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A genetic model for neurodevelopmental disease

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The genetic basis of neurodevelopmental and neuropsychiatric diseases has been advanced by the discovery of large and recurrent copy number variants significantly enriched in cases when compared to controls. The pattern of this variation strongly implies that rare variants contribute significantly to neurological disease; that different genes will be responsible for similar diseases in different families; and that the same 'primary' genetic lesions can result in a different disease outcome depending potentially on the genetic background. Next-generation sequencing technologies are beginning to broaden the spectrum of disease-causing variation and provide specificity by pinpointing both genes and pathways for future diagnostics and therapeutics.

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Introduction

High-throughput genetic analyses, including current advances in detecting copy number variants (CNVs) and single nucleotide variants (SNVs), are leading to an explosion in the number of candidate genes and genomic regions contributing to neurodevelopmental disease [1••,2••,3]. This has been accompanied by a change in focus from a genetic model involving common genetic variants (>1% frequency) to rare variants of high impact that are collectively common. CNV analyses, in particular, have led to the identification of numerous genomic regions, which, when deleted or duplicated, increase risk for autism, schizophrenia, epilepsy, and numerous intellectual disability phenotypes. Several themes have emerged from these and recent genome sequencing studies. First, every human carries a surprisingly large number of essentially disruptive mutations that are extremely rare (estimated at 250–300 genes per individual) [4]. Second, for certain neurological diseases there is an emerging view that there is an overall increase in the burden of the most disruptive mutations (i.e. larger CNVs). Third, dozens of mutations in different regions and different genes have been identified for seemingly identical neurodevelopmental disorders. This is in stark contrast to earlier Mendelian disease models where one gene was primarily responsible for diseases such as Huntington disease, Duchenne muscular dystrophy, and familial Parkinsonism. Finally, mutations in the same gene or seemingly identical large CNVs may result in very different disease outcomes. Interpretations of these findings are compounded by the lack of a consensus phenotyping criteria and the notion of various subtypes for a given 'umbrella disorder.' These observations have suggested a more complicated genetic model underlying the etiology of neurodevelopmental disorders. Given their population prevalence and the cost to the healthcare system, genetics provides the best prospect to furthering our understanding of their cause, genetic counseling options, and eventually improved treatments. In this review we will highlight the current status of whole-genome efforts to identify genes and discuss their implications in the context of a common neurodevelopmental model for disease.

Copy number variation in neurodevelopmental disorders

Genetic linkage analysis and chromosome karyotype analyses initially played a key role in the discovery of genes important in neurological disease [5,6,7••,8,9]. Many of these disorders were clinically well-defined and relatively quite rare facilitating their rapid genetic delineation. Other more common and complex phenotypes, including developmental delay, epilepsy, schizophrenia, and autism, in the general sense, have been genetically more elusive although successful linkage studies suggested a model where different genetic loci (each in a different family) contributed to disease. Genome-wide association studies (GWAS) have identified relatively few common variants of large effect, leading to increased interest in a rare-variant common-disease model to help explain the missing heritability [10].

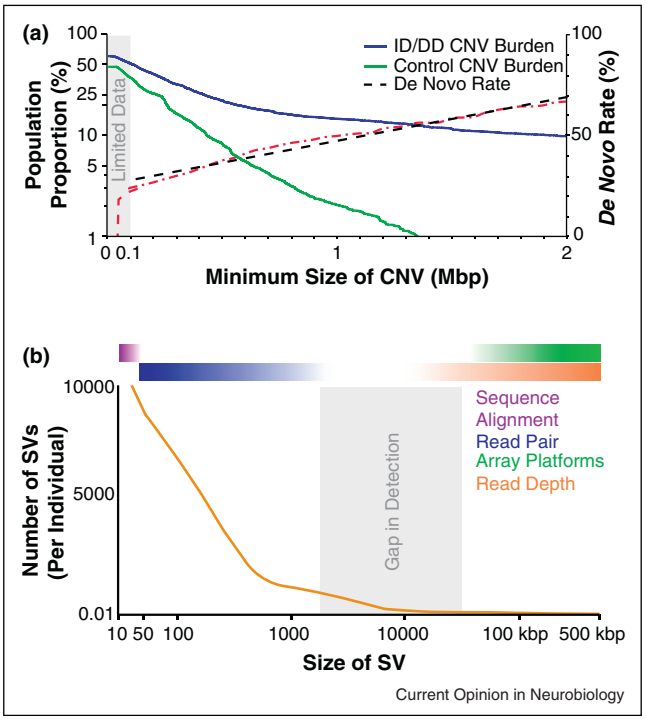
Strong support for this model arose from the initial studies of large copy number variation of idiopathic cases of disease [11,12•,13–15]. CNV studies using array comparative genomic hybridization (arrayCGH) or single nucleotide polymorphism (SNP) microarrays identified numerous large deletions and duplications among patients with neurodevelopmental disease. While very few specific loci initially reached statistical significance, a consistent pattern of increased CNV burden, particularly

