in Equation 1. Platform and dataset specificity filters were then created by turning the CNV frequency into a distribution as shown in Equation 2.

Equation 1: $$CNV\ Frequency\ (Platform/Dataset) = \frac{\#\ of\ CNV\ counts\ within\ (Platform/Dataset)}{\#\ of\ Samples\ within\ (Platform/Dataset)}$$

Equation 2: $$Platform\ or\ Dataset\ Specificity = \frac{CNV\ Frequency\ (Platform/Dataset)}{\sum_i CNV\ Frequency\ (Platform/Dataset)_i}$$

CNVs that appeared on multiple platforms/datasets have a platform/dataset specificity with low values across different platforms/datasets while CNVs that only appear on 1 platform/dataset will have a single high value for that platform/dataset and low values for the rest. Therefore, the maximum value of platform/dataset specificity can be used to determine if a platform/dataset is contributing a CNV that is not present elsewhere and introduce spurious associations. To determine a threshold for filtering CNVs with this method, we conducted a breakpoint-level CNV GWAS on the SCZ subsample and tagged known SCZ loci from the previous SCZ CNV GWAS (Marshall et al. 2017). Scatterplots were made to visualize the distribution of maximum specificity across all breakpoints in our current dataset (Fig. 1). Previously identified SCZ loci were present on multiple platforms and clustered at low specificity values while high values were associated with spurious associations. A threshold value of 0.6 was chosen to keep the known loci and filter spurious associations.

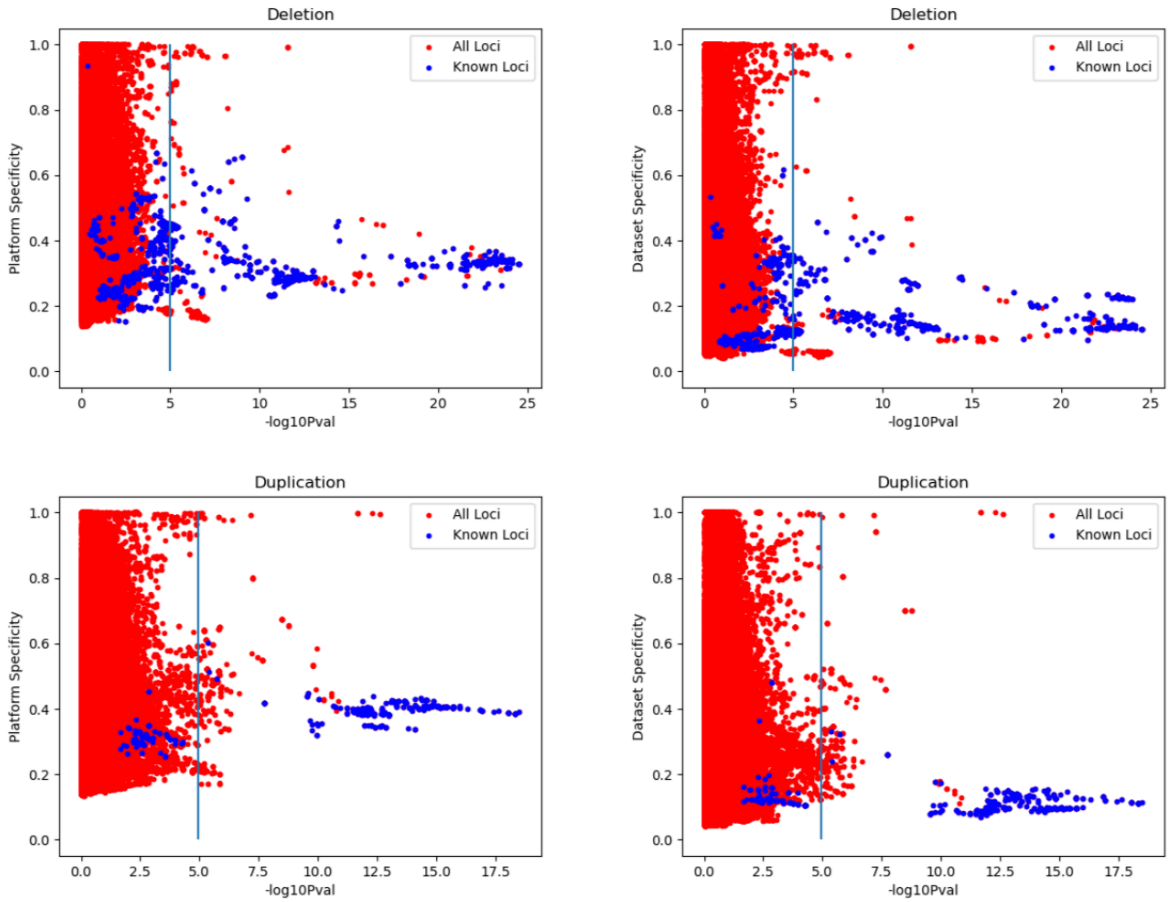


Figure 1: Platform/dataset specificity in SCZ

Platform specificity values vs. -$\log_{10}$(pvalue) from the CNV-GWAS are shown in the left column and dataset specificity values are shown in the right column. Deletions are across the top row while duplications are along the bottom row. Previously identified SCZ loci are shown in blue and the rest of the breakpoints are shown in red. The known loci cluster near the bottom and have lower specificity values while the spurious associations that need to be filtered cluster at the top (high values). A threshold of 0.6 was chosen to filter out CNVs coming from a single platform or dataset.

