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Convergence and Divergence of Rare Genetic Disorders on Brain Phenotypes
A Review

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IMPORTANCE Rare genetic disorders modulating gene expression—as exemplified by gene dosage disorders (GDDs)—represent a collectively common set of high-risk factors for neuropsychiatric illness. Research on GDDs is rapidly expanding because these variants have high effect sizes and a known genetic basis. Moreover, the prevalence of recurrent GDDs (encompassing aneuploidies and certain copy number variations) enables genetic-first phenotypic characterization of the same GDD across multiple individuals, thereby offering a unique window into genetic influences on the human brain and behavior. However, the rapid growth of GDD research has unveiled perplexing phenotypic convergences and divergences across genomic loci; while phenotypic profiles may be specifically associated with a genomic variant, individual behavioral and neuroimaging traits appear to be nonspecifically influenced by most GDDs.

OBSERVATIONS This complexity is addressed by (1) providing an accessible survey of genotype-phenotype mappings across different GDDs, focusing on psychopathology, cognition, and brain anatomy, and (2) detailing both methodological and mechanistic sources for observed phenotypic convergences and divergences. This effort yields methodological recommendations for future comparative phenotypic research on GDDs as well as a set of new testable hypotheses regarding aspects of early brain patterning that might govern the complex mapping of genetic risk onto phenotypic variation in neuropsychiatric disorders.

CONCLUSIONS AND RELEVANCE A roadmap is provided to boost accurate measurement and mechanistic interrogation of phenotypic convergence and divergence across multiple GDDs. Pursuing the questions posed by GDDs could substantially improve our taxonomical, neurobiological, and translational understanding of neuropsychiatric illness.

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Supplemental content

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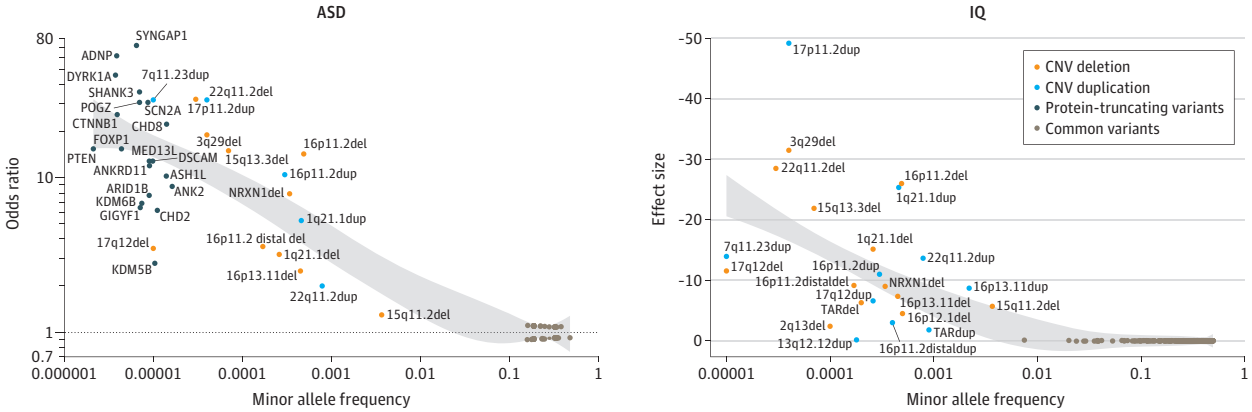
Gene dosage disorders (GDDs), including aneuploidies and copy number variations (CNVs; defined as deletions or duplications of genomic segments greater than 1000 base pairs) associated with neurodevelopmental disorders, provide a powerful yet relatively untapped means of studying genotype-phenotype mappings in humans. Because GDDs are defined by haploinsufficiency or triplosensitivity of specified sets of genes, they provide a solid genetic grounding unavailable for most common single-nucleotide variants (SNVs). GDDs also affect human brain and behavior with effect sizes typically an order of magnitude greater than individual common variants (**Figure 1**[1-6]; eTable in the Supplement). Moreover, the incidence rates of aneuploidies and the most frequent recurrent CNVs are sufficiently high (eg, prevalence between 0.001 and 0.004) that each variant can be phenotyped at the group level—typically, in samples of more than 50 carriers. The large effect sizes and prevalence rates for some GDDs provide a unique opportunity to test for convergent and divergent genetic effects within and across behavior, cognition, and brain structure (eFigure 1 in the Supplement). The unambiguous gene content of GDDs means that observed phenotypic convergences and divergences can be easily contextualized against existing functional genomic annotations of the human brain at diverse cellular, temporal, and spatial scales.[7]