for large CNVs affecting multiple genes, was reported. This heterogeneity meant that sample sizes of a several hundred patients were insufficient to claim significance at the individual CNV level. Two studies recently examined CNVs in some of the largest cohorts (~15 000) of children with developmental delay and intellectual disability [1••,2••]. This has led to the discovery of new sites of potentially pathogenic variation and refinement of the smallest region of overlap of previously identified loci [1••]. There are now 59 CNVs corresponding to 39 distinct genomic regions that show enrichment in CNVs among cases when compared to controls. The majority are large (>300 kbp), comprising on average 10–15 genes. Each CNV locus is extremely rare, with the most recurrent flanked by segmental duplications, which elevate local CNV mutation rates as a result of unequal crossover [14,16,17]. For Intellectual Disability/Developmental Delay (ID/DD), 25.7% of ascertained cases carry a CNV greater than 400 kbp in size, compared to only 11.5% of the control population (Figure 1a) [1••]. It is, thus, predicted that 14.2% of disease may be associated with large CNVs. This matches well with the diagnostic yield of 14.7% described by Kaminsky *et al.*, which also focused on large CNVs (primarily >500 kbp) [2••], and previous studies reviewed in Hochstenbach *et al.*, 2011 [18].

Comparisons of CNV burden for different diseases suggest increasing CNV burden in disorders with greater phenotypic severity (defined here in terms of increasing comorbid cognitive impairment and congenital abnormalities) [1••,19•,20]. Cases with congenital malformations demonstrate the greatest increase in CNVs followed by ID/DD. Intermediate burdens were observed for idiopathic generalized epilepsy (IGE), autism spectrum disorder (ASD) and schizophrenia. While CNV studies for children with ID/DD show an increase of 14.2% for large CNVs, the burden is lower for ASD [1••,21,22] with a diagnostic yield around 6–8% predominantly from *de novo* CNVs [18,21,22]. Studies of adults with schizophrenia and epilepsy demonstrate lower diagnostic yields of ~5% [11,12•,18,23,24]. For other neurodevelopmental conditions there is either conflicting evidence for increased CNV burden, such as for bipolar disorder [25,26••], or no evidence, as for Tourette's syndrome and dyslexia [19•,20,27]. In all cases burden statistics are more significant when considering *de novo* events exclusively [15,18,21,22,26••].

One possible interpretation of these results is that large CNVs, by virtue of affecting more genes by way of dosage imbalance, demonstrate a larger effect size than small CNVs and SNP variants. Consistent with this observation, the odds of a CNV being *de novo* is linearly proportional to its size with CNVs larger than 1 Mbp being more likely to arise *sporadically* than inherited from a parent (Figure 1a). There is compelling evidence, then, that CNVs are under strong purifying selection in the general population [24,26••,28]. Remarkably, as much as

