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The Distribution of Disease-Associated Copy Number Variants Across Distinct Disorders of Cognitive Development

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Abstract

Objective—The purpose of the present study is to discover the extent to which distinct *DSM* disorders share large, highly recurrent copy number variants (CNVs) as susceptibility factors. We also seek to identify gene mechanisms common to groups of diagnoses and/or specific to a given diagnosis based on associations with CNVs.

Method—Systematic review of 820 PubMed articles on autism spectrum disorder (ASD), intellectual disability (ID), schizophrenia, and epilepsy produced 54 CNVs associated with one or several disorders. Pathway analysis on genes implicated by CNVs in different groupings was conducted.

Results—The majority of CNVs were found in ID with the other disorders somewhat subsumed, yet certain CNVs were associated with isolated or groups of disorders. Based on genes implicated by CNVs, ID encompassed 96.8% of genes in ASD, 92.8% of genes in schizophrenia, and 100.0% of genes in epilepsy. Pathway analysis revealed that synapse processes were enriched in ASD, ID, and schizophrenia. Disease-specific processes were identified in ID (actin cytoskeleton processes), schizophrenia (ubiquitin-related processes), and ASD (synaptic vesicle transport and exocytosis).

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Conclusions—Intellectual disability may arise from the broadest range of genetic pathways, and specific subsets of these pathways appear relevant to other disorders or combinations of these disorders. It is clear that statistically significant CNVs across disorders of cognitive development are highly enriched for biological processes related to the synapse. There are also disorder-specific processes that may aid in understanding the distinct presentations and pathophysiology of these disorders.

Keywords

autism; epilepsy; intellectual disability; schizophrenia; copy number variation

Genome-wide association studies (GWAS) have identified a large number of recurrent copy number variants (CNVs) that are associated with disease and are also frequently shared as susceptibility factors by several disorders of cognitive development.[1–7] However, the distribution of these CNVs across clinically distinct neurodevelopmental disorders, such as autism spectrum disorders (ASD), intellectual disability (ID), schizophrenia, or epilepsy, has not been systematically studied. For example, are there CNVs that are common to all disorders? Are there CNVs that are specific only to a subset of these disorders? Are there CNVs, either deletions or duplications, that are specific to only one disorder? Detailed and systematic examination of the distribution of disease-associated CNVs across these disorders will aid in the nosology of psychiatric disorders and will also provide insight into shared and distinct biological processes underlying the *DSM* diagnoses.

Overlapping symptoms are found across *DSM* categories of neurodevelopmental disorders. In particular, ID, ASD, and schizophrenia are all considered together here as disorders of cognitive development, as all conditions share central symptoms such as cognitive impairment and all have neurodevelopmental causes in a majority of cases.[4] Epilepsy is similarly considered among this group of clinical conditions given high rates of co-occurrence and many known shared etiologies with the other diagnoses.[8] Likewise, based on a large number of studies, specific CNVs have been identified across *DSM* categories including ID, ASD, schizophrenia, and epilepsy. For example, 16p11.2 CNVs are significantly associated with disease in ASD (deletions[9–12] and duplications[9–11]), schizophrenia (duplications only[13–17]), and ID (deletions[18–21] and duplications[19–21]). 16p11.2 CNVs have also been found in patients with epilepsy[8]. In addition, 1q21.1 CNVs have been confirmed in case-control studies as significantly associated with ID (deletions and duplications[19, 20, 22]) and schizophrenia (deletions[14, 17, 23–25] and duplications[14]). By a similar logic, attention-deficit/hyperactivity disorder (ADHD) may be grouped with the above conditions as a disorder of cognitive development. In one ADHD GWAS study, large rare CNVs were highest among ADHD patients with co-morbid ID and identified the locus of 16p13.11 as significantly enriched.[26] However, given the relatively low number of large, genome-wide studies in CNVs associated with ADHD, we have excluded ADHD from the current analysis.

Studies of CNVs also promise to identify potential susceptibility mechanisms associated with specific neurodevelopmental disorders. For example, post-synaptic mechanisms have been implicated in ASD as a result of genome-wide CNV studies.[27] Specific post-synaptic pathways include *SHANK3*[28, 29] and neuronal cell-adhesion (*NLGN3* and *NLGN4X*[30]). Some of these loci may be shared by other conditions, in particular ID, but also schizophrenia[31] and epilepsy[32] in other cases. The present study attempts to clarify the distribution of disease-associated CNVs across four disorders of cognitive development, namely ID, ASD, schizophrenia, and epilepsy.

First we identify the specific CNVs (considering deletions and duplications separately) that are associated with ASD, ID, schizophrenia, and epilepsy. We then examine the groups of CNVs that emerge as common to all disorders, specific to subsets of disorders, or unique to a given single disorder. Next we apply gene pathway analysis techniques to specific subsets of genes within CNVs associated with isolated disorders or given combinations of disorders. We first analyze groups of CNVs based on their association with one given *DSM* category. We then examine genetic pathways associated with CNVs from specific combinations of disorders (i.e. CNVs found in two or more *DSM* disorders) in order to uncover potential shared genetic mechanisms. In addition, we examine subgroups of CNVs that are associated with relatively isolated conditions (for example, ID without autism, schizophrenia, or epilepsy) and schizophrenia (without ID, ASD, or epilepsy), with the hope of uncovering mechanisms that may be relatively specific to a given disorder. Our study provides an important and unique approach to the study of CNVs in neurodevelopmental disorders and begins to uncover some of the shared as well as distinct pathways that are at the root causes of the *DSM* diagnoses.

METHOD

Identification of highly recurrent CNVs

A systematic review of CNVs was pursued based on the outline in Figure S1A, available online. CNVs associated with neurodevelopmental disorders were searched in PubMed through June 2012. Specific searches were employed for ASD ("*copy number*" and "*autism*"), ID ("*copy number*", "*intellectual disability*", and "*mental retardation*"), schizophrenia ("*copy number*" and "*schizophrenia*"), and epilepsy ("*copy number*" and "*epilepsy*"). Searches were limited to English language, humans, and publications after 2005. CNVs were considered highly recurrent and associated with disease if they were identified in a PubMed publication with the following features: (a) genetically tested in a large disease cohort (N>400); (b) included a comparison control sample; (c) statistically compared the CNV frequencies in cases and controls; (d) and the CNV was significantly enriched in the case sample. CNV significance was based on criteria established by the given publication. In all cases, this represented $p<0.05$, but the majority of studies used much stricter genome-wide criteria for significance. All CNV coordinates are reported in NCBI build 36, hg18. In general, we were able to consider deletions and duplications as separate CNVs.

