ARTICLE

The Genetic Variability and Commonality of Neurodevelopmental Disease

BRADLEY P. COE, SANTHOSH GIRIRAJAN, AND EVAN E. EICHLER*

Despite detailed clinical definition and refinement of neurodevelopmental disorders and neuropsychiatric conditions, the underlying genetic etiology has proved elusive. Recent genetic studies have revealed some common themes: considerable locus heterogeneity, variable expressivity for the same mutation, and a role for multiple disruptive events in the same individual affecting genes in common pathways. Recurrent copy number variation (CNV), in particular, has emphasized the importance of either de novo or essentially private mutations creating imbalances for multiple genes. CNVs have foreshadowed a model where the distinction between milder neuropsychiatric conditions from those of severe developmental impairment may be a consequence of increased mutational burden affecting more genes.

KEY WORDS: copy number variants; variable penetrance; genomic disorders; autism; schizophrenia; intellectual disability

How to cite this article: Coe BP, Girirajan S, Eichler EE. 2012. The genetic variability and commonality of neurodevelopmental disease. Am J Med Genet Part C Semin Med Genet 160C:118–129.

INTRODUCTION

Neurodevelopmental disorders are characterized by impairment of growth and development of the brain often associated with cognitive, neurological, or psychiatric dysfunction. It is an umbrella term that can traverse, to varying degrees, diverse disease classifications including intellectual disability (ID), developmental delay (DD), autism, schizophrenia, bipolar disease, etc. Despite seemingly distinct primary diagnoses, considerable clinical heterogeneity as well as overlap has been appreciated for many years. Individuals with autism, for example, can present with or without cognitive impairment or ID [Kaufman et al., 2008; Matson and Shoemaker, 2009]; this is also reflected in the observed effect of IQ on portions of the Autism Diagnostic Observation Schedule (ADOS) diagnostic criteria [Kamp-Becker et al., 2011]. Such clinical overlap has also been observed for psychiatric disorders, such as bipolar disorder and schizophrenia [Grozeva et al., 2010; Malhotra et al., 2011]. Similarly, it is well known that individuals with schizophrenia also demonstrate comorbidity with cognitive impairments of varying severities [Woodberry et al., 2008] as well as, in some cases, structural defects of the brain [Weinberger, 1995]. Epilepsy patients are more likely to develop psychoses and both ID and schizophrenia patients are more prone to seizure [Hyde and Weinberger, 1997; Cascella et al., 2009]. There are convincing epidemiological links between these diseases that support a model that at least part of the etiology may be neurodevelopmental in origin [Weinberger, 1987].

The genetics of these diverse conditions have also begun to converge. Large copy number variants (CNVs), in particular, have been implicated in these diseases to different degrees. This has included reports of overall increases in CNV burden, higher rates of de novo or sporadic mutation, and the discovery of specific recurrent CNVs observed across diverse phenotypes. With few exceptions, CNVs have been large affecting numerous genes and are extremely rare for any specific locus (<1%) but collectively common on the whole. An emerging model has been that certain CNVs disrupt the homeostasis of normal neuronal development resulting in a range of disorders

Bradley P. Coe is a postdoctoral fellow in Evan Eichler's group in the Department of Genome Sciences at the University of Washington School of Medicine, where he is supported by a fellowship from the Canadian Institutes of Health Research. His current work focuses on the identification and study of rare copy number variation in intellectual disability and developmental delay.

Santhosh Girirajan is a postdoctoral fellow in Evan Eichler's group in the Department of Genome Sciences at the University of Washington School of Medicine. His research interest involves unraveling the genetic basis of variable phenotypes associated with pathogenic CNVs (i.e., genomic disorders).

Evan E. Eichler is a professor and Howard Hughes Medical Institute investigator in the Department of Genome Sciences at the University of Washington School of Medicine. He received his Ph.D. in 1995 from the Department of Molecular and Human Genetics at Baylor College of Medicine in Houston, Texas, USA. He is a fellow of the American Association for the Advancement of Science and was a recipient of the American Society of Human Genetics Curt Stern Award in 2008. His research group develops experimental and computational methods for studying genome structural variation in evolution and human disease.