Figure 1



CNV burden and *de novo* rates. **(a)** CNV burden becomes significantly greater at >100 kbp in cases (blue line) of developmental delay when compared to controls (green). The observed size of a large CNV (>100 kbp) is linearly proportional (black line) to the odds that it originates sporadically. We anticipate that this trend (red line) will hold below 100 kbp (dropping exponentially as it approaches the size of an indel). In conjunction with an increase in CNV rates for smaller events, this implies that a significant amount of *de novo* CNV load remains to be discovered in the under-ascertained 10–50 kbp range. **(b)** The relative number of structural variants (SVs) detected in a normal individual is displayed as a function of SV size. The number of SVs begins to climb exponentially below ~500 bp reaching on the order of 10 000 events per person at 50 bp. Conversely, large events are significantly rarer with 500 kbp events detected in only a subset (9%) of individuals. Current paired-end sequence methodologies lose detection sensitivity above ~10 kbp, while array-based platforms rapidly lose sensitivity below 50–100 kbp. As a result, CNVs in this moderate size range are under-ascertained by the majority of methodologies.

8–10% of the general population carries such extremely rare or private CNVs suggesting that they must play an important role in human health.

Size spectrum of copy number variation

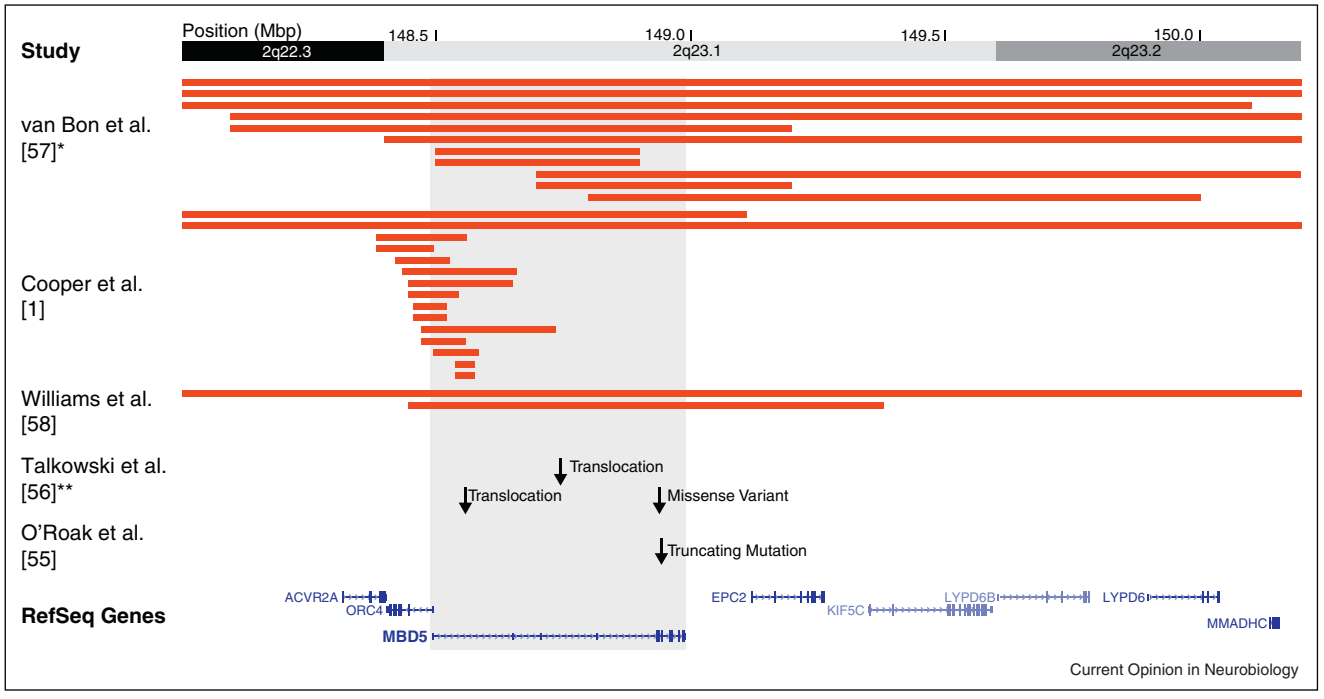
The majority of CNV loci convincingly classified as pathogenic to date are large (>500 kbp). We posit that this reflects both a technological limitation and an ascertainment bias as a result of the mutation severity. Affordable whole-genome sequencing [29] has revealed a plethora of uncharacterized genetic variation below the lower limits of arrayCGH and SNP array platforms, which rapidly lose genome-wide sensitivity below 50 kbp for most commercial arrays [30]. The number of CNVs per

individual increases linearly as sizes approach 100 kbp (closely related to the *de novo* rate and matching observations of selection against large CNVs), but then begins to increase exponentially for CNVs less than 10 kbp in size (Figure 1b) [31]. This poses a significant challenge in the study of smaller variants that are more likely to be inherited (Figure 1a) but present at a far greater count in any given individual (Figure 1b). Larger, ethnically matched control populations in conjunction with information regarding the inheritance will be required to assess significance as 'the haystacks get larger and the needles become smaller.'