Statistics for CNV burden and CNV-GWAS analysis

Logistic regression was used to investigate the relationship between genotype and psychiatric disorder in order to adjust for confounding variables using sex, genotyping platform, and 10 ancestry principal components (PCs) derived from SNP genotypes as covariates. For CNV burden, the number of genes that overlapped a CNV genome-wide was used as the independent variable (Equation 3). Genes stratified by probability of loss-of-function intolerance (pLI) were

also tested. A null model consisting of a logistic regression using only the covariates was used to measure the contribution of genes. A chi-square test was then performed on the 2 models to obtain a p-value.

Equation 3: $aff \sim \#\ of\ Genes\ overlapping\ CNV + sex + platform + PCs$

Equation 4: $aff \sim sex + platform + PCs$

The ASD dataset contained families, so a conditional logistic regression with an extra covariate corresponding to family ID was introduced. The same method was used at the gene level and breakpoint level to obtain associations at finer resolutions. The independent variable at the gene level is the # of CNVs that overlap the gene and at the breakpoint level it is the # of CNVs that overlap the breakpoint. Tests were only included at each gene or breakpoint if there were at least 12 overlapping CNVs including at least 1 case and 1 control.

Family-wise error rate (FWER) was calculated as an adjusted Bonferroni correction. The total number of tests was replaced with the total number of independent tests (Equation 5). Independent tests were counted after identifying tests with >70% Jaccard similarity as too similar to be independent.

Equation 5: $FWER = \frac{0.05}{\#\ of\ independent\ tests}$

Assembling HiFi reads from samples carrying the SMYD3 duplication

HiFi long-read whole genome sequencing was performed on 3 samples using the PacBio Revio platform. Minimap2 v2.24 was used for alignment, DeepVariant v1.5 for variant calling, WhatsHap v2.0 for phasing and haplotagging reads, and Flye v2.9.2 for assembly.

Chapter 3 The role of rare CNVs in the genetic architecture of major psychiatric disorders

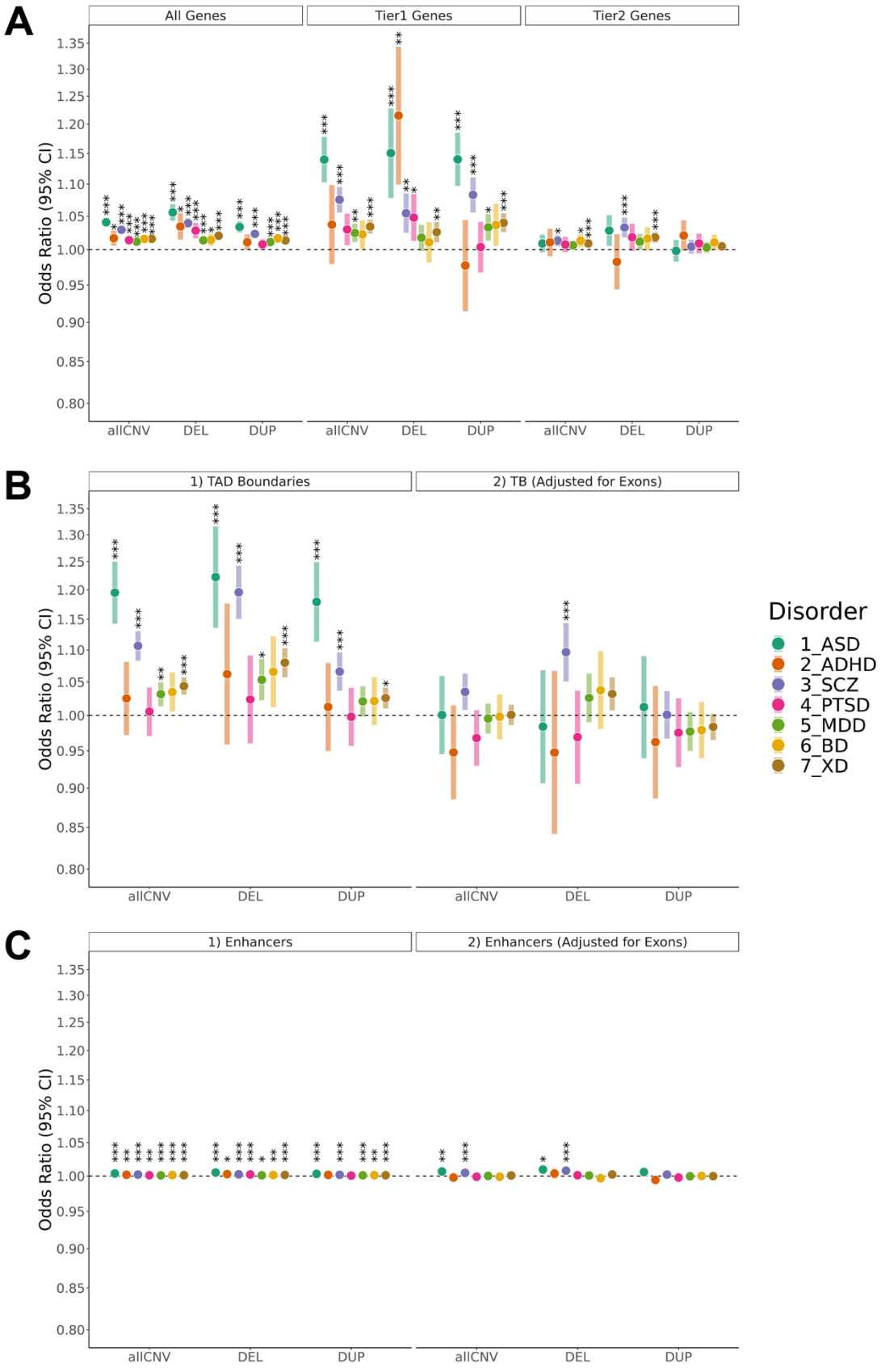
Association of rare CNV burden with psychiatric disorders in genes and regulatory elements