*Correspondence to: Evan E. Eichler, Department of Genome Sciences and Howard Hughes Medical Institute, University of Washington School of Medicine, Seattle, WA.
E-mail: eee@gs.washington.edu

DOI 10.1002/ajmg.c.31327
Article first published online in Wiley Online Library (wileyonlinelibrary.com): 12 April 2012

With few exceptions, CNVs have been large affecting numerous genes and are extremely rare for any specific locus (<1%) but collectively common on the whole. An emerging model has been that certain CNVs disrupt the homeostasis of normal neuronal development resulting in a range of disorders as part of a neurodevelopmental continuum.

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CNV LANDSCAPE OF NEUROPSYCHIATRIC AND NEURODEVELOPMENTAL CONDITIONS

Despite high heritability estimates for bipolar, epilepsy, schizophrenia, autism, and ID ranging from 73% to more than 90%, relatively few common single nucleotide polymorphisms (SNPs) have been convincingly associated with these diseases [Marshall et al., 2008; Stefansson et al., 2008; Wang et al., 2009; Kasperaviciūte et al., 2010; de Kovel et al., 2010; Pregelj, 2011; Psychiatric GWAS Consortium Bipolar Disorder Working Group, 2011; Shi et al., 2011; Yue et al., 2011]. This has led to a shift to the discovery of rarer genetic variation including CNV as a potential source for the missing heritability [Manolio et al., 2009]. In the past few years, studies of large cohorts have revealed several highly penetrant loci associated with neurodevelopmental disorders and a generalized increase in CNV burden compared to unaffected siblings and controls.

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[Cooper et al., 2011; Kaminsky et al., 2011]. Performing a systematic assessment of population frequency of CNVs at different size ranges, Cooper et al. [2011] showed a significant increase in large CNV burden in affected individuals compared to controls. Further analysis of comorbid phenotypes within the ID/multiple congenital anomalies cohort demonstrated a gradation for autosomal CNV burden, where children with developmental anomalies, such as craniofacial and cardiovascular defects showed the highest CNV burden, while those with no clinically recognized developmental issues other than autism or seizure, for example, showed the lowest (Fig. 1). Similarly, studies in large collections of idiopathic autism [1,124 Simons Simplex Collection (SSC) probands; Sanders et al., 2011] and schizophrenia (>4,500 combined cases) [The International Schizophrenia Consortium, 2008; Stefansson et al., 2008] have demonstrated significant enrichments in large rare/de novo CNV burden in cases compared to controls and unaffected siblings. Although a more subtle increase overall, the effect for schizophrenia appears more pronounced when considering CNVs which disrupt genes in neurodevelopmental pathways [Walsh et al., 2008]. More recently, the spectrum of increased CNV burden diseases has widened to include idiopathic generalized epilepsy (IGE) [de Kovel et al., 2010; Heinzen et al., 2010; Mefford et al., 2010]. The evidence for an increased CNV burden is more conflicting for bipolar disorder. Although no increase in CNV burden was detected in a study of rare CNVs (>100 kbp and <1% of the population) in 1,697 cases of bipolar disorder [Grozeva et al., 2010], a recent study that focused on rare de novo CNVs detected a significant increase in the de novo rate in a set of 199 cases [Malhotra et al., 2011]. Similarly, there is no evidence for CNV burden enrichment in dyslexia [Girirajan et al., 2011] or Tourette syndrome [Fernandez et al., 2011]. The strongest burden enrichments in all phenotypes tends to associate with large CNVs (typically defined as 500 kbp and larger), which are under purifying selection in the general population [Stefansson et al., 2008; Itsara et al., 2010; Malhotra et al., 2011], and thus represent promising candidates for pathogenicity. Additionally, burden increases are often limited to rare and de novo CNVs [Marshall et al., 2008; Pinto et al., 2010; Malhotra et al., 2011; Sanders et al., 2011]. These two parameters are tightly linked, as we have recently demonstrated that the size of a CNV is proportional to its probability of arising de novo [Cooper et al., 2011].