Whole-genome sequencing experiments focus primarily on detecting SNPs and indels (typically below ~20 bp in length). The analysis of copy number and structural variation is frequently an afterthought requiring specialized and computationally intensive methods [4,29,30]. No method is comprehensive and each differs in its sensitivity as a function of size and class of CNVs. Read-pair methodologies, for example, are most sensitive to events between 40 bp and 1 kbp (depending on library insert sizes and consistency) [30–33]. Read-depth methodologies are powerful for detecting copy number changes greater than 10 kbp and are dependent on sequence coverage, which limits the number of genomes that can be analyzed [29,30,34–37]. This leaves a gap in our detection abilities between about 1 kbp and 50 kbp where performance is suboptimal (Figure 1b).

Despite these challenges, studies are beginning to approach the gap in genetic variation from both ends. In addition to point mutations and indels [38••,39•], exome sequencing data can be used to discover larger events of potential relevance to disease [40,41]. Similarly, higher resolution and targeted array studies have identified numerous candidate CNVs well below 500 kbp [42–46]. Some recent prominent examples include a small duplication of *VIPR2* in schizophrenia, and focal partial deletions of *TMLHE* in ASD [44,47,48]. Smaller CNVs also confer the advantage of reducing the smallest region of overlap for large CNV regions, such as the potential refinement of the 15q13.3 microdeletion to *CHRNA7*, the 17q21.31 microdeletion to *MAPT/KANSL1* [1••], and the 16p11.2 deletion to *SEZ6L* [49,50,51•]. Importantly, small CNVs are converging at sites where other events such as rare point mutations and translocation breakpoints have highlighted candidate genes. One such example is the 2q23.1 deletion syndrome, which has been associated with intellectual disability, seizures, microcephaly, and speech delay. Recently, the minimal region has been fine mapped via deletions as small as 37 kbp to a single gene — *MBD5* [1••,52–55]. This gene has also been discovered to contain both a rare mutation and common variants as

Figure 2



2q23.1 microdeletion syndrome refinement. Highlighted are deletion cases from three recent studies that detected focal deletions (37.7 kbp to >1 Mbp) and point mutations converging on *MBD5* as the critical gene for the 2q23.1 microdeletion syndrome. In a panel of 8329 controls only two deletions were detected [1••]. *Breakpoints for van Bon *et al*. [54] are rounded to the nearest 100 kbp. **CNVs from Talkowski *et al*. [53] overlap with cases from Cooper *et al*. [1••] and are not shown.