Classification of CNV to specific disorders and determination of CNV co-ordinates/genes

Highly recurrent CNVs were assigned to one or more disorder based on the following approach (Figure S1B, available online). CNVs were assigned to the phenotype for which they met rigorous case-control criteria based on criteria described above. This was "strict" criteria for association. Further, significant CNVs were assigned to additional disorder categories based on "broad" criteria if a study participant with a primary disorder is reported to have symptoms meeting criteria for another disorder. An example of broad criteria is if a child with a recurrent CNV from an ASD study is described as having co-occurring ID, then the given CNV was coded for both ASD and ID disorders.

Three CNV categories were defined: A, B, and C (Figure S2, available online). Category A consists of stereotyped, recurrent CNVs whereby multiple cases of a particular CNV encompassed the same region. Category A CNVs are widely known to be generated in stereotyped fashion due to flanking segmental duplications and non-allelic homologous recombination (such as 16p11.2 deletions/duplications). Category B consists of CNVs that may be variable but hit a singular, common gene (such as *NRXN1* deletions/duplications). Category C consists of non-stereotyped, recurrent CNVs that overlap with a common region,

which contains many genes (for example, 1p36 deletions/duplications). To determine CNV category, we reviewed *Decipher* CNV cases (when possible) and entered CNV coordinates into the UCSC Genome Browser database searching for "segmental dups" (http://www.genome.ucsc.edu/cgi-bin/hgTrackUi?hgsid=263029387&c=chr2&g=genomicSuperDups). If a CNV was positive for flanking segmental duplications, then it provided further evidence for Category A inclusion.

We used a systematic approach to determine CNV intervals. For a given locus within a given disorder, if multiple intervals were determined, we chose intervals that were inclusive of all such CNVs, ie the largest interval covering all CNVs. If a CNV was found in two or more disorders, for the gene pathway analysis examining overlap across those disorders, we used the minimum interval, in the intersection of all relevant intervals. Genes were included in the pathway analysis if they were within or intersected by the genetic intervals determined as described above.

Mean CNV sizes for all disorders were compared with Wilcoxon rank test using STATA[33] 11.0. Fisher's exact test in R was used to compare both the number of deletions and duplications, as well as CNV type across disorders.

Visualization of gene groupings by Venn diagrams

Gene groupings were visualized via VennMaster software.[34] List of genes in all categories were imported as text files to the program.

Gene pathway analysis and test subgroups

Gene groups were analyzed by hypergeometric statistical methods using the Database for Annotation, Visualization and Integrated Discovery v6.7 software.[35] DAVID parameters used the recommended Gene Ontology categories (GOTERM_BP_FAT, GOTERM_CC_FAT, and GOTERM_MF_FAT) with "high" classification stringency to ensure a strong association between genes. An additional pathway analysis investigated if there were differences in gene ontology depending on CNV type. Three CNV categories were defined: A, B, and C (Figure S2, available online).

RESULTS

Distribution of CNVs Across Disorders

Based on Pubmed searches and review of references, a total of 820 unique articles were identified: 223 ASD, 373 ID, 164 schizophrenia, and 60 epilepsy articles. After full review of all articles, 37 articles met stringent search criteria: 8 ASD[9–12, 27, 36–38], 9 ID[18–20, 22, 39–43], 15 schizophrenia[13–17, 23–25, 37, 44–49], and 5 epilepsy[8, 50–53] (Table S1, available online). We categorized CNVs to disorders based "strict" criteria and "broad" criteria (see Method and Figure S1, available online). From these articles, 79 CNVs (counting deletions and duplications separately) met strict criteria: 39 were assigned to ID (26 deletions, 13 duplications), 14 to ASD (8 deletions, 6 duplications), 23 to schizophrenia (13 deletions, 10 duplications), and 3 to epilepsy (3 deletions, no duplications) In summary, 54 unique loci (now combining deletions and duplications) encompassing 1,416 unique genes, were determined to be highly recurrent and associated with disease (Table 1). Ten out of the 54 CNVs did not contain any genes and were not included in the pathway analysis. The assignment of CNVs to the broad criteria are also shown in Table 1.

Strict Criteria for CNV Assignment—The distribution of CNVs conferring susceptibility across the four disorders was characterized using Venn diagrams for CNV groupings and gene groupings. These data for strict criteria are shown in Figure 1 and Table

S2, available online. ID had the largest grouping of CNVs out of all *DSM* disorders (27 of 54, 50% of CNVs) and these CNVs were the most gene rich (27 of 44, 61.4% of genic CNVs which encompassed 1,198 of 1,416 or 84.6% of total genes). As a consequence, one striking result of this study is that, based on gene distributions, all disorders were largely subsumed by the ID gene group even for the strict criteria (Figure 1A). This pattern was supported also when gene groupings were separated into those implicated by deletions or duplications (Figure 1B and 1C). With the distribution of genes across disorders using strict criteria, ID was associated to an even greater degree with 96.8% (244 of 252) of genes in ASD, 92.8% (386 of 416) of genes in schizophrenia, and 100% (111 of 111) of genes in epilepsy. Broad criteria again demonstrated high association with ID: 99.3% (933 of 940) of genes in ASD, 91.5% (303 of 331) of genes in schizophrenia, and 100% (1,008 of 1,008) of genes in epilepsy.