This narrative review harnesses GDDs to provide a fresh window into both basic and clinical aspects of genotype-phenotype mappings in the human central nervous system. We survey available behavioral, cognitive, and neuroimaging data and assess the degree to which different GDDs induce distinct phenotypic outcomes in humans. Then, we consider methodological and biological phenomena that might account for the observed patterns of phenotypic convergence and divergence across GDDs. The answers to these 2 broad questions have major implications for our theoretical and empirical understanding of genotype-phenotype mappings with direct consequences for how we understand and try to treat psychiatric illness.

Convergence and Divergence of GDDs on Behavior, Cognition, and Brain

The notion that different genetic disorders may be associated with distinct profiles of cognition and behavior was first encapsulated in

Figure 1. Using Gene Dosage Disorders (GDDs) to Study Genetic Influences on the Human Brain and Behavior



The association between allele frequency and effect sizes of genetic variation on autism spectrum disorder (ASD) risk and intelligence quotient (IQ). Note how recurrent copy number variants (CNVs) have a higher frequency than similarly impactful rare SNVs (protein-truncating variants). ASD common variant data are from Grove et al[1] and Savage et al[2]. Effect sizes for CNVs are from Huguet et al[3] and Jacquemont et al.[4] The odds ratio of ASD-associated rare variants was calculated by comparing the protein-truncating variant rate between the ASD population[5] and general population.[6] Effect sizes for IQ are shown as the difference between reported mean IQ in the GDD and 100 (1 IQ SD, 15).

the concept of *behavioral phenotypes*, a term coined by William Nyhan, MD, PhD, in 1971 when referring to the distinctive profile of self-injurious behavior in Lesch-Nyhan syndrome.[8] Our field is well-poised to reappraise this classical behavioral phenotype construct[9] given greater access to large genetic cohorts and increased use of standardized tools for cognitive and psychiatric assessment. Together, these research advances are fueling an intense debate regarding whether or not different GDDs can induce different cognitive and behavioral profiles (eFigure 2 in the Supplement). For the purposes of this article, phenotypic convergence and divergence are used to refer to the degree to which different GDDs show similar or dissimilar, respectively, clinical or biological profiles. We distinguish phenotypic convergence and divergence from the notion of pleiotropy (eg, does a given GDD similarly increase risk for elevated scores on several dimensions of psychopathology or does it selectively affect risk for only one, eg, autism-related dimension).

Psychiatric Phenotypes

The bulk of existent associations between GDDs and psychiatric outcomes have come from (1) comparison of variant rates between psychiatric cases and controls (eTable and eFigure 3 in the Supplement) and (2) psychiatric assessment of cohorts ascertained for carriage of a known GDD. Both approaches suggest that individual GDDs may induce partly distinct profiles of psychiatric risk.[10] For example, independent studies of del22q11.2[11,12] and del16p11.2[13] suggest that anxiety disorder diagnoses may be 3-fold more prevalent in del22q11.2 carriers compared with del16p11.2 carries, whereas rates of autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) are equivalent. However, such comparisons are difficult given varying ascertainment and assessment procedures across constituent studies.