Genome-wide analysis of rare CNV burden in case-control samples is a well-powered test of whether rare variants confer risk for a given disorder (Walsh et al. 2008; Marshall et al. 2017). To determine the genome-wide contribution of rare CNVs in six psychiatric disorders, we conducted a CNV burden test using a logistic regression model (see Methods). Disorders were ordered by age-at-onset and tests were conducted for all CNVs, DELs only, and DUPs only. We see rare variants contributing to all psychiatric disorders with the strongest effects in early-onset disorders (Fig. 1A). Moderate effects can be seen in the late-onset disorders (PTSD, MDD, BD). We hypothesize that disruptions to loss-of-function intolerant genes have different effects than loss-of-function tolerant genes. To test this, we partitioned genes into two tiers according to their pLI score: high pLI (T1; pLI > 0.5) and low pLI (T2; pLI <= 0.5). Rare CNVs disrupting genes with high pLI were seen to drive global CNV burden for both DELs and DUPs (Fig. 1A). Rare deletions disrupting low pLI genes are only associated with SCZ cases and are much weaker.

Annotating rare CNVs with noncoding functional elements finds weak association with transcribed enhancers and topologically associated domains (TADs) in SCZ DELs (Fig. 1B and 1C). We originally saw effects for TAD boundaries and transcribed enhancers in all disorders, but this was mainly due to contribution from coding regions. We were able to regress out the effect of exons and the coding effect as a covariate in the logistic regression model used for the noncoding tests.

Figure 2: Effect Sizes of rare CNVs differ by disorder, genes, and regulatory elements

A) Genes were stratified by their probability of loss of function intolerance (pLI) and a CNV burden test was performed for each disorder. Tier1 Genes are defined as pLI < 0.5 and Tier 2 genes have pLI <= 0.5. Rare CNVs contribute to risk in all disorders at different magnitudes. CNVs overlapping Tier 1 genes are enriched in cases, with the largest effects in ASDADHD, and SCZ. B) The enrichment of TAD boundaries (TBs) to risk was tested in all disorders. SCZ DELs were enriched in TBs for cases. C) Contribution of transcribed enhancers was tested in the same way as TAD boundaries. The enrichment pattern is very similar to the All Genes category in panel A before adding # of exons as a covariate in the model. ASD and SCZ DELs show enrichment of CNVs overlapping transcribed enhancers in cases after controlling for # of exons.


A
All Genes
Tier1 Genes
Tier2 Genes
Odds Ratio (95% CI)
1.35
1.30
1.25
1.20
1.15
1.10
1.05
1.00
0.95
0.90
0.85
0.80
allCNV
DEL
DUP
B
1) TAD Boundaries
2) TB (Adjusted for Exons)
C
1) Enhancers
2) Enhancers (Adjusted for Exons)
Disorder
1_ASD
2_ADHD
3_SCZ
4_PTSD
5_MDD
6_BD
7_XD

Rare CNV GWAS identifies 36 genome-wide significant associations at 21 loci including 4 novel loci

The contribution of CNVs towards global burden showed an enrichment in all disorders, so a CNV genome-wide association study (rare CNV-GWAS) was conducted to identify novel loci that contribute to the etiology of psychiatric risk. A rare CNV-GWAS was performed at the gene-level as well as the breakpoint level in ASD, ADHD, SCZ, MDD, PTSD, BD, and XD for DELs and DUPs separately. The gene-level rare CNV-GWAS has previously been well-powered for novel loci discovery, but our large sample size has given us the ability to conduct a well-powered rare CNV-GWAS at a finer resolution. Utilizing a breakpoint rare CNV-GWAS allows us to identify regions within genes that contribute to psychiatric risk.

Association analyses identified 36 genome-wide significant associations involving 21 independent loci (Fig. 2A). Both previously implicated loci and novel loci can be seen in the rare CNV-GWAS. All associations occurred in genomic regions that are prone to high rates of structural mutation. 14 were hot-spots for non-allelic homologous recombination (NAHR) and 7 were fragile sites (ASTN2, DLG2, DLGAP2/CSMD1, IMMP2L, NRXN1, SHANK3, SMYD3). Some associations are strongest at the gene level like NRXN1 and SHANK3, but most are stronger at the breakpoint level. Novel associations include a genome-wide significant hit in MDD (16p13.11), associations that reached genome-wide significance in XD but not in individual disorders (ASTN2, DLG2), and association of SMYD3 DUPs in SCZ which has not been previously described in the literature. There are only 3 loci that show a significant association with controls (IMMP2LDel, 22q11.2Dup, MAGEA11Dup). Many rare CNVs are associated with multiple diagnoses, providing evidence of significant genetic overlap between disorders. A zoom into the 15q locus shows how the duplication of 15q11.2-13.1 has the strongest effect for ASD, yet the DUP is genome-wide significant in SCZ and nominally significant in MDD (Fig. 2B). On

the other hand, a deletion of 15q11.2 or 15q13.2-13.3 only has strong effects in SCZ. A zoom at the 16p locus shows how the CNV type at 16p11.2 determines association between SCZ (DUP) or ASD (DEL) (Fig. 2C). The 16p13.11 locus is genome-wide significant in MDD, but a closer look reveals nominal significance in ASD and SCZ that contribute to a stronger association in XD.