Visualization of the data with regard to the distribution of CNVs across disorders for strict criteria using CNV groupings also demonstrated a high degree of overlap between all disorders and ID, yet less so than when visualized by gene groupings. ID was associated with 46.2% (6 of 13) of CNVs associated with autism, 43.0% (9 of 21) of CNVs in schizophrenia, and 100% (3 of 3) of CNVs in epilepsy. Almost half of ASD CNVs (6 of 13, 46.2%) and all epilepsy CNVs (3 of 3, 100%) were also found in schizophrenia. There was no overlap among significant ASD and epilepsy CNVs using strict criteria. The distinction between the extent of overlap across disorders based on gene-content as compared to based on CNVs appears to reflect the genic content of CNVs implicated in each disorder under strict criteria. Specifically, the average number of genes per CNV for each disorder was as follows: ID—49 genes; ASD—28 genes; schizophrenia—32 genes; and epilepsy—47 genes. Notably, ID CNVs were significantly larger than ASD CNVs (p=.009) (Figure 2). Also CNVs were categorized as either deletion or duplication. As shown in Figure 2A, ID demonstrated a majority of deletions, 67% as compared 33% duplications, yet by contrast schizophrenia exhibited 57% deletions and 43% duplications. However, there were no statistically significant differences between deletions and duplications across *DSM* disorders.

Despite the high degree of overlap that was apparent, disorders showed distinct profiles of type of CNV (Figure 2B). We categorized CNVs as category A if they showed highly stereotyped intervals likely based on non-allelic homologous recombination due to flanking segmental duplications, category B if the CNV involved single genes, or category C if the CNVs affected multiple genes and occurred in a given locus but with highly variable intervals (See Method and Figure S2, available online). There were significantly more category A CNVs in ID (n=17) than in either ASD (n=5, p=.004) and epilepsy (n=3, p<.001). Similar findings were noted for category C with ID (n=8) encompassing significantly more than ASD (n=2, p=.04) or epilepsy (n=0, p=.002). There were significantly more category B CNVs in schizophrenia (n=9) than in either ID (n=2, p=.03) and epilepsy (n=0, p<.001). In general, the patterns seemed to favor more category A and C in ID, and more category B (single gene CNVs) in autism and schizophrenia.

Disorder-specific CNVs and Broad Criteria for Assignment of Disorders—In addition to the high degree of sharing, each disorder (with the exception of epilepsy) has a set of genes implicated by CNVs that were disorder-specific under strict criteria: ID (16 CNVs, 719 genes; 59.3% of ID CNVs), ASD (5 CNVs, 8 genes, 38.5% of CNVs), and schizophrenia (10 CNVs, 28 genes, 47.6%) had a subset of genes from CNVs that were disorder-specific.

Schizophrenia was the disorder with the least amount of overlap with ID. Using strict criteria there were a total of ten CNVs that were specific to schizophrenia (Table 1). In

general, these CNVs were smaller on average at approximately 379 kb and contained fewer genes, 2.8 genes on average. The majority of these schizophrenia-only CNVs were Category B (7 of 10).

Using the broad criteria, the extent of disorder-specific genes was substantially reduced. Using broad criteria, disorder-specific CNVs and genes were reduced in number: ID (2 CNVs, 40 genes; 6.7% of ID CNVs), ASD (3 CNVs, 5 genes, 10.7%), and schizophrenia (9 CNVs, 26 genes, 42.9%). Of note, given the high degree of overlap across disorders using broad criteria, schizophrenia was the disorder that stood out in greatest distinction from ID and other conditions.

PATHWAY ANALYSIS

Our systematic groupings of CNVs provided opportunities to investigate gene pathways that may be unique or shared across *DSM* diagnoses or within sub-groups of these disorders. Pathway analysis identified significant biological, cellular, and molecular gene processes, some of which were shared across disorders and others were unique to given sub-groupings. We first examined enriched gene pathways in gene groups associated with each of the four *DSM* diagnoses separately under strict criteria (e.g. ASD, ID, schizophrenia) (Figure 3A–C and Table S3, available online). Epilepsy was excluded because of the small number of CNVs under strict criteria, only three in total. The majority of significant findings across disorders pinpointed processes at the synapse. For example, synapse processes were significant for ASD ($p<.001$), ID ($p=.007$), and schizophrenia ($p=.003$). In addition, synaptic transmission was significant in ASD ($p<.001$) and schizophrenia ($p<.001$). Post-synaptic membrane was highly enriched in ASD ($p=.003$) and ID ($p=.003$). Extracellular ligand-gated ion channel activity was significant in ASD ($p=.002$), ID ($p=.02$), and schizophrenia ($p=.007$). Also, glycerophospholipid metabolic process was noted in ID ($p=.02$) and schizophrenia ($p=.002$).

Analysis of gene groupings based on *DSM* disorders also identified pathways that were specific to individual disorders. Significant ASD processes included exocytosis ($p=.002$), vesicle ($p=.009$), synaptic vesicle transport ($p=.002$), and regulation of neurotransmitter levels ($p<.001$). Notable ID processes identified actin cytoskeleton organization ($p<.001$), actin filament-based process ($p<.001$), tumor necrosis factor binding ($p<.001$), and regulation of acute inflammatory response ($p=.02$). Schizophrenia pathways were related to protein ubiquitination ($p<.001$) and ubiquitin-protein ligase activity ($p<.001$).

We then examined “co-morbid” groupings, for example, CNVs that are shared by two disorders such as ASD and ID, or CNVs found in 3 diagnostic groups (Table S4, available online). CNVs that only overlapped among ID-ASD CNVs were enriched for cell junction ($p=.01$), calcium-independent cell–cell adhesion ($p=.03$), and protein heterodimerization activity ($p=.03$). Significant CNVs that only overlapped with ID-schizophrenia identified endoplasmic reticulum membrane ($p<.001$) and glycerophospholipid biosynthetic process ($p=.003$). Significant results from “ID-ASD-schizophrenia” grouping included GABA receptor activity ($p=.003$), synaptic transmission ($p=.006$), and vesicle ($p=.006$). Interesting gene mechanisms emerged from the relatively “pure” groupings (Table S4, available online). For example, isolated ID processes included tumor necrosis factor binding ($p<.001$), positive regulation of apoptosis ($p=.02$), and actin cytoskeleton organization ($p=.03$). Channel regulator activity ($p=.03$) was the only significant process for isolated schizophrenia. Pathway analysis of gene groupings determined by broad criteria replicated many of the findings described above (Table S5, available online).