More recent studies have sought to address such limitations through one of 2 strategies. First, researchers have identified GDD carriers through national registries[14] or population-based cohorts[15,16] to limit ascertainment biases. To date, this approach has focused on the most frequent CNVs,[15,16] yielding penetrance estimates that are often lower than those from earlier case-control studies. Second, newer comparative studies of clinically ascertained GDD cohorts have harmonized dimensional measurement instruments across cohorts[17,18] and concluded that GDDs vary in both the overall severity of multiple neuropsychiatric features and (albeit to a lesser degree) the profiles of severity across these features. However, owing to the limited inclusion of cognitive measures in such analyses to date, it remains unclear if, for example, different levels of verbal ability across GDDs could inflate apparent similarities in psychopathology by biasing standard clinical assessments that rely on verbal reports.[19]

Thus, although it is clear that multiple GDDs share the capacity to increase risk for neuropsychiatric diagnoses like ASD, ADHD, schizophrenia, and intellectual disability (ID),[20] it remains unclear if different GDDs converge on the same profile of relative risks across these diagnostic outcomes. Addressing this question will require population-based comparisons using the same assessments or diagnostic outcomes across groups.[15] Furthermore, diagnostic outcomes themselves may be fundamentally limited in their resolution to capture phenotypic convergences and divergences between GDDs given the multidimensional and often diagnostically ambiguous nature of psychiatric symptomatology (eFigure 2 in the Supplement).

Cognitive Phenotypes

To date, the vast majority of cognitive genomics research has focused on general intelligence (IQ or *g*)[2,21,22] rather than specific cognitive domains or tests, finding that GDDs are associated with decrements in general cognitive ability, although the effect size of this decrement varies across disorders[5,22,23] (eTable in the Supplement). A similar observation holds for the broader landscape of the ultra-rare or nonrecurrent CNVs too rare to be studied individually.[22,24] This research focus on general intelligence reflects the clinical relevance of intelligence and methodological issues with comparing cognitive performance across samples.[25] Although it is now well established that different GDDs have the

capacity to lower general cognitive ability, it remains unknown if such clinical convergence necessarily reflects mechanistic convergence at other levels of analysis, such as transcriptomes, cell types, or macroscale brain networks.

Analysis of finer-grained subcomponents of cognition provides some evidence for dissociable profiles of cognitive impairment across different GDDs. For example, dosage abnormalities of the X chromosome have preferential effects on either verbal or nonverbal functioning based on the direction of dosage abnormality; visuospatial impairments tend to exceed verbal impairments in Turner syndrome (45,XO), whereas the opposite is true for X supernumerary disorders, such as XXY syndrome or XXX syndrome.[26] Relative effects on measures of verbal and visuospatial skills have also been reported for many other GDDs, including del7q11.23 (William syndrome; visuospatial impairment more than verbal[27]) and del16p11.2 (visuospatial impairment more than verbal[28,29]).

Several attempts to investigate recurrent CNVs across cognitive domains in unselected populations have provided evidence that individual CNVs differently influence specific cognitive abilities[23,30] (**Figure 2**; eFigure 4 in the Supplement). However, given psychometric concerns about tasks used and the relatively small number of variants investigated, this area of research is still an open topic. Because current estimates suggest that half of the coding genome (approximately 10 000 genes) with the highest intolerance to haploinsufficiency affect cognitive abilities when deleted,[22] it is unlikely that we will have access to cohorts sufficiently powered to investigate specific cognitive profiles for very rare or nonrecurrent GDDs in the near future.