The common theme amongst these studies is that rare/de novo CNV burden appears at a higher odds ratio in more severe phenotypes than populations with milder phenotypes. Here, we define a more severe phenotype as one with a higher degree of cognitive impairment and/or the presence

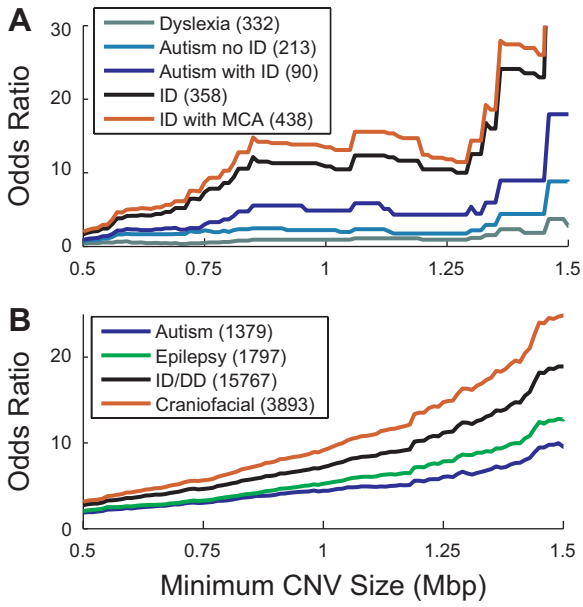

Figure 1. Autosomal CNV burden across various neurodevelopmental phenotypes. Displayed are the odds ratios as a function of CNV size across various phenotypes from two recent studies. **A**: A comparison of multiple sample cohorts, ascertained using standard diagnostic criteria for each phenotype, profiled on the same targeted micro array CGH platform [Girirajan et al., 2011]. Odds ratios were calculated compared to 306 National Institute of Mental Health controls. **B**: Information obtained from 15,767 cases with a general diagnosis of ID/DD [Cooper et al., 2011]. The autism, epilepsy, and craniofacial abnormality phenotypes represent subsets of this overall ID/DD population. Odds ratios were calculated against 8,329 control samples [Cooper et al., 2011].

of congenital abnormalities. Three recent studies explicitly compared the autosomal CNV burdens of dyslexia, bipolar disorder, idiopathic epilepsy, autism, schizophrenia, and ID. The lowest CNV burden is observed in dyslexia and bipolar cases, with the most severe CNV burden in cases with dysmorphic features and cardiac defects, followed by ID [Cooper et al., 2011; Girirajan and Eichler, 2011; Girirajan et al., 2011]. In between these extremes are schizophrenia and autism (Fig. 1), which appear to share a similar burden of large CNVs [Cooper et al., 2011; Girirajan and Eichler, 2011; Girirajan et al., 2011; Malhotra et al., 2011; Sanders et al., 2011].

In all studies the case-enriched CNVs are typically very rare with the most common loci being hotspots where the copy number of flanking segmental duplications lead to an elevated local mutation rate [Sharp et al., 2005; Ballif et al., 2008]. In general, potentially pathogenic duplications are more enriched for the larger size range (>500 kbp) while deletions begin to manifest enrichments at a smaller size range. This fits well with a model of stronger purifying selection for haploinsufficiency when compared to increased dosage and predicts less severe outcomes for duplications. In this light, it is interesting that schizophrenia shows an enrichment for CNV duplications; similarly in autism, duplications are most significantly enriched in the 500+ kbp range, while deletions are significantly enriched in the 30–500 kbp range [The International Schizophrenia Consortium, 2008; Pinto et al., 2010]. CNV enrichment in familiar bipolar disorder is biased towards duplications [Malhotra et al., 2011]. In ID/DD, deletions are more commonly interpreted as pathogenic [Kaminsky et al., 2011] and tend to be more penetrant than duplications [Cooper et al., 2011]. In fact, reciprocal duplication events for known genomic disorders, such as Smith-Magenis and Williams syndrome, are often missed during clinical diagnosis or present as mild manifestations [Somerville et al., 2005; Potocki et al., 2007]. These data all support a stronger effect size for deletions.