Finally, we conducted pathway analysis based on the category of the CNV (ie type A, B, or C). This showed distinct mechanisms for each CNV categories A, B, and C (Table S6,

available online). Of note, category B (single gene) findings highlight synaptic processes, such as regulation of synaptic transmission (p=.001) and postsynaptic membrane (p=.02). Interesting, category A (recurrent intervals) identified Ras protein signal transduction as enriched (p=.03).

DISCUSSION

Classic studies heralded the importance of CNVs in neuropsychiatric disorders.[54–58] Explosive progress in this area resulted from microarray methods that permitted genome-wide discovery of CNVs in large population samples.[59–61] While evidence for association of large, highly recurrent CNVs with disease represents among the strongest findings in psychiatric genetics, this result has to contend with two challenges: 1) each CNV generally contains numerous genes; and 2) there is a high degree of loci sharing across disorders. The present study seeks to address these challenges through a novel and highly systematic approach to establishing the distribution of CNVs (deletions and duplications separately) as susceptibility factors across common disorders of cognitive development. The most prominent finding of our study was the high extent to which all disorders are subsumed by ID. Even under strict criteria, 96% of all genes identified by CNVs were associated with ID and greater than 90% of genes for the other disorders were also found in ID. In addition to this contribution, our study has elucidated mechanisms that are enriched in a given disorder or may be shared by disorders.

There are very few previous studies that have taken this sort of approach to studying CNVs in *DSM* diagnoses. Crespi *et al.*[62] examined 7 highly recurrent CNVs (all included in the present analysis) implicated in ASD and schizophrenia to determine the genetic relationship between the two psychiatric disorders. The degree of overlap supported either a (1) diametric hypothesis whereby ASD and schizophrenia are on diametric ends of the diagnostic spectrum or (2) an overlapping hypothesis whereby the two disorders share some overlapping genetic risk. An alternative “subsumed” hypothesis, where ASD is a sub-category of schizophrenia was ruled out. With regard to autism and schizophrenia, our results also largely rule out the subsumed hypothesis, and are most in agreement with an overlapping hypothesis. However, with regard to ID and the remaining disorders, a subsumed hypothesis is most consistent. This is particularly so for autism and epilepsy. While schizophrenia stood out the most from ID, under broad criteria schizophrenia’s relationship with ID would be most consistent with a subsumed model as well. However, the schizophrenia specific CNVs should be interpreted with caution as some have been found thus far only in a single study. The interpretation of these findings suggests that ID may represent a disorder with the broadest possibilities of genetic mechanisms and susceptibility pathways, and the other disorders appear to have more restricted susceptibilities.

The results presented here also strongly implicate gene networks that regulate synaptic function, which have been identified in previous studies, and this was found here across all disorders. A recent gene-set enrichment analysis of *de novo* CNVs in schizophrenia found synaptic processes to be highly enriched.[63] Specifically postsynaptic gene networks, including the NMDAR complex, were significant. A pathway analysis of rare *de novo* CNVs in ASD was recently conducted using a network-based analysis of genetic associations (NETBAG).[64] Enriched gene networks identified processes related to actin network dynamics and reorganization, synaptogenesis, axonogenesis, cell–cell adhesion, small GTPase signaling, and neurite development. One GWAS ASD study conducted a pathway analysis of rare CNVs (deletions only as they were significant over controls) and identified cell proliferation, cell projection, cell motility, GTPase/Ras signaling, and kinase activity/regulation.[36] The same study analyzed ASD/ID genes and found enriched processes related to microtubule cytoskeleton, glycosylation, and central nervous system (CNS)

development/adhesion. Our results support these findings and demonstrate that cytoskeleton organization may be more associated with the ID phenotype.

While there were notable overlapping gene networks, the pathway analysis also identified more distinct disorder-specific processes. For example, processes related to actin cytoskeleton organization and tumor necrosis factor were preferentially enriched in ID. Ubiquitin processes were highly associated with schizophrenia. Category B CNVs have the ability to pinpoint individual genes and taken as a group, these genes were enriched for processes related to synapse/postsynaptic density and enriched in autism and schizophrenia relative to ID. Caution would be warranted in interpreting these studies of Catergory B CNVs if the studies reviewed had chosen these as candidate genes based on function; however, each of the Category B genes found in this study has been identified at some point in genome-wide studies. Category C also identified synaptic processes, however, not to the degree of Category B. Notably, Category A (those CNVs with stereotyped intervals) identified the Ras signaling pathway as an enriched gene class. Indeed, the genes involved in a number of well-known monogenic ID syndromes, such as Tuberous sclerosis, the diverse syndromes resulting from PTEN mutations and others, are well known to interact with the Ras pathway, and this pathway has been suggested previously to play a role at least in the pathophysiology of autism.[65]

The strength of the current study is that we have provided a novel analysis of CNV distribution across disorders which is critical to understanding the nosology and pathophysiology of neuropsychiatric disorders, especially given the high degree of comorbidity. There are several limitations with the current analysis. The broad CNV overlap data are likely not complete as not all studies detail secondary medical/psychiatric diagnoses and often such diagnoses are difficult to make in the setting of a primary disorder. While these data may be incomplete, the broad CNV distribution analysis does have a high degree of overlap already. In addition, as described, we found fewer studies in the area of epilepsy so these data in particular may be incomplete. Also, we were not able to substantially compare the frequency of CNVs across disorders. This is hampered in particular because of potentially different ascertainment biases for each disorder. An example of a difference in ascertainment methods is that ID studies include data from clinical referrals, whereas CNV data are acquired for schizophrenia generally only in the research setting where it may be difficult to ascertain the most severely affected patients. These biases need to be considered carefully and in theory could have contributed to a broadening of the ID diagnostic group; however, we suspect that these potential biases are unlikely to impact the major findings of our study that emphasize the vast degree of loci sharing across these disorders. In follow-up studies to this one when sample sizes get even larger, there may be a dimension to this sort of analysis whereby the frequency of a given CNV in a disorder is considered as opposed to simply the categorical association alone which was the subject of the current analysis. Finally, the high degree of overlap across disorders is clear in this study for these most common among the rare, large CNVs; however, it is possible that as sample sizes reach hundreds-of-thousands, we may observe very rare CNVs (frequency approximately 1/10,000 or less), and subsequently the distribution of these very rare CNVs across disorders will need to be studied.