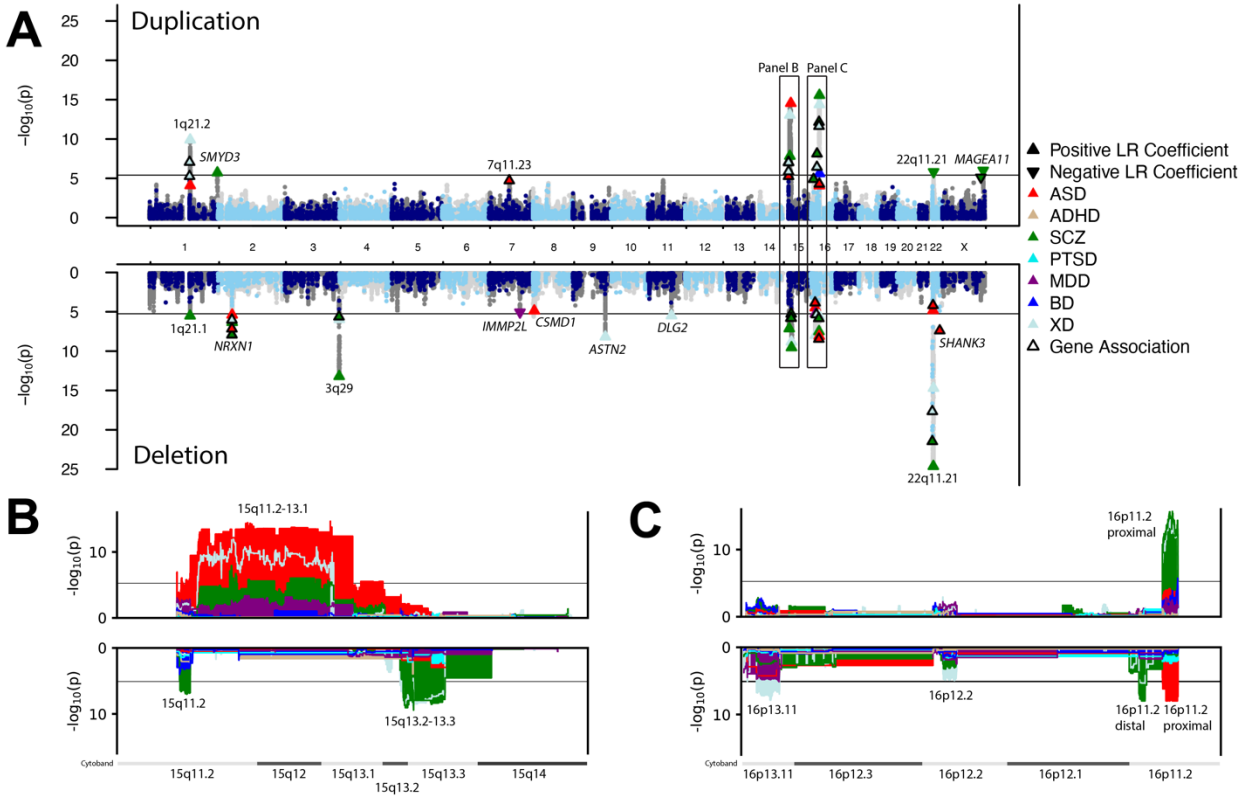


Figure 3: Detection of 36 genome-wide significant associations at 21 loci

A CNV-GWAS was performed at both the breakpoint (gray dots) and gene (blue dots) level. CNV-GWAS for all individual disorders were superimposed on top of each other to reveal the most significant associations in each disorder. The directionality of effect for each genome-wide significant hit is indicated by upward (positive) an downward (negative) facing triangles. Although there is a lot of overlap between gene-level associations (bordered triangle) and breakpoint-level associations (non-bordered triangle), the identified loci differ slightly. Novel loci are identified at SMYD3, IMMP2L, ASTN2, DLG2, 16p13.11. B) Zooming into the cluster of associations on chr15 shows how psychiatric associations differ substantially between CNVs. SCZ is strongly associated with DELs in 15q11.2 and 15q13.2-13.3 while a DUP at 15q11.2-13.1 switches the strongest association to ASD while SCZ has a weaker yet genome-wide significant association. C) Zooming into the cluster of associations on chr16 shows how CNV type can result in different psychiatric outcomes within a locus. A DUP at 16p11.2 proximal is strongly associated with SCZ while a DEL in the same location is strongly associated with ASD.

The genetic architecture of major psychiatric disorders spans the full range of frequencies and effect sizes

Previous studies of rare and common variants have had more success in some psychiatric disorders than others (Andreassen et al. 2023). Whole exome sequencing and studies of rare CNVs (Sebat et al. 2007) and SVs (Brandler et al. 2018) have had consistent success in early-onset neurodevelopmental disorders such as ASD, intellectual disability, as well as schizophrenia (Walsh et al. 2008; Marshall et al. 2017, Singh et al. 2022). Rare variants have also been implicated in BD (McCarthy et al. 2009), MDD (Kendall et al. 2019) and PTSD (Maihofer et al. 2022) but with a comparatively low yield of significant associations. A reasonable interpretation of these results is that the overall genetic architectures (i.e. the distribution of risk alleles as a function of allele frequency) differ between psychiatric disorders, with the contribution of rare variants being greatest in disorders with early onset and significant cognitive impairments (Gratten et al. 2014).