Recurrent CNV regions have been identified across multiple disparate disorders (discussed below). Numerous hotspot and nonhotspot CNV loci have been implicated suggesting considerable locus heterogeneity with hundreds of potentially underlying genes. A minority of specific CNVs have been observed with sufficient counts to be individually detected as enriched in a case–control paradigm with multiple testing corrections. In addition to hotspot and large CNV burden, many of these studies have demonstrated significant enrichment within the 30–500 kbp range, primarily for deletions [Itsara et al., 2010; Pinto et al., 2010; Sanders et al., 2011]. Analysis of smaller CNVs is complicated by the increasing number of rare small CNVs in the general population. Only 8% of the general population carries a CNV greater than 500 kbp (as opposed to 25% for patients with developmental delay) [Itsara et al., 2010; Cooper et al., 2011]. As the size diminishes, the number of events increases rapidly with a smaller fraction contributing to disease. Typically, tens of events (less than 10 in array studies) are seen between 100 and 500 kbp per sample, with hundreds of CNV events per sample in the 1–10 kbp range, and thousands in the 100 bp to 1 kbp range [Iafrate et al., 2004; Tuzun et al., 2005; Hormozdiari et al., 2009; Conrad et al., 2010; The 1000 Genomes Project Consortium, 2010; Alkan et al., 2011; Cooper et al., 2011]. Despite this complication, small CNVs represent a promising avenue for future studies with sufficiently powered study populations (both in sample size and resolution) and parental cases for determining de novo status. Specific examples of small CNVs are beginning to arise in genome-wide studies, such as VIPR2 duplications in schizophrenia, partial TMLHE deletions in autism, a collection of significant events in ID/DD subtypes, and events overlapping with genes identified to contain de novo mutations and

indels [Boone et al., 2010; Celestino-Soper et al., 2011; Cooper et al., 2011; Kirov et al., 2011; Vacic et al., 2011].

VARIABLE EXPRESSIVITY OF SPECIFIC LOCI

Numerous CNV loci have been recurrently observed across seemingly disparate neurological phenotypes [Helbig et al., 2009; McCarthy et al., 2009; Girirajan and Eichler, 2010; Rosenfeld et al., 2010; Cooper et al., 2011; Sanders et al., 2011]. Among these are 59 pathogenic CNVs which have reached at least nominal statistical significance with respect to enrichment in cases of ID/DD [Cooper et al., 2011]. In some cases, a specific CNV is necessary and sufficient to result in a suite of characteristic features. These "syndromic CNVs" most often result in patients with moderate-to-severe ID and are by-and-large sporadic in origin. Examples include the 17q21.31 microdeletion syndrome and the Williams syndrome deletion on chromosome 7q11.23 (Fig. 2, Table I). Contrasting with these "syndromic CNVs" are CNVs which are much more variable in their outcome and more likely to be inherited. Here, we highlight this observation of variable expressivity (defined as either qualitative or quantitative phenotypic variation among individuals carrying the same CNV) by focusing on a few of these CNV loci.

One locus that has received considerable attention in recent years is the 16p11.2 microdeletion/microduplication. Both the deletion and duplication have been observed in multiple conditions with significant enrichment compared to healthy controls (range: <0.01–1%).

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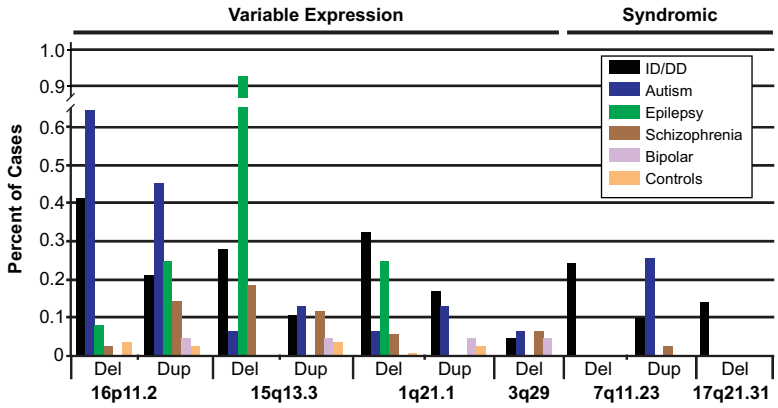

Figure 2. Variable expressivity of hotspot CNVs. The frequency of CNV deletions and reciprocal duplications for six genomic hotspots associated with neurological disease are shown (ID/DD, autism, epilepsy, schizophrenia, and bipolar disorders). Data sources are as follows. ID/DD: all sites n = 31,516 [Cooper et al., 2011; Kaminsky et al., 2011]. Autism: all sites n = 1,551 [Marshall et al., 2008; Sanders et al., 2011]. Epilepsy: all sites n = 399 [Mefford et al., 2010]; 15q13.3 n = 647 [Helbig et al., 2009; Mefford et al., 2010]; 16p11.2 n = 1,234 [de Kovel et al., 2010; Mefford et al., 2010]. Schizophrenia: all sites n = 4,168 [The International Schizophrenia Consortium, 2008; Malhotra et al., 2011], 15q13.3 n = 6,948 [The International Schizophrenia Consortium, 2008; Stefansson et al., 2008; Malhotra et al., 2011], 1q21.1 n = 12,117 [The International Schizophrenia Consortium, 2008; Stefansson et al., 2008; Malhotra et al., 2011], 3q29 n = 4,413 [The International Schizophrenia Consortium, 2008; Mulle et al., 2010; Malhotra et al., 2011]. Bipolar disorders: all sites n = 2,053 [Grozeva et al., 2010; Malhotra et al., 2011]. Controls: n = 8,329 [Cooper et al., 2011].