Genome-wide approaches to study CNVs are currently being applied to other psychiatric disorders such as ADHD and bipolar disorder. Further research is necessary to conclusively determine whether large, recurrent CNVs that confer susceptibility to these psychiatric disorders overlap, subsume, or are independent of the current models. Early results have shown mixed findings in terms of genetic burden of CNVs in the few studies emerging for these disorders. GWAS ADHD results did not find an increase in rare CNVs[66] yet an increase was noted in large, rare CNVs.[26] This finding has now been replicated in a very

convincing CNV study in a large cohort of twins with attentional problems.[67] Specific CNVs identified in ADHD include 15q13.3[68] and 16p13.11[26] (especially significant in comorbid ADHD and ID) and these CNVs have both been found in ID, ASD, schizophrenia, and epilepsy. Bipolar disorder GWAS studies have been mixed in terms of CNV burden.[69–71] McCarthy *et al.*[16] conducted a meta-analysis and found 16p11.2 (specifically duplications) highly enriched in bipolar disorder, which has also been identified in ID, ASD, schizophrenia, and epilepsy. However, additional studies have not identified any significant specific CNVs.[69, 71] Overall, our studies strongly suggest that, in general, there is a little evidence that single CNVs confer susceptibility to individual disorders. Instead it seems as if individual CNVs large confer susceptibility to a broad array of disorders. These results lead to the question: As CNVs confer susceptibility to neuropsychiatric disorders (a fact that is now unequivocal), how is disorder specificity established? Is it stochastic, dependent on interaction with other genetic and/or environmental factors? Indeed, one recent study has demonstrated that approximately 10% of people with ID and a single large CNV may have a second large CNV.[72] This study suggests at least two possible hypotheses with regard to genetics. First, that disorder specificity may not be encoded in individual CNVs but in combination of CNVs; or alternatively, second, that disorder specificity may be coded in the overall burden measures with distinct thresholds for different disorders. Of course, these hypotheses will await deep genotyping in large population cohorts with quality phenotypic assessments. Further, we also should point out, that while in general there is a low level of specificity, there are some exceptions. For example, there are some CNVs that generally lead to specific syndromes, for example, 7q11.2 deletions are almost always recognized in William syndrome and rarely recognized in other disorders.[73] Also, in our data, schizophrenia may standout as the disorder with the least amount of overlap with ID. For example, 16p11.2 deletions and duplications are associated with ASD[9–12] and ID[18–20, 42], but only 16p11.2 duplications are associated with schizophrenia.[13–16, 71]

Through discovery of point mutations, novel genome-wide sequencing approaches will pinpoint individual genes in disorders of cognitive development. These new approaches provide further precision regarding susceptibility mechanisms as compared to CNV studies. However, early sequencing studies already suggest that the heterogeneity of individual molecular causes will remain broad.[74, 75] Early studies have already implicated genetic loci shared by multiple disorders. For example, *de novo SCN1A* have been discovered in autism.[76, 77] *SCN1A* mutations had been previously well-known for their role in epilepsy with and without intellectual disability.[78–80] Further sequencing studies and examination of smaller CNVs may refine the rules regarding overlapping susceptibility. Nonetheless, large, highly recurrent CNVs will remain as important causes of developmental disorders, and indeed a follow-up study to this one may need to examine combinations of large CNVs or genetic factors across these disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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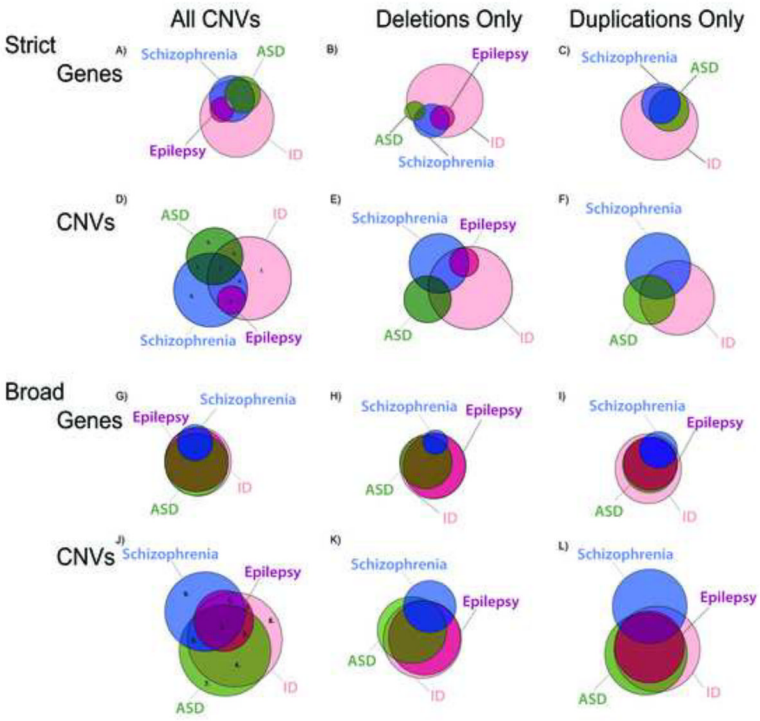

Figure 1.

Distribution of copy number variants (CNVs) and genes for autism spectrum disorder (ASD), intellectual disability (ID), schizophrenia, and epilepsy. Note: Figure 1A shows the distribution of genes contained within CNVs using strict criteria among all 4 disorders, as well as separates strict gene distribution by deletions (1B) and duplications (1C). Figure 1D shows the distribution of CNVs using strict criteria and is also separated into deletions (1E) and duplications (1F). Figure 1G shows the distribution of genes contained within CNVs for broad criteria, as well as deletions (1H) and duplications (1I). Broad CNV distribution is shown in Figure 1J and also categorized into deletions (1K) and duplications (1L). For Figure 1D, #1–8 represent strict CNV distributions that were analyzed in the pathway analysis (results in Table S4, available online), while in Figure 1J, #1–9 represent broad CNV distributions (results in Table S5, available online).