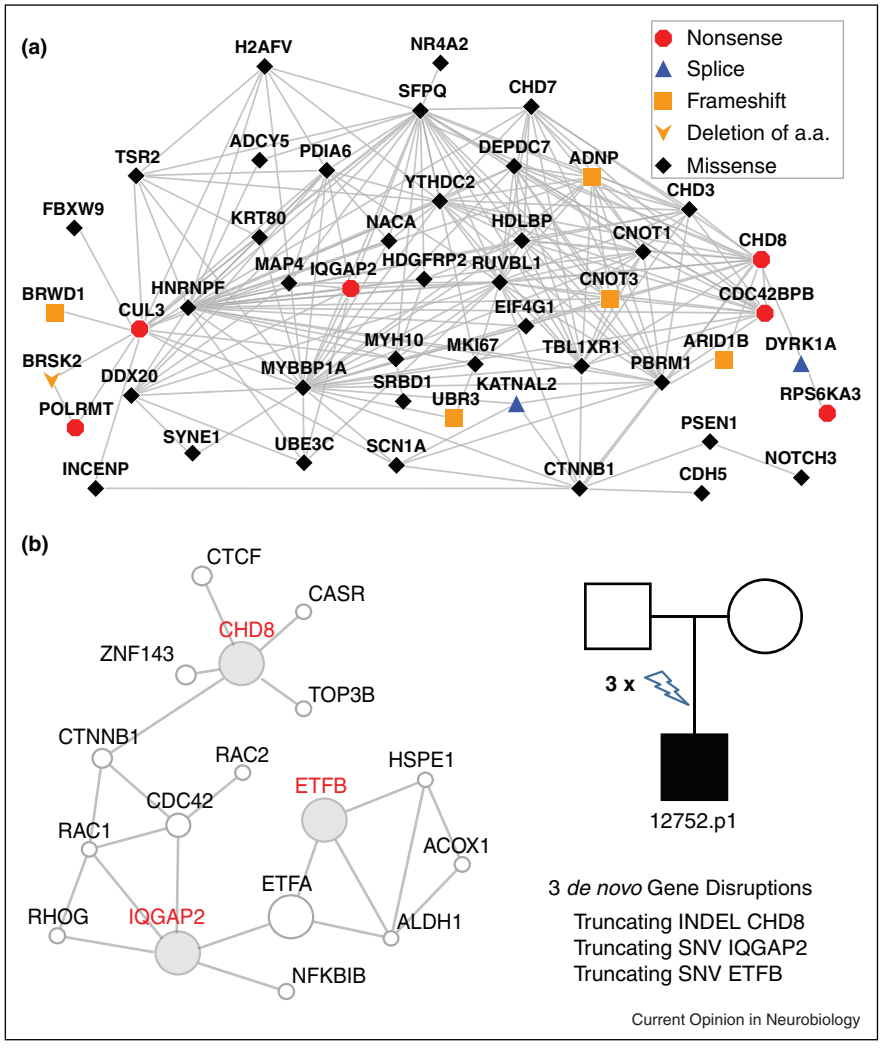
well as translocation breakpoints by sequencing studies of ID, epilepsy, and ASD (Figure 2) [52,53].

These results hint that smaller CNVs are a promising direction for future studies complementing screens for disruptive point mutations by providing stronger priors for rare singleton mutations in the limited populations studied. This is especially important given our current abilities to apply arrayCGH in a clinical and basic research setting to tens of thousands of individuals, while sequencing is typically restricted to smaller cohorts (hundreds) for any given disease. Eventually, as we progress to more affordable sequencing of larger populations, a more comprehensive view of all forms of genetic variation will emerge. Integrating both CNV and sequence data will be mutually beneficial in pinpointing the most likely candidate genes.

A genetic model of neurodevelopmental disease

An interesting observation to emerge from CNV research has been the distinction between syndromic CNVs (e.g. Williams Syndrome deletion at 7q11.23) and CNVs that are much more variable in their outcome. The 15q13.3 microdeletion, for example, is significantly enriched in cases of autism, schizophrenia, and epilepsy being found in as many as 1% of IGE cases but absent in ethnically matched controls [1••,2••,22–24,56,57•,58,59]. These and other observations imply that seemingly diverse disease states may share some common genetic, and perhaps

Figure 3



Protein–protein interaction network for ASD gene mutations. **(a)** Shown is a highly interconnected protein–protein interaction network consisting of 49/125 severe *de novo* gene mutations identified from 209 children with simplex autism described in O'Roak *et al*. [52]. The pathway is enriched in upstream and downstream regulators of beta-catenin. It ranks significantly with respect to autism genes and is not identified in similarly characterized unaffected siblings. **(b)** An example of a patient with autism who carries three *de novo* truncating mutations in genes that encode proteins that are part of a beta-catenin linked network.