The deletion is associated with more severe phenotypes, including cases with dysmorphic features, and is strongly enriched in ID and autism with a strong association to obesity [Walters et al., 2010]. The reciprocal duplication is not associated with any common dysmorphic features and is seen in a wider range of conditions, including clinically underweight cases mirroring the obesity phenotype for the deletion (Fig. 2, Table I) [Marshall et al., 2008; Weiss et al., 2008; Bochukova et al., 2010; Rosenfeld et al., 2010; Walters et al., 2010; Girirajan et al., 2011; Jacquemont et al., 2011; Sanders et al., 2011]. Recent work in autism has identified atypical deletions and point mutations highlighting SEZ6L2 as a strong candidate for the deletion phenotype [Kumar et al., 2008; Crepel et al., 2011; Konyukh et al., 2011]. There is also conflicting evidence that phenotypic variability at this locus may be controlled by second-site CNVs in humans. Girirajan et al. [2010], for example, noted an excess of additional larger CNVs in 9.9% of pediatric cases with ID and 16p11.2 deletions concurrent with an inheritance rate of 25.7%. However, a recent study on 16p11.2 in the context of obesity and developmental delay failed to detect evidence for an enrichment of second-hits [Jacquemont et al., 2011].

The 15q13.3 microdeletion is also detected across multiple phenotypes, with the strongest enrichment observed in cases of IGE where frequency reaches nearly 1% of cases [Dibbens et al., 2009; Helbig et al., 2009]. The microdeletion was originally discovered among patients with ID [Sharp et al., 2008; Cooper et al., 2011; Kaminsky et al., 2011]. Later, the same CNV was discovered in cases of autism, schizophrenia, and epilepsy [The International Schizophrenia Consortium, 2008; Marshall et al., 2008; Stefansson et al., 2008; Cooper et al., 2011; Kaminsky et al.,

TABLE I. Characteristics of Variably Expressive Hotspot CNVs

CNV locus	Start (Mbp)	End (Mbp)	RefSeq genes (unique space)	Duplication inheritance[a]	Deletion inheritance[a]
16p11.2	29.56	30.11	28	77.78% (21/27)	36.73% (18/49)
15q13.3	28.92	30.27	8	100% (11/11)	78.79% (26/33)
1q21.1	145.04	145.86	9	75.61% (31/41)	77.78% (28/36)
3q29	197.23	198.84	27	—	28% (4/14)
7q11.23	72.38	73.78	26	44.44% (4/9)	0% (0/45)
17q21.31[b]	16.65	20.42	10	—	0% (0/32)

— Indicates no data available.

[a]All loci (except 3q29) [Girirajan et al., unpublished], 7q11.23 deletion [Perez Jurado et al., 1996], 3q29 deletion [Willatt et al., 2005; Ballif et al., 2008], and 17q21.31 [Koolen et al., 2008].

[b]17q21.21 does not demonstrate variable expressivity.

2011; Sanders et al., 2011] (Fig. 2, Table I). Atypical smaller deletions in patients with similar phenotypes have strongly implicated the nicotinamide acetylcholine receptor (CHRNA7) as the most likely candidate gene for disease especially as it relates to the seizure and ID [Shinawi et al., 2009]. While deletions of this locus have been replicated in numerous studies involving patients with idiopathic epilepsy, the deletion is not detected in focal epilepsies [Heinzen et al., 2010]. The reciprocal duplication has not been observed in cases of IGE; while it is enriched in cases of ID with respect to controls, it is more variably expressed across neurological phenotypes (ID/DD, bipolar disorder, and autism among others) and its role in pathogenicity remains unclear [Helbig et al., 2009; Shinawi et al., 2009; Szafranski et al., 2010; Cooper et al., 2011].