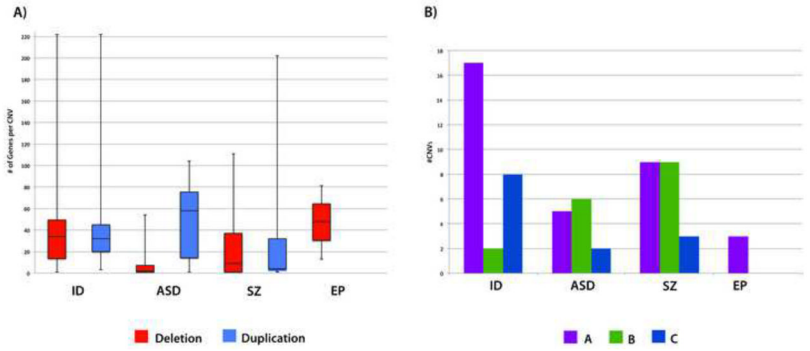

Figure 2.

Figure 2A shows the number of genes per copy number variant (CNV) for all significant CNVs in autism spectrum disorder (ASD), intellectual disability (ID), schizophrenia (SZ), and epilepsy (EP) and is separated into deletions (red) and duplications (blue). Note: The median number of genes per CNV is shown in the center of each box and the whiskers indicate the range. Figure 2B shows the number of CNV categories (e.g. A, B, and C) for all 4 disorders. ID had a greater number of category A CNVs in both ASD (p=.004) and epilepsy (p<.001). Also, ID had a significantly greater number of category C CNVs for ASD (p=.04) and epilepsy (p=.002).

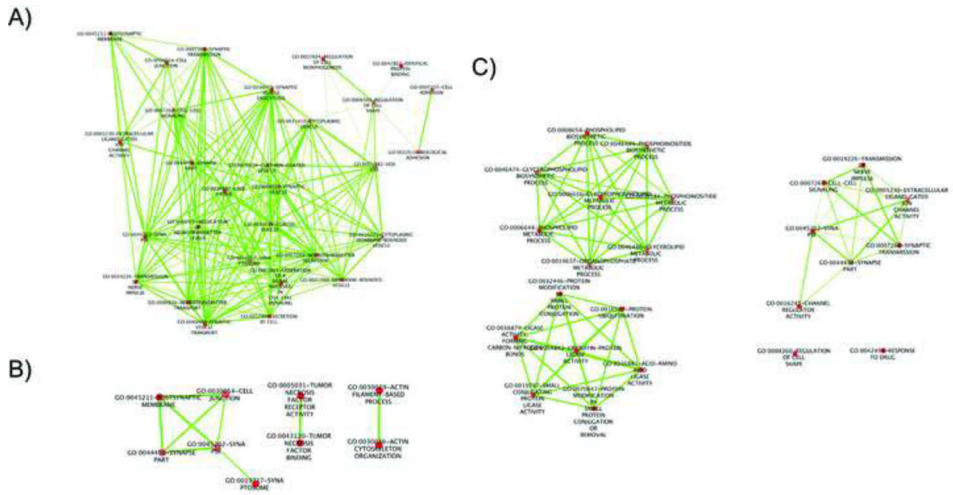

Figure 3.

Enriched gene networks of significant pathway analysis results for autism spectrum disorder (ASD) (3A), intellectual disability (ID) (3B), and schizophrenia (3C). Note: ASD processes shown include vesicle and synaptic processes. Synaptic, necrosis factor, and actin filament-based processes are enriched in ID. Significant schizophrenia networks consist of phospholipid, ubiquitin, and synaptic processes.

Table 1

List of Highly Recurrent, Eligible Copy Number Variants (CNVs) From Genome-Wide Association Studies (GWAS) Studies.

CNV	Group	Disorder (Strict Criteria)	Disorder (Broad Criteria)	Coordinates	Size (kb)	Number of Genes (Strict Criteria)	Coordinate Source
1p33 (*AGBL4*)	B	ASD^{Del}	ID^{Del}, ASD^{Del}	49,685,647–49,770,826	85	1	**Pinto et al. 2010**[36]
1p36	C	ID^{B}	ID^{B}, ASD^{Del}, Epilepsy^{Del}	0–10,000,000	10,000	222	**Cooper et al. 2011**[19]
1q21.1	A	ID^{B}, Schizophrenia^{B}	ID^{B}, ASD^{B}, Schizophrenia^{B}, Epilepsy^{B}	144,600,000–146,300,000	1,700	29	**Levinson et al. 2011**[14], Mefford et al. 2008[22], Cooper et al. 2011[19], Kaminsky et al. 2011[20], ISC 2008[23], Stefansson et al. 2008[24], Kirov et al. 2009[25], Grozeva et al. 2012[17]
2p16.3 (*NRXN1, DKFZp313P2036*)	B	Schizophrenia^{Del}	ID^{Del}, Schizophrenia^{Del}, Epilepsy^{Del}	49,900,000–51,500,000	1,600	2	**Rujescu et al. 2009**[44], Levinson et al. 2011[14]
2p21 (*PRKCE, SRBD1, UNQ6975*)	C	ID^{Dup}	ID^{Dup}	45,200,000–45,900,000	700	3	**Cooper et al. 2011**[19]
2p25.3(*MYT1L, PXDN*)	C	Schizophrenia^{Dup}	Schizophrenia^{Dup}	1,618,945–1,857,129	238	2	**Lee et al. 2012**[45]
2q13	A	ID^{B}	ID^{B}, ASD^{B}, Epilepsy^{Del}	110,180,000–110,340,000 111,050,000–112,950,000	160 1,900	36	**Cooper et al. 2011**[19]
2q37	C	ID^{Del}	ID^{Del}, ASD^{Del}, Epilepsy^{Del}	239,370,000–242,120,000	2,750	42	**Cooper et al. 2011**[19]
3p26.2(*SUMF1*)	B	ASD^{Del}, Schizophrenia^{Del}	ASD^{Del}, Schizophrenia^{Del}	4,199,731–4,236,304 4,063,809–4,074,877	37 11	1	**Glessner et al. 2009**[27], Glessner et al. 2010[13]
3p26.3 (*CNTN4*)	B	ASD^{Dup}	ASD^{Dup}	2,548,148–2,548,531	0.4	1	**Glessner et al. 2009**[27]
3q26.31(*NLGN1*)	B	ASD^{Dup}	ASD^{Dup}	174,754,378–174,771,975	18	1	**Glessneret al. 2009**[27]
3q29	A	ID^{Del}, Schizophrenia^{B}	ID^{Del}, Schizophrenia^{B}, Epilepsy^{Del}	197,240,451–198,829,062	1,589	36	**Kaminsky et al. 2011**[20], Levinson et al. 2011[14], Vacic et al. 2011[15], Mulle et al. 2010[46], Grozeva et al. 2012[17]
4p16.3 (Wolf-Hirschhorn Syndrome) (*SCARNA22, WHSC1, WHSC2*)	C	ID^{Del}	ID^{Del}, Epilepsy^{Del}	1,840,000–1,980,000	140	3	**Cooper et al. 2011**[19]