Combining our results on rare CNVs with GWAS results from the same PGC cohorts helps us to make comparisons of the genetic architecture of psychiatric disorders that include both rare and common risk alleles. Genome-wide significant loci identified in Figure 2 were tested in each disorder, and associations that were significant after statistical correction for 21 tests were used to plot effect sizes as a function of allele frequency (Fig. 3A). We combined our results with summary statistics from the recent PGC GWASs of ASD (Grove et al. 2019), SCZ (Trubetskoy et al. 2022), BD (Mullins et al. 2021), MDD (Howard et al. 2019), PTSD (Nievergelt et al. 2019), and ADHD (Demontis et al. 2019) (Fig. 3A-B), and we fit the curves for each disorder to an exponential model (Fig. 3B). Fitting the rare and common variant associations to disorder-specific models of the genetic architecture provides an estimate of the upper bounds for the effect sizes of risk alleles, including low-frequency variants of moderate effect, the vast gap in the center in which no risk alleles have yet been discovered.

These results highlight how genetic architectures differ between several disorders, the most dramatic being differences in the effect sizes of risk alleles that were remarkably consistent across the full range of frequencies. Effect sizes of rare CNVs were comparatively small in MDD and were larger in (by rank order) BD, SCZ, and ASD (Fig. 3A). An identical trend was observed for common SNPs in these disorders (Fig. 3B) (Romero et al. 2022). Our results suggest that differences in the relative yield of rare variant associations in different disorders could reflect a difference in the overall discoverability of variants at all frequencies.

Many rare CNVs were associated with multiple disorders, consistent with major psychiatric disorders having overlapping etiologies (Sebat et al. 2009; Cross-Disorder Group of the PGC et al. 2013). Visualizing genetic associations across six disorders as a radar plot, we illustrate the psychiatric spectrum associated with deletion and duplication at 15q11.2 (Fig. 3C), 22q11.2 (Fig. 3D), and 16p11.2 proximal (Fig. 3E), highlighting distinct genotype-phenotype relationships that differ between risk alleles. Notably, if rare variants were primarily associated with early onset cognitive impairments, the radar plots would be consistently skewed to the upper right. However, this is clearly not the case. Different alleles can be concentrated in different quadrants of the phenotype spectrum. Deletions and duplications in particular show contrasting spectrum of associations.

Rare variants consisted predominantly of positive associations with cases (Fig. 3A), consistent with rare variants generally having deleterious effects on mental health. However, rare variants associated with SCZ, BD, and MDD were not exclusively “risk” alleles, but in fact showed a mixture of positive and negative associations. A rare variant that has a negative association with one disorder can have a positive association with another. For instance, 15q11.2Del was positively associated with SCZ and negatively associated with BD (Fig. 3C). 22q11.2Dup was positively

associated with MDD and PTSD and negatively associated with SCZ (Fig. 3D). IMMP2L did not show a positive association with another disorder in this study; however previous studies have implicated deletions of IMMP2L in Tourette's Syndrome (TS) (Petelk et al. 2001; Patel et al. 2011; Bertelsen et al. 2014). Thus, negative associations are not protective for psychiatric risk.