The 3q29 microdeletion is particularly rare (<1/1,000) and has been associated with severe schizophrenia [Mulle et al., 2010], ID, and autistic features with mild dysmorphism present in the majority of cases [Willatt et al., 2005; Ballif et al., 2008]. Recently, Carroll et al., [2011] identified rare mutations in one gene (DLG1) highlighting its potential involvement in the schizophrenia phenotype. The variability in expression is further supported by a case report of a child with autistic features, an elongated face, and normal IQ [Cobb et al., 2010]. Pathogenicity of the reciprocal duplication remains uncertain with the loci failing to reach significance in ID/DD and the observation that a family carrying the duplication also carries a second CNV that may explain the clinical features [Ballif et al., 2008; Cooper et al., 2011].

Finally, 1q21.1 deletions and duplications demonstrate some of the most pronounced variability in phenotypic outcome with the highest rates of deletions observed among ID and IGE patients [Mefford et al., 2010; Cooper et al., 2011; Kaminsky et al., 2011] and the highest rates of duplications found in ID and autism [Marshall et al., 2008; Cooper et al., 2011; Kaminsky et al., 2011; Sanders et al., 2011].

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The variable expressivity between cases has been explained by secondary insults including environmental exposure, stochastic variation during development, or differences in the genetic backgrounds. Studies involving large panels of patients with the deletion [Mefford et al., 2008] suggest a relatively finite number of "sub-syndromic" outcomes including mild-to-moderate ID, microcephaly, cardiac abnormalities, and cataracts. The commonalities and differences between duplication and deletion phenotypes may be explained, in part, by the variable dosage sensitivity of the genes contained in the CNV region. To this end, Harvard et al. [2011] performed functional analyses on two genes with a strong correlation between expression levels and copy number state. In a cell model the authors observed that one gene (CHD1L) demonstrated a functional deficit under both over- and underexpression conditions, while another gene (PRKAB2) only affected its associated functions in a deletion state. The complex comorbidities of these loci mirror the complex interactions of the clinical phenotypes and highlight not just locus heterogeneity but variable expressivity and overlap in neurodevelopmental conditions [Matson and Shoemaker, 2009; Girirajan and Eichler, 2010; Rosenfeld et al., 2010; Auerbach et al., 2011]. While deletions and duplications of specific loci may yield drastically different phenotypes, the contradictory observation of both deletions and duplications leading to similar phenotypes is also common. This may be explained by the general sensitivity of certain cellular functions to dosage imbalance, such as that observed for the 1q21.1 region [Harvard et al., 2011]. This model is also supported in an

alternative gene context by Auerbach et al. [2011], who recently demonstrated that fragile X and tuberous sclerosis mouse models affect the same pathway (glutamate receptor 5) in opposite directions with both disruptions resulting in syndromic autism and ID features. This complex variability in phenotypic expression is not limited to the hotspots discussed here but has been observed for many CNV loci, and variable expressivity has been explained by both variable breakpoints and the interaction of these CNVs with secondary mutation events. This model is particularly striking for 16p12.1 deletions where phenotypic severity is strongly associated with additional CNVs and appears to be most strongly correlated with phenotypic modification of inherited CNV sites [Girirajan et al., 2010]. Additional evidence has suggested that variable expressivity can be the result of genetic background and additional subclinical phenotypes, only obvious in studies of large populations with detailed clinical information, may exist in cases defined as normal or with other assigned phenotypes [Mefford et al., 2008].