Neuroimaging Phenotypes

Most neuroimaging studies of GDDs involve measures of brain anatomy from structural magnetic resonance imaging (sMRI[31-33]). Available publications suggest that almost all GDDs investigated to date have well-replicated effects on total brain volume (TBV),[32] consistent with the highly polygenic nature of brain size.[34] However, the directionality and magnitude of brain size change can vary greatly across GDDs (**Figure 3**A), and this variability is not clearly related to GDD size (eFigure 5A in the Supplement) or the severity of IQ change (eFigure 5B in the Supplement). Of note, the weak relationship between TBV and IQ changes across different GDDs (in terms of both direction and magnitude) echoes the relatively weak association (R^2 = 0.18) between intelligence and TBV in the general population.[35]

GDD effects on global and adjusted regional anatomy also seem to be mechanistically distinct. For example, (1) deletions at the 22q11.2, 16p11.2 proximal, 1q21.1 distal, and 15q11.2 are associated with decreased cingulate and supplementary motor cortex volumes irrespective of their directional effects on TBV,[36] and (2) carriage of supernumerary sex chromosomes increases the volume of parieto-occipital cortices above and beyond any observed changes in TBV.[37] The same GDD can also induce spatially distinct alterations of cortical thickness and surface area,[37-40] highlighting the importance of considering multiple neuroimaging features when assessing the degree of convergence vs divergence of different GDDs on brain organization.

Although most prior investigations have taken a piecemeal approach to assessing the relationship between GDD and brain phenotypes, 2 recent studies have compared regional sMRI changes across multiple (clinically ascertained) GDDs. Seidlitz et al[31] compared profiles of cortical anatomic change across 6 GDDs (Turner syndrome, supernumerary X chromosome aneuploidies, supernumerary Y chromosome aneuploidies, trisomy 21, del22q11.2 syndrome, and del11p13 syndrome) reporting evidence for GDD-differentiated profiles (Figure 3B) that were associated with gene expression patterns for genes within the GDD region, as measured in postmortem tissue from genetically unselected individuals.[31,41] Modenato et al[42] conducted a multivariate analysis of regional brain anatomy in 8 CNVs (22q11.2, 16p11.2 proximal, 1q21.1 distal, and 15q11.2 loci), and identified the cingulate gyrus, insula, supplementary motor cortex, and cerebellum as top regions contributing to shared alterations across these 8 GDDs. While 60% of brain morphometry variance (Cohen *d* profiles) was explained by 2 canonical components, most of the brain alteration profiles were distinct for each CNV. In summary, available studies[31,42] suggest that different GDDs induce different spatial patterns of neuroanatomical change, although there may be a core set of brain features that are vulnerable to many different GDDs.

The diverse psychiatric, cognitive, and neuroimaging literatures reviewed above paint a mixed picture regarding the degree to which different GDDs induce convergent vs divergent effects on psychopathology, cognition, and neuroanatomy. However, a few broad conclusions can be drawn despite the aforementioned limitations of available data. First, publications to date suggest that GDDs that increase risk for psychopathology also tend to negatively affect IQ and also modify global and regional brain anatomy. Second, GDD effects on IQ are well predicted by the cumulative intolerance to haploinsufficiency of genes contained within the deleted or duplicated genomic region, although the proximal neurobiological effectors for this association remain unclear. Third, GDD effects on cognition and behavior appear to be more convergent than those on regional brain anatomy, although this observation could reflect the degree of phenotypic richness and granularity in neuroimages (hundreds of morphometric properties at thousands of spatial locations) that is arguably lacking for measurements of behavior and cognition. It remains to be seen if this apparent discordance in the degree of GDD convergence at neuroimaging and clinical levels will be altered by use of more advanced sMRI analytics or more diverse neuroimaging modalities, such as functional connectivity and diffusion-weighted imaging in GDD research.