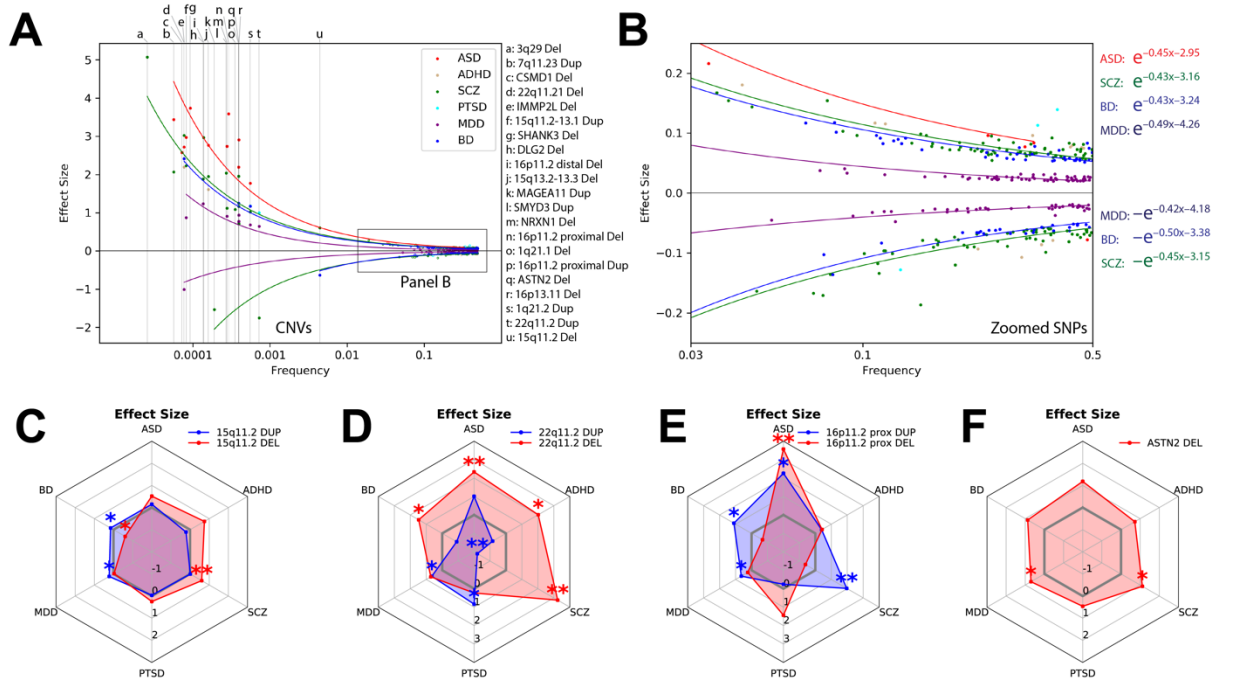


Figure 4: Effect size as a function of frequency

A) Effect sizes of significant loci in the CNV-GWAS are shown as a function of frequency. Additionally, effect sizes for disorders at any of the 21 genome-wide significant loci that were not genome-wide significant but met a Bonferroni correction for 21 tests were included. ASD and SCZ show high effect sizes for rare CNVs while BD and MDD show weaker effects. Negative associations can be seen for SCZ (MAGEA11 Dup, 22q11.2 Dup), BD (15q11.2 Del), and MDD (IMMP2L Del). B) Effect sizes for significant SNPs from previous SNP-GWAS were included to model variation effects across the full frequency spectrum. Zooming into the common SNP region, the pattern of effects is shown to be the same as the CNV loci across disorders. C-F) Effects sizes for 15q11.2, 22q11.2, 16p11.2 proximal, and ASTN2 Del/Dup are displayed for each disorder with an '*' indicating significance after a Bonferroni correction for 21 loci and '**' indicating genome-wide significance. Positive associations can be seen for all disorders while a negative association is only seen in BD Dels (15q11.2 Del) and SCZ Dels (22q11.2 Dup).

Several associations are located in common fragile sites prone to recurrent structural mutation

Common fragile sites (CFS) are regions in the genome that exhibit breakage upon replication stress. CFS are often associated with very long neural genes that are expressed in the brain and have functions related to neuronal development (Lopes et al. 2021). Transcription of very long genes can take multiple replication cycles to complete, resulting in collisions between transcription and replication machinery that causes double stranded breaks in the DNA (Helmrich et al. 2011). CFSs in long genes are also associated with TAD boundaries (Sarni et al. 2020), suggesting that 3D genome organization may also be a factor contributing to genome instability. Several of the CNV associations identified in this study have a characteristic signature consisting of a fragile site within a long neural gene and located at a TAD boundary. Examples of genetic associations with this signature include positive associations of deletions of NRXN1 with SCZ (Fig. 4A), ASTN2 with XD (Fig. 4B), DLG2 with XD (Fig. 4C), and a negative association of deletions of IMMP2L with MDD (Fig. 4D). In each case, the association peak intersects with a recurrent double strand break cluster (RDC, Fig. 4A) or an annotated CFS (Fig. 4B,C,D) and also intersects with an annotated TAD boundary. A majority of the deletions under the association peaks of NRXN1, ASTN2, and DLG2 intersect with exons. When we stratified deletions by predicted functional consequence, the associations in these genes were driven by loss-of-function-intolerance (LoF) variants that are predicted to result in truncation of the protein. A possible exception is the association peak adjacent to IMMP2L where deletions were negatively associated with MDD (Fig. 4D). In this case, the negative association was not concentrated within one functional consequence. Instead, the association may be driven by intergenic, intronic, and coding variants.

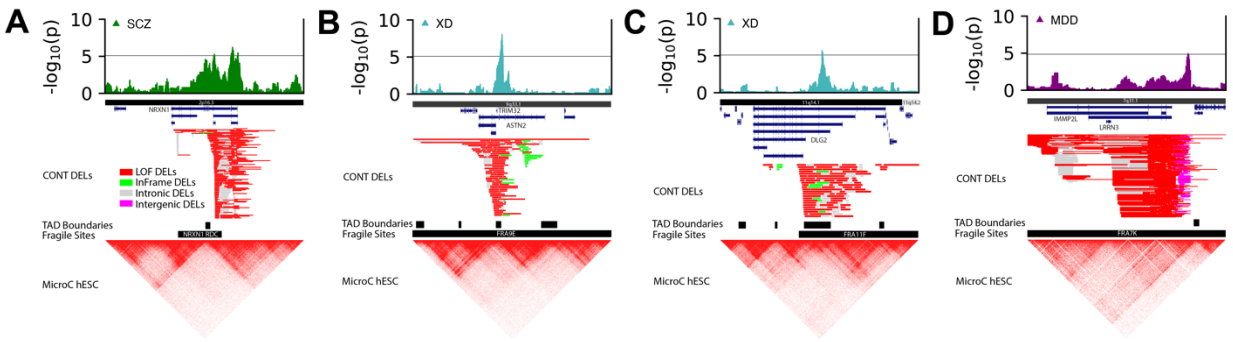


Figure 5: CNV associations implicate large neural genes within common fragile sites.

Four genome-wide significant loci that overlap fragile sites and TAD boundaries are shown for A) NRXN1 B) ASTN2 C) DLG2 and D) IMMP2L. Associations at each locus are shown for the most significant disorder in the CNV-GWAS. NRXN1 showed SCZ DEL association peaks at exons 1-3. ASTN2 and DLG2 showed XD peaks at a singular exon. IMMP2L showed an MDD peak with a negative association in the intergenic region and is being driven by DELs that span both the peak and short isoform of the IMMP2L gene. Peaks for all 4 loci occur at TAD boundaries located within fragile sites.

Recurrent duplications of SMYD3 are associated with schizophrenia

A new association for the duplication of the gene SET and MYND domain containing 3 (SMYD3) with SCZ was identified and is located within common fragile site FRA1I (Supp Table X). Duplication breakpoints were tightly clustered, and all duplications spanned the short isoform ENST00000403792.7 encoding a 182 amino acid protein including the first zinc finger domain of SMYD3. Based on microarray data alone, the functional impact of each structural variant was not clear. It was not clear whether multiple duplications of SMYD3 shared similar breakpoints or similar functional consequence.