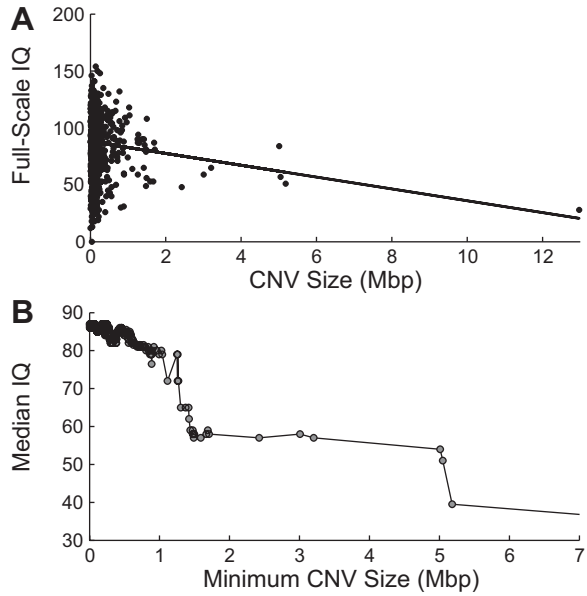

Figure 3. Phenotypic severity as an outcome of CNV burden. Rare CNVs (defined as present in <0.1% of controls and unaffected siblings) were analyzed in the context of full-scale IQ for 841 Simons Simplex autism probands. **A**: Full-scale IQ weakly correlates with the largest rare CNV carried by an individual (Pearson's $r = -0.11$, >500 kbp, $r = -0.36$); however, when we split the population at increasing CNV size cutoffs (**B**), we observe a striking drop in median IQ, most noticeable past 500 kbp. When we filter CNVs <500 kbp, we observe a striking correlation between median IQ and CNV size (Spearman's $r = -0.97$, $P = 0.0009$). The calculation of *P*-values was performed by computing 10,000 random permutations of IQ across samples and repeating the median IQ calculations. The *P*-value represents the fraction of permutations with a more extreme correlation than that observed for the raw data.

CNV BURDEN AND PHENOTYPE SEVERITY

Taken together, the results of recent genome-wide screens of CNVs of neurodevelopmental disorders reveal a striking correlation of effect size and the number of genes affected (both by large CNVs and multiple loci) [Itsara et al., 2010; Cooper et al., 2011; Girirajan and Eichler, 2011; Malhotra et al., 2011]. A simple additive model may be that these diseases are part of a neurodevelopmental continuum where more rare and disruptive mutations in an individual lead to increasing severity. In this model, larger CNVs create imbalance for more genes during neurodevelopment leading to a more severe outcome. In the study by Girirajan et al. [2011], we noted an increased CNV burden in cases of autism with ID compared to cases without ID; this is further supported by the increased CNV burden in the autism cohorts highlighted in Figure 1. To further investigate the relationship between CNV burden and effect size, we performed a meta-analysis of rare CNVs from a study with a quantitative measurement of severity. In the SSC autism cohort (ascertained by multiple criteria described by Risi et al. [2006]) studied by Sanders et al. [2011], each sample has an associated full-scale IQ score. We reanalyzed CNVs using the algorithm described by Itsara et al. [2009] to include CNVs that would be excluded due to the stringent size filtering in Sanders study and filtered CNVs by their frequency in both siblings (<0.1%) and an independent cohort of 2,090 controls (<0.1%) also profiled on Illumina SNP arrays with similar density [Cooper et al., 2011]. CNV calls were filtered to exclude those not detectable on all three ~1 M Illumina platforms represented. This resulted in 2,227 rare CNV calls in 841 probands with no events detected in >1% of probands. Although the individual level correlation between the largest rare CNV carried and full-scale IQ (Fig. 3a) is relatively weak, we note that a general trend does appear to indicate reduced IQ for cases with larger CNVs similar to the observation of Sanders et al. [2011]. When we examine the median IQ for populations of cases with increasing minimum CNV size cutoffs, we note an emerging trend (Spearman's $r = -0.7894$, permutation $P = 0.074$) with the effect appearing strongest past ~500 kbp (Fig. 3b). Filtering of cases with CNVs smaller than 500 kbp resulted in a striking correlation of minimum CNV size and median IQ (Spearman's $r = -0.97$, $P = 0.0009$). To confirm that the effect is not solely due to large outliers, we repeated the analysis excluding very large CNVs (>3 Mbp) and noted that the correlation remained significant (Spearman's $r = -0.96$, $P = 0.0056$). We also note that a statistically significant

reduction in median IQ compared to the general SSC cohort is reached at a cutoff of 670 kbp ($P = 0.0321$). Thus, within this limited cohort we can confirm that large CNVs have an increasing effect size on quantifiable phenotypic severity. To further investigate the role of rare and de novo CNVs on phenotypic severity and the potential for multiple rare CNVs in a single case [Girirajan et al., 2010; Sanders et al., 2011], we repeated the analysis using the number of genes affected by rare CNVs and observed a striking downward trend in IQ with an increasing number of genes, with the median IQ crossing the threshold for ID at $\geq$18 genes affected ($P = 0.00225$). These data support a significant role for rare CNVs in phenotypic severity with both individual large CNVs and the combined effect of multiple rare CNVs leading to an increased effect size.