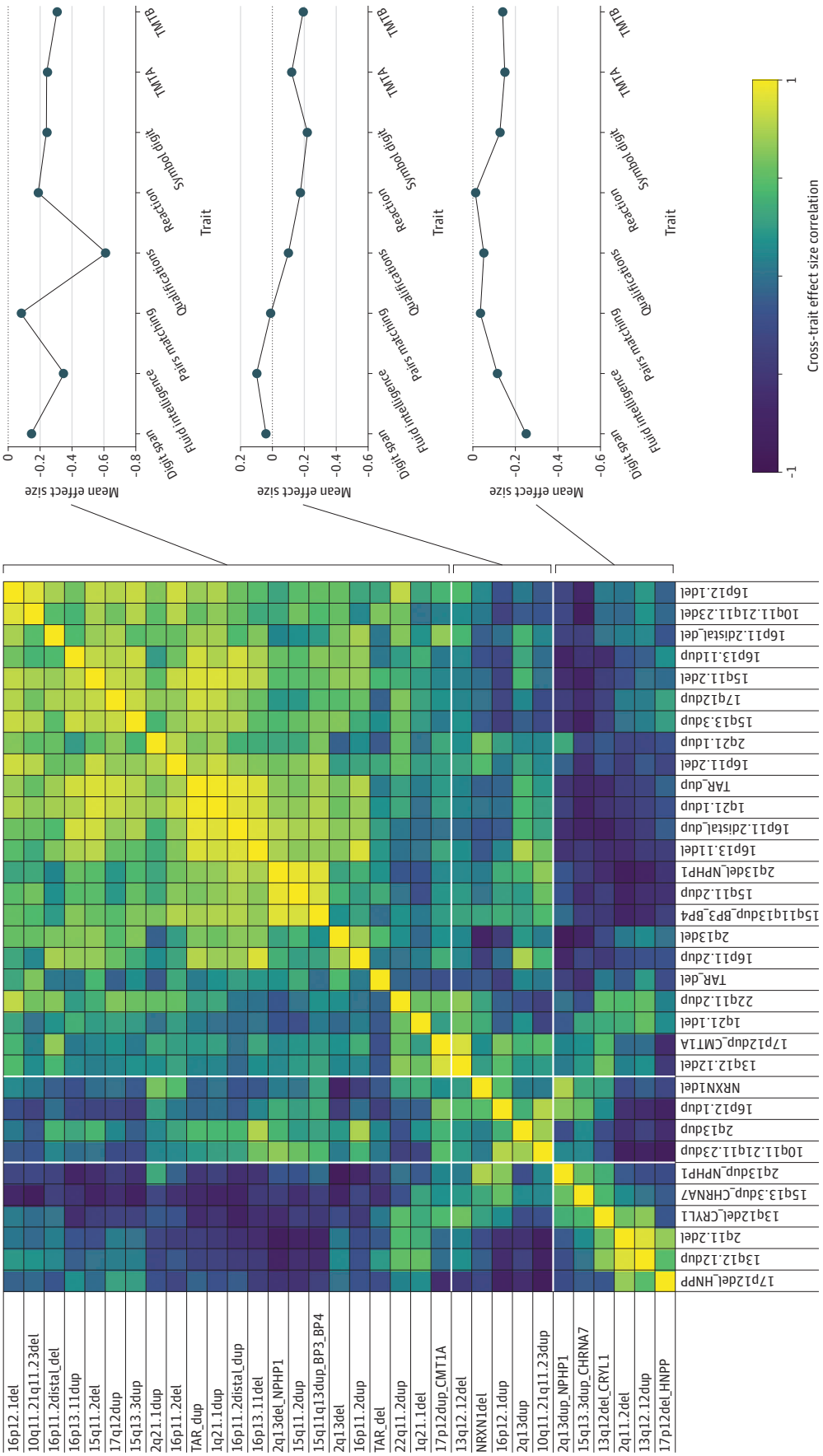
Frameworks for Understanding Phenotypic Convergence and Divergence Across Different Genetic Disorders

Methodological Determinants of Phenotypic Convergence and Divergence

Participant Ascertainment

In most research settings, patients and controls recruited into a study represent a subsample of the total target population. Ascertainment bias occurs when membership of this recruited subsample is nonrandom with respect to other variables of interest. Comparison of clinical phenotypes across different GDD case-control studies will obviously be biased toward finding convergence if different GDDs were ascertained for a specific diagnosis, ie, GDDs identified