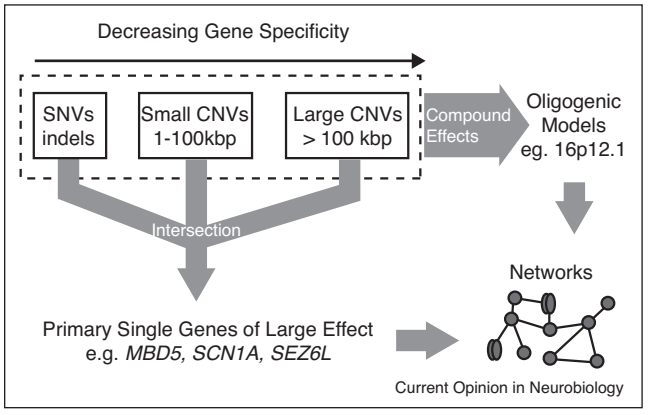
neurodevelopmental, etiology. Moreover, the syndromic CNVs are most frequently *de novo* indicating that they are necessary and sufficient while the variable expressive CNVs are much more likely to be inherited from less severely affected parents. This indicates that they are, by themselves, insufficient to determine disease outcome [1••,60•]. The mechanisms for this variable expression are not clear but there is compelling evidence of an oligogenic model where multiple rare private variants of moderate to large effect compound to determine final phenotypic outcome [52,60•,61]. This model is perhaps strongest for the 16p12.1 microdeletion. In this case, the deletions are almost always inherited; developmental delay patients carrying this microdeletion are significantly enriched for additional CNVs — so-called second-site hits; and carrier parents of the 16p12.1 deletion are more likely to suffer from neuropsychiatric disease than non-carrier parents for the deletion [60•]. These results suggest that the 16p12.1 microdeletion creates a sensitized state and that additional modifier loci (i.e. CNVs) are required to result in a child that is more severely developmentally disabled.

The implication of this model is both sobering and exciting. CNV and early genome sequencing experiments both implicate hundreds to thousands of different genes underlying various neurological phenotypes [22,39•]. Analyses of candidate genes, however, are beginning to converge on a subset of protein–protein interaction networks or biological processes, many of which are strongly tied to neurodevelopment [18,52,62,63,64••]. Genes involved in synaptic function have been repeatedly shown to play a role in neurological disorders [62,63,65,66]. Recent studies of ASD have identified overrepresentation of CNS development genes in addition to several other pathways [21,65,67]. In our own recent analysis of 209 exomes from patients with sporadic autism, we found that 39% of the *de novo* disruptive mutations formed a highly interconnected protein–protein interaction network involving beta-catenin upstream and downstream regulation (Figure 3) [52]. Notably, this pathway was not observed to be enriched in unaffected siblings and ranked significantly with respect to other autism candidate genes. Interestingly, several cases demonstrated multiple disruptive *de novo* events within this same network.

Future directions

The development of the human brain is complex involving thousands of different genes. With respect to disease, we envision that this process can be perturbed either by individual mutations of singularly large effect or by a few disruptive mutations in different genes (oligogenic) that compound at the molecular level to lead to variable outcomes with respect to neurodevelopmental disease. The former mutations are largely sporadic in origin while the latter are more likely to be inherited. In both cases, we propose that individual pathogenic or modifier loci are extremely rare but collectively common in the population. Under this model, the focus should be on the discovery of disruptive mutations in cases that are largely absent from the general population. The extreme locus heterogeneity implies that most initial sequencing studies will be woefully underpowered to prove pathogenicity of any given gene [52]. Power will arise from first, the integration of both CNV and SNV data to triage specific regions or candidate genes; secondly consideration of disruptive mutations across different diseases (e.g. meta-analyses of epilepsy, schizophrenia, autism cohorts, *etc.*); and finally, pathway and functional analyses that converge on specific networks (Figure 4). Once identified, pathways of clinical significance will become the target of both better diagnostics and, ultimately, therapeutics.

Figure 4



A model for neurodevelopmental disease. Two paths are shown involving either mutation events of singularly large effect (e.g. a *de novo* CNV) resulting in disease or rare mutations that compound to lead to disease of varying severity and expressivity. The intersection of CNV, indel, and point mutation can be used to readily identify primary genes where imbalance is sufficient to cause disease. In the second pathway, multiple events will need to co-exist in an individual to elicit a disease phenotype. Mutations in both converge on common protein interaction networks and genetic pathways important in neurodevelopment.

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- •• of outstanding interest

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