SUMMARY

The neurodevelopmental conditions of bipolar disorder, epilepsy, schizophrenia, autism, and ID share a highly similar large CNV landscape with pathogenicity ascribed to a plethora of individually rare, collectively common CNVs that are both restricted to and shared between these and other phenotypes. The most significant enrichment at a single locus in all conditions is predominantly associated with segmental duplication mediated hotspots [Bailey et al., 2002], such as 16p11.2 deletions in autism and 15q13.3 deletions in IGE, which have both been observed in up to 1% of cases for these specific phenotypes [Helbig et al., 2009; Sanders et al., 2011]. Analysis of hotspot loci has demonstrated remarkable heterogeneity of clinical features supporting a similar mechanism of neurodevelopmental impairment across neurological conditions, particularly those with an increased CNV burden compared to unaffected controls (Figs. 1 and 2). In most conditions discussed here, an increased burden of large rare/de novo CNVs has been reported, although evidence is conflicting for bipolar disorders, which demonstrate the lowest burden increase. Larger CNVs are associated with more severe IQ deficit and the disruption of an increasing number of genes by both single large and multiple small rare CNVs leading to a reduction in median IQ. This effect is also supported by the increasing burden of large CNVs in more severe phenotypes [Cooper et al., 2011; Girirajan and Eichler, 2011; Girirajan et al., 2011].

In the phenotypes with fewer large CNVs, whole-genome or exome studies are very likely to yield fruitful results specifying particular candidate genes. Proving pathogenicity will be challenging as the equivalent of genomic hotspots prone to recurrent mutation are not known to exist for most smaller mutational events. Current analyses indicate that the burden of point mutations and indels is only subtly enriched in schizophrenia and autism versus controls [Awadalla et al., 2010; Girard et al., 2011; O'Roak et al., 2011; Xu et al., 2011]. It is thus likely that a similar model will apply to smaller CNVs where the effect is not simply the number of events but the specific events observed, such as the type of genes or the nature of the copy number event (e.g., gene-disruptive or leading to a gene fusion). Given the current estimates of locus heterogeneity (~1,000), this will necessitate the screening of extremely larger numbers of cases and controls or detailed family studies where additional evidence from linkage can be leveraged to increase the likelihood of discovering the pathogenic mutation. Large CNVs are expected to have a significant effect size as they perturb dosage of many genes, while small events will need to either individually hit a critical gene or combine to have a significant effect. The extent of locus heterogeneity is supported by observations of 50 distinct and novel gene mutations observed in 136 consanguineous families with recessive ID [Najmabadi et al., 2011]. The notion of multiple hits has been demonstrated in the context of idiopathic high-functioning autism where multiple inherited and de novo mutations have been demonstrated to lead to a clinical phenotype, while select single-gene events can lead to syndromic autism [Schaaf et al., 2011]. In addition, evidence supports a combination of these models in autism with both de novo and rare point mutations/indels and structural variants coming together in specific individuals to converge on particular molecular pathways related to disease [O'Roak et al., 2011, 2012].

Together these data support an oligogenic model for phenotypic expression of CNVs. As more, or larger, rare de novo genic CNVs are present, severity markedly increases with bipolar disorders demonstrating the least CNV burden and ID demonstrating the most significant burden (Fig. 4). Importantly, these mutations are very rare, they are gene disruptive, and they exist in the heterozygous state but collectively different mutations or imbalances converging on common pathways lead to disease. If this model holds, exome and whole-genome sequencing should identify hundreds of genes underlying

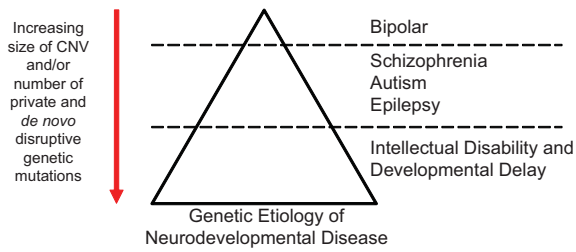

Figure 4. An oligogenic model for neurodevelopmental phenotypes. Presented is a model where an increasing number of genes disrupted by rare CNVs correlates with an increase in phenotypic severity (defined as increasing comorbidity of ID and congenital abnormalities).

neuropsychiatric and neurodevelopement disease as both disruptive point mutations as well as smaller CNVs are systematically discovered [Hardenbol et al., 2003; Porreca et al., 2007; Turner et al., 2009]. The prospects for understanding the genetic etiology and the biological pathways underlying the development of the human brain have never been better.

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