Figure 2. Phenotypic Convergence and Divergence for Cognitive Outcomes Across Different Gene Dosage Disorders

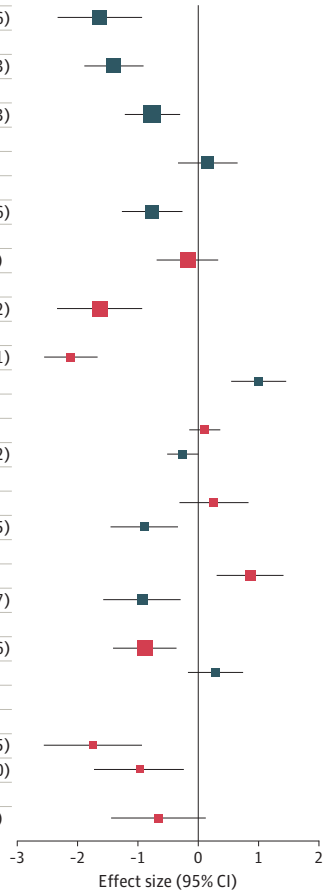


Heatmap generated from data in Kendall et al[30] showing pairwise correlations between 33 different gene dosage disorders for their observed effect sizes on 8 different cognition-related traits (7 cognitive tests plus qualifications). Note the prominent substructure in this correlation matrix (k = 3 suggested by kmeans scree plot), pointing toward partly dissociable profiles of cognitive alteration between subsets of the 33 gene dosage disorders. However, most recurrent copy number variants included in this study showed generally congruent effect size profiles across phenotypes (large cluster with mostly positive inter–copy number variant correlations). Side panels show mean phenotype effects sizes per copy number variant cluster. See eFigure 4 in the Supplement for an example of selected positive and negative cross-trait effect size correlations between selected copy number variant pairs. TMTA and TMTB refer to 2 measures of working memory from the Trail Making Test.

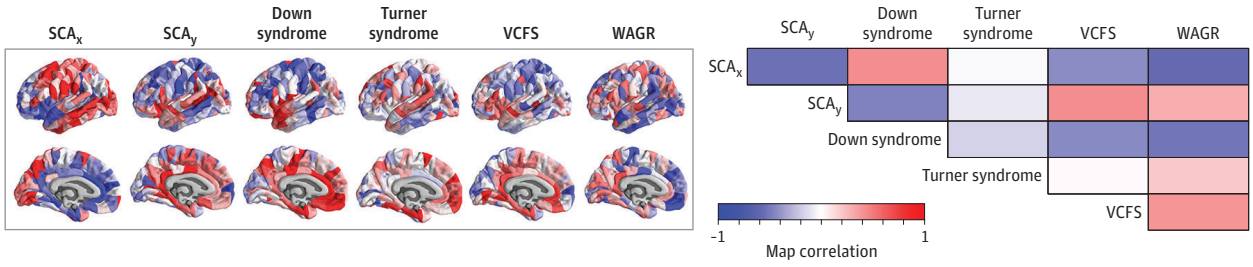
Figure 3. Convergence and Divergence for Structural Neuroimaging Phenotypes Across Different Gene Dosage Disorders