To clarify the structure and functional impact of SMYD3 duplications, DNA samples from 3 duplication carriers were obtained, and HiFi long-read whole genome sequencing was performed on each sample using the PacBio Revio platform to a total coverage of >20X (Fig. 5A). To resolve the structure of each duplication, duplication breakpoints were identified by aligning short reads

to the GRCH38 assembly using PBMM2, and breakpoint contigs were assembled from breakpoint-spanning reads using Flye. Contigs assembled from the 3 samples revealed the precise structure of each SV. Even though the left boundaries of the 3 CNV calls were similar, each of the SVs had distinct breakpoints and structures. The SVs included a tandem duplication of 666,289 bp spanning isoform ENST00000403792.7 (Fig, 5B), non-tandem duplication of 516,050 bp with a similar functional consequence duplicating isoform ENST00000403792.7 but with a very different structure, the SMYD3 gene being inserted within a cluster of olfactory receptor genes >2MB distal (Fig. 5D), and a tandem duplication of 1.6 Mb spanning >10 genes including all isoforms of SMYD3 (Fig. 5D). All breakpoint positions were unique and did not share specific sequence motifs or repetitive elements. All alleles in Figure 5 result in the partial duplication and genomic fusion of genes, including CNST/SMYD3 (Fig. 5B), SMYD3/OR2G6 (Fig. 5C), or KIF26B/ZNF496 (Fig. 5D). Two of these cases fused genes that were not transcribed from the same strand and are not predicted to form fusion transcripts. However, the non-tandem duplication inverted the duplicated portion and was inserted within the OR2G6 olfactory receptor gene. The short isoform was fully duplicated, but the long isoform was truncated and partially duplicated. The inversion oriented the direction of transcription of SMYD3 to be the same as OR2G6 and exons 1-5 of the long isoform were fused with exon 2 of OR2G6 (Fig. 5C). The only functional consequence common between all three SVs is the increased copy number of SMYD3, particularly the short isoform.

The diverse structures, breakpoints and breakpoint sequences of SVs spanning SMYD3 are a hallmark of common fragile sites (CFS). In contrast to mutational mechanisms such as NAHR and MMBR where rearrangement is catalyzed short or long stretches of sequence homology between breakpoints, structural rearrangements within CFS regions often result from collisions of

RNA and DNA polymerase that occur during prolonged transcription of long neural genes (Wei et al. 2011).