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CNV	Group	Disorder (Strict Criteria)	Disorder (Broad Criteria)	Coordinates	Size (kb)	Number of Genes (Strict Criteria)	Coordinate Source
4q21.21-q21.22	C	ID^{Del}	ID^{Del}, ASD^{Del}, Epilepsy^{Del}	81,950,000–83,350,000	1,400	4	**Cooper et al. 2011**[19]
5q35.2-q35.3 (Sotos Syndrome)	C	ID^{Del}	ID^{Del}, Epilepsy^{Del}	175,650,000–176,990,000	1,340	45	**Cooper et al. 2011**[19], Kaminsky et al. 2011[20],
6q26 (*PARK2*)	B	ASD^{Del}, Schizophrenia^{Dup}	ASD^{Del}, Schizophrenia^{Dup}	162,584,576–162,587,001 162,835,583–162,997,592	2 162	1	**Glessner et al. 2009**[27], **Vacic et al. 2011**[15]
7q11.22-q11.23 (Williams-Beuren Syndrome)	A	ID^{B}, ASD^{Dup}	ID^{B}, ASD^{Dup}, Epilepsy^{B}	72,380,000–73780449	1,400	32	**Cooper et al. 2011**[19], Kaminsky et al. 2011[20], Sanders et al. 2011[9]
7q36.3 (*BC041429*, *BC042556*, *VIPR2*)	B	Schizophrenia^{Dup}	Schizophrenia^{Dup}	158,448,321–158,630,000	182	3	**Vacic et al. 2011**[15], Levinson et al. 2011[14]
8p23.1	C	ID^{Del}	ID^{Del}	8,156,705–11,803,128	3,646	37	**Kaminsky et al. 2011**[20]
9q34.3 (9q subteleometric deletion syndrome)	C	ID^{Del}	ID^{Del}, ASD^{Del}, Epilepsy^{Del}	136,950,000–140,200,000	3,250	132	**Cooper et al. 2011**[19]
10q11.21 (*RET*)	B	Schizophrenia^{Del}	Schizophrenia^{Del}	42,932,615–42,934,354	2	1	**Glessner et al. 2010**[13]
10q23.2(*GRID1, KIAA1220*)	B	ID^{Del}, ASD^{Del}	ID^{Del}, ASD^{Del}	87,941,666–87,949,029	7	2	**Glessner et al. 2009**[27], Cooper et al. 2011[19]
11q25(*GLB1L3*)	B	Schizophrenia^{Del}	Schizophrenia^{Del}	133,650,000–133,690,000	40	1	**Levinson et al. 2011**[14]
15q11.2	A	ID^{Del}, Schizophrenia^{Del}, Epilepsy^{Del}	ID^{Del}, ASD^{Del}, Schizophrenia ^{Del}, Epilepsy^{Del}	20,306,549–20,691,555	385	6	**Mefford et al. 2009**[41], Cooper et al. 2011[19], Stefansson et al. 2008[24], Zhao et al. 2012[47], Kirov et al. 2009[25], Grozeva et al. 2012[17], de Kovel et al. 2010[50], Mefford et al. 2010[8]
15q11-q13 (Prader-Willi/Angelman Syndrome)	A	ID^{B}, ASD^{Dup}, Schizophrenia^{Dup}	ID^{B}, ASD^{Dup}, Schizophrenia^{Dup}, Epilepsy^{B}	21,309,483–26,208,861	4,899	104	**Kaminsky et al. 2011**[20], Cooper et al. 2011[19], Glessner et al. 2009[27], Ingason et al. 2011a[48]

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CNV	Group	Disorder (Strict Criteria)	Disorder (Broad Criteria)	Coordinates	Size (kb)	Number of Genes (Strict Criteria)	Coordinate Source
15q13.3	A	ID[B], Schizophrenia[Del], Epilepsy[Del]	ID[B], ASD[B], Schizophrenia[Del], Epilepsy[B]	28,000,000–31,000,000	3,000	78	**ISC 2008**[23], Sharp et al. 2008[40], Cooper et al. 2011[19], Kaminsky et al. 2011[20], Levinson et al. 2011[14], Stefansson et al. 2008[24], Vacic et al. 2011[15], Kirov et al. 2009[25], Grozeva et al. 2012[17], de Kovel et al. 2010[50], Dibbens et al. 2009[51], Mefford et al. 2010[8], Helbig et al. 2009[52]
16p11.2	A	ID[B], ASD[B], Schizophrenia[Dup]	ID[B], ASD[B], Schizophrenia[Dup], Epilepsy[B]	29,474,810–30,110,000	635	46	**Cooper et al. 2011**[19], **Sanders et al. 2011**[9], Bachmann-Gagescu et al. 2010[18], Rosenfeld et al. 2010[42], Kaminsky et al. 2011[20], Weiss et al. 2008[10], Kumar et al. 2008[12], Marshall et al. 2008[11], McCarthy et al. 2009[16], Glessner et al. 2010[13], Levinson et al. 2011[14], Vacic et al. 2011[15], Grozeva et al. 2012[17]
16p11.2-p12.2	A	ID[B]	ID[B], ASD[Dup], Epilepsy[B]	28,680,000–29,020,000	340	15	**Cooper et al. 2011**[19]
16p12.1	A	ID[Del]	ID[Del], ASD[Del], Epilepsy[Del]	21,850,000–22,374,785	525	13	**Cooper et al. 2011**[19], Girirajan et al. 2010[39]
16p13.11	A	ID[B], Schizophrenia[Dup], Epilepsy[Del]	ID[B], Schizophrenia[Dup], Epilepsy[Del]	14,700,000–16,770,000	2,070	27	**Hannes et al. 2009**[43], Mefford et al. 2009[41], Cooper et al. 2011[19], Kaminsky et al. 2011[20], Ingason et al. 2011b[49], de Kovel et al. 2010[50], Heinzen et al. 2010[53], Meffford et al. 2010[8]

CNV	Group	Disorder (Strict Criteria)	Disorder (Broad Criteria)	Coordinates	Size (kb)	Number of Genes (Strict Criteria)	Coordinate Source
16p13.2 (*AK057657, C16orf72*)	B	Schizophrenia^{Dup}	Schizophrenia^{Dup}	9,090,000–9,120,000	30	2	**Levinson et al. 2011**[14]
16q22.1	C	Schizophrenia^{Del}	Schizophrenia^{Del}	68,743,639–68,770,545	27	4	**Glessner et al. 2010**[13]
17p12	C	Schizophrenia^{Del}	Schizophrenia^{Del}	14,048,304–15,357,533	1,309	9	**Kirov et al. 2009**[25]
17p12-p11.2 (Potocki-Lupski/Smith-Magenis Syndromes)	A	ID^{B}	ID^{B}, ASD^{Dup}, Epilepsy^{B}	16,650,000–20,420,000	3,770	113	**Cooper et al. 2011**[19], Kaminsky et al. 2011[20]
17p13.3-p13.2 (Miller-Dieker Syndrome)	C	ID^{Del}	ID^{Del}, ASD^{Del}, Epilepsy^{Del}	500,000–1,300,000	800	13	**Cooper et al. 2011**[19]
17q12	A	ID^{B}, ASD^{Del}, Schizophrenia^{Del}	ID^{B}, ASD^{B}, Schizophrenia^{Del}, Epilepsy^{B}	31,893,783–33,277,865	1,384	20	**Moreno-De-Luca et al. 2010**[37], Cooper et al. 2011[19], Kaminsky et al. 2011[20]
17q21.3	A	ID^{Del}	ID^{Del}, ASD^{Del}, Epilepsy^{Del}	41,060,000–41,650,183	590	10	**Cooper et al. 2011**[19], **Kaminsky et al. 2011**[20]
18q12.3 (*LOC284260*)	B	Schizophrenia^{Del}	Schizophrenia^{Del}	38,310,567–38,311,765	1	1	**Glessner et al. 2010**[13],
18q21.31(*KIAA0439, NEDD4L, NEDL3*)	B	Schizophrenia^{Dup}	Schizophrenia^{Dup}	53,860,000–54,220,000	360	3	**Levinson et al. 2011**[14]
19q13.33(*CLEC11A, SHANK1, SYT3*)	C	ASD^{Del}	ASD^{Del}	55,808,307–55,935,995	128	3	**Sato et al. 2012**[38]
22q11 (Velocardiofacial/DiGeorge Syndrome)	A	ID^{B}, ASD^{Dup}, Schizophrenia^{Del}	ID^{B}, ASD^{B}, Schizophrenia^{Del}, Epilepsy^{B}	17,400,000–18,676,130	1,276	40	**Cooper et al. 2011**[19], Kaminsky et al. 2011[20], Pinto et al. 2010[36], ISC 2008[23], Levinson et al. 2011[14], Vacic et al. 2011[15], Kirov et al. 2009[25], Glessner et al. 2010[13], Mulle et al. 2010[46], Grozeva et al. 2012[17]
22q11.2	A	ID^{Del}	ID^{Del}, ASD^{Del}, Epilepsy^{Del}	20,240,000–21,980,000	1,740	31	**Cooper et al. 2011**[19]
22q13 (Phelan-Mcdermid Syndrome) (*SHANK3*)	B	ID^{Del}	ID^{Del}, ASD^{Del}, Epilepsy^{Del}	49,460,000–49,520,000	60	1	**Cooper et al. 2011**[19]
Xp22.1 (*DDX53, PTCHD1*)	C	ASD^{Del}	ID^{Del}, ASD^{Del}, Epilepsy^{Del}	22,829,183–23,214,712 23,116,188–23,280,628	386 164	2	**Pinto et al. 2010**[36]
Highly Recurrent CNV Regions with No Genes							

CNV	Group	Disorder (Strict Criteria)	Disorder (Broad Criteria)	Coordinates	Size (kb)	Number of Genes (Strict Criteria)	Coordinate Source
CNV		Disorder		Coordinates			Coordinate Source
1q25.2		ASD^{Dup}		174,500,555–174,543,675	43	0	Glessner et al. 2009[27]
2p16.3		ASD^{Del}		51,120,644–51,147,600	27	0	Glessner et al. 2009[27]
2p24.3		ASD^{Dup}		13,119,667–13,165,898	46	0	Glessner et al. 2009[27]
3p26.3		ASD^{Del}		1,915,190–1,915,922	0.7	0	Glessner et al. 2009[27]
3q26.1		Schizophrenia^{Del}		165,610,000–165,660,000	50	0	Levinson et al. 2011[14]
4p16.1		Schizophrenia^{Del}		9,881,886–9,884,092	2	0	Glessner et al. 2010[13]
4q31.21		ASD^{Dup}		144,847,402–144,854,579	7	0	Glessner et al. 2009[27]
7q36.3		Schizophrenia^{Dup}		158,731,401–158,810,016	79	0	Vacic et al. 2011[15]
9q34.3		Schizophrenia^{Del}		140,145,139–140,152,969	8	0	Glessner et al. 2010[13]
22q11		ASD^{Dup}		19,351,264–19,358,946	8	0	Glessner et al. 2009[27]

Note: Fifty-four loci, including 10 non-genic CNVs are listed. For each CNV, deletions (del), duplications (dup), and both (B) are noted for significant disorder(s). All coordinates in NCBI 36/hg 18 build. Studies in bold indicate that coordinates from these studies reported in table.

ASD = autism spectrum disorder; ID = intellectual disability.