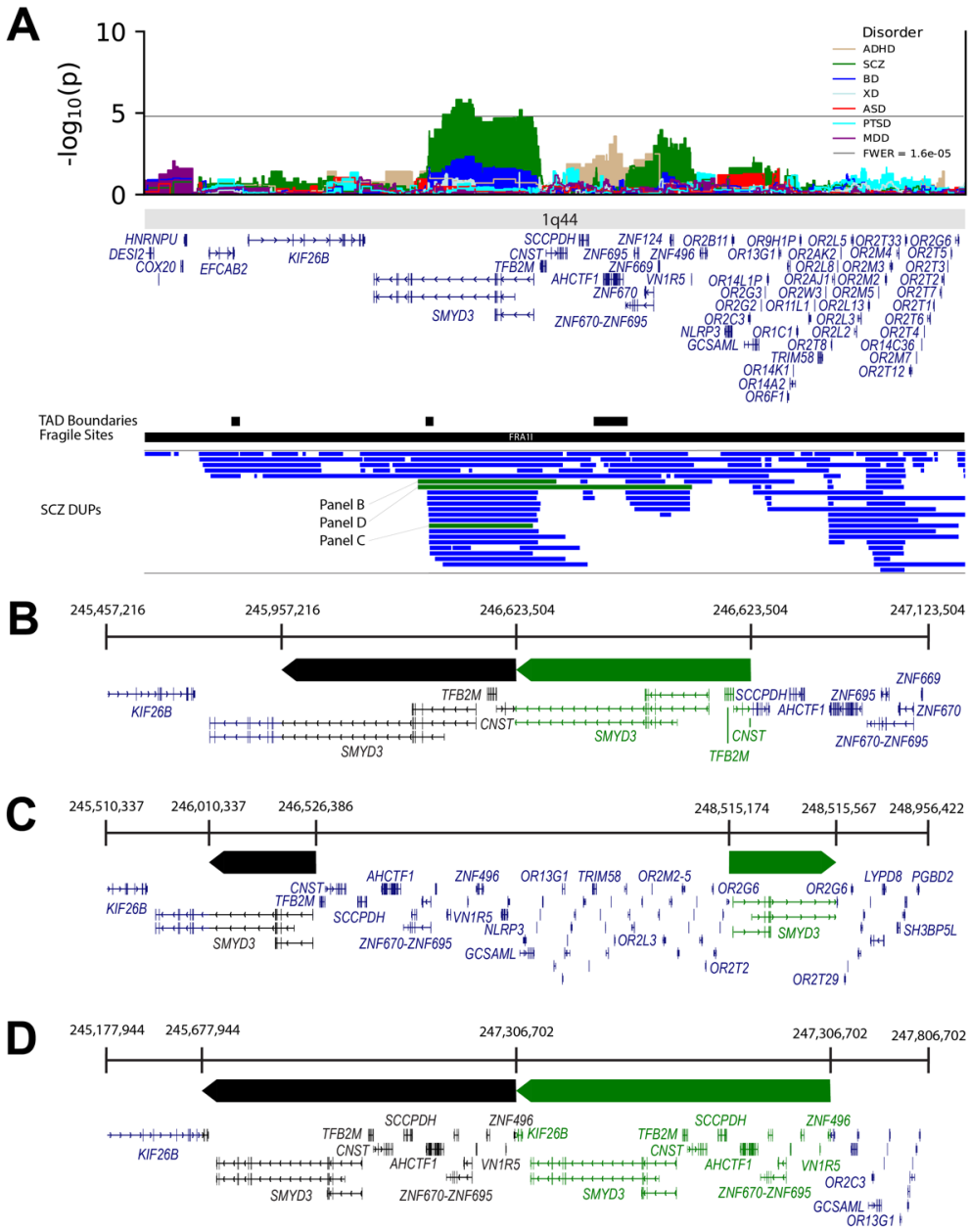


Figure 6: SMYD3 duplication with PacBio sequencing in 3 cases

A) The association peak spans exons 1-3 of the SMYD3 gene while the CNVs themselves have variable breakpoints that duplicate different nearby genes. Pacbio sequencing was performed on 3 cases with the SMYD3 Dup and the corresponding microarray CNV calls are shown (green) on the SCZ DUPs track. B) The first sample is a tandem duplication that spans the full short isoform of SMYD3. The duplicated portion truncates the long isoform of SMYD3 on the proximal side as well as the CNST gene on the distal side. C) The next sample is an inserted DUP that spans the full short isoform of SMYD3. It does not include any extra genes and is inserted next to the olfactory receptor genes with a small deletion of 393bp. D) The last sample is another tandem duplication that spans all isoforms of SMYD3. This DUP cuts KIF26B on the proximal side of SMYD3 and ZNF496 on the distal side.

Chapter 5 Discussion

This study includes the largest sample size in a rare CNV study to date and spans the psychiatric spectrum across six disorders. We find that rare CNVs contribute to risk in all disorders, yet the strength of the effects differs by disorder. The largest effect of CNVs appear in ASD and SCZ with weaker effects in BD, MDD, PTSD, and ADHD. Genome-wide CNV burden is being driven by genes with a high probability of loss-of-function intolerance meaning that mutations to these genes are more likely to have a deleterious effect of clinical relevance. The results also reveal small CNV burden effects in noncoding annotations such as TAD boundaries and transcribed enhancers. Both effects appear in SCZ deletions and provide evidence that there are regions in the genome that are susceptible to structural rearrangement and can influence psychiatric outcomes that are not driven by protein coding genes.

We have identified 36 genome-wide significant associations across 21 different loci after completing CNV-GWAS for 6 individual disorders and a combined cross disorder cohort. Our large sample-size was able to provide enough power to see associations from a breakpoint-level test that was previously underpowered. All the identified loci were located within hotspots for NAHR or CFS. Novel CNVs have been identified at SMYD3, ASTN2, DLG2, and IMMP2L. SMYD3 (SCZ) and IMMP2L (MDD) are disorder-specific loci while ASTN2 and DLG2 only appear in the XD study. This shows that there are loci that contribute to general psychiatric risk across all disorders but are not being driven by any individual disorder. The novel associations all have partial overlap with a gene and does not span the full length of the gene. A possible reason that they were undetectable in previous studies is the lack of power to test associations at the breakpoint level which is a finer resolution than testing at the gene-level. All of our novel associations were only present in our breakpoint-level study and were not detected in gene-level

studies. Testing multiple disorders from CNVs that were all processed in the same pipeline allows us to draw comparisons between disorders. We see that CNV type as well as CNV location have massive impacts on clinical presentation. The 16p11.2 proximal region illustrates this clearly as a deletion is primarily associated with ASD while a duplication of the exact same region is associated with SCZ. On the other hand, the 15q region switches between ASD and SCZ associations depending on genomic location and CNV type.

Our study observes rare CNVs from a wide range of allele frequencies in all disorders with the magnitude of association effects differing by disorder. ASD is seen to have the largest effect sizes across all allele frequencies while MDD is seen to have the smallest effect sizes. SCZ and BD both have moderate effect sizes. This provides evidence that differences between association signal in different disorders is not attributable to disorder-specific CNVs at different allele frequencies, but the contribution of CNVs to disorder-specific association is systematically different across all allele frequencies. The same trend was observed for common variants and higher allele frequencies.

We were also able to see multiple negative associations in our study. Notably, 22q11.2 DUP and MAGEA11 in SCZ were previously nominally significant and now genome-wide significant. IMMP2L is a novel negative association that is genome-wide significant in MDD while 15q11.2 DEL is only nominally significant in BD. These associations appear protective when observing individual disorders, but there is always a corresponding positive association in a different disorder. While negative associations can inform clinical outcomes, they do not provide protection from psychiatric risk.

Several of our genome-wide significant associations appeared within CFS regions that also overlap a TAD boundary. Collisions between transcription and replication machinery are seen in

long neural genes because transcription can take multiple cell cycles to complete. NRXN1, ASTN2, DLG2, and IMMP2L are all long genes that show an association peak at a TAD boundary in a CFS. The genomic instability of this region is more susceptible to structural variation and is likely contributing to the deletions in these disorders more than any cis-regulatory elements. SMYD3 is another long gene that is seen inside of a fragile site, but the association is seen in a TAD instead of a TAD boundary. PacBio HiFi long-read sequencing allowed us to assemble the breakpoints for 3 subjects with a SMYD3 DUP. The results show that even though the breakpoints all looked similar using microarray data, the actual breakpoints and functional consequence of the SMYD3 DUP were vastly different in all samples. Microarray has allowed us to identify many associations by genotyping a large number of samples and this information can be used as a guide for more targeted experiments to further explain the functional impact of structural variation in these regions.

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