A Changes in TBV

CNV	Studies with TBV	Summary effect size (95% CI)
Down syndrome		
Duplication	7	-1.65 (-2.34 to -0.96)
XXX		
Duplication	6	-1.40 (-1.87 to -0.93)
XXY		
Duplication	9	-0.76 (-1.19 to -0.33)
XYY		
Duplication	5	0.13 (-0.33 to 0.59)
XXYY		
Duplication	6	-0.76 (-1.26 to -0.26)
TS		
Deletion	8	-0.18 (-0.70 to 0.35)
7q11.23		
Deletion	8	-1.63 (-2.34 to -0.92)
1q21.1 distal		
Deletion	1	-2.12 (-2.53 to -1.71)
Duplication	1	1.03 (0.56 to 1.50)
15q11.2		
Deletion	1	0.09 (-0.15 to 0.33)
Duplication	1	-0.25 (-0.48 to -0.02)
16p11.2 distal[a]		
Deletion	1	0.26 (-0.32 to 0.84)
Duplication	1	-0.90 (-1.45 to -0.35)
16p11.2 proximal		
Deletion	3	0.87 (0.36-1.36)
Duplication	3	-0.93 (-1.52 to -0.37)
22q11.2		
Deletion	9	-0.92 (-1.42 to -0.36)
Duplication	1	0.29 (-0.14 to 0.72)
15q11-q13		
Deletion		
AS	2	-1.76 (-2.56 to -0.95)
PWS	4	-0.99 (-1.69 to -0.20)
SHANK3		
Deletion	1	-0.62 (-1.42 to 0.18)



B Maps of cortical anatomy change



A, Summary of reported changes in total brain volume (TBV) for multiple gene dosage disorders. Effect sizes are Cohen *d* values. See eFigure 5 in the Supplement for scatterplots comparing effect sizes of gene dosage disorders on TBV vs gene dosage disorder gene count and gene dosage disorder effect sizes on IQ. B, Maps of cortical anatomy change (altered regional morphometric similarity) in 6 gene dosage disorders and the correlation of these maps to spatial profiles of expressions in the human cortex of the respective gene dosage disorder genes (from Seidlitz et al[31]). The orange color represents a deletion, and the blue color represents a duplication. AS indicates Angelman syndrome; CNV, copy number variant; Down syndrome (trisomy chromosome 21); NA, not applicable; PWS, Prader-Willi syndrome; SCA_x, carriage of supernumerary X chromosome; SCA_y, carriage of supernumerary Y chromosomes; TS, Turner syndrome (X monosomy); VCFS, velocardiofacial syndrome (del22q11.2); WAGR, Wilms tumor, aniridia, genitourinary problems, and mental retardation (del11p13).

in an ASD clinic will show increased convergence. More generally, 2 GDDs will tend to show greater phenotypic overlap if there is a shared predictor of ascertainment as a case for both GDDs. This bias can operate on at least 2 different levels.

First, identification of GDDs in most clinical settings is dependent on the presence of motor and language delays, cognitive deficits, or behavioral difficulties. These phenotypes therefore often show inflated prevalence and comorbidity across multiple GDD

cohorts ascertained clinically.[43,44] This phenomenon is amplified by the fact that multiple comorbidities and greater impairment increases the likelihood of recruitment into clinical cohorts.[44,45] There is direct evidence from studies of diverse GDDs including sex chromosome aneuploidies[46,47] and CNVs[12,14,16] that clinically ascertained carriers tend to show more severe phenotypes than nonclinically ascertained carriers.

Second, use of supercontrols as the comparison group for different GDD cohorts may also artificially increase phenotypic convergence between GDDs. For example, unselected cohorts, such as the UK Biobank, tend to be composed of individuals with lower levels of socioeconomic deprivation and self-reported health conditions than the general population.[48] Because similar biases are shared by convenience samples of controls,[49,50] then any dimensions of psychopathology that correlate with these variables are likely to be biased toward showing shared impairments across different GDDs in comparison with such controls.

Several study design choices can help limit ascertainment biases (**Box**). One approach involves sampling GDD carriers and noncarrier controls in a population-based sample or birth cohorts.[51] A second approach is comparing phenotypes in GDD carriers with their noncarrier first-degree relatives as a control group,[52,53] as some sources of ascertainment bias will be shared within families. Partial control for ascertainment bias can also be achieved by focusing on prenatally diagnosed GDD carriers, for whom receipt of a diagnosis cannot be predicated on behavioral phenotypes.[46,54] Such research approaches have been shown to modify penetrance estimates when applied to individual GDDs,[15,16,52] and an important goal for future research will be probing their consequences for the degree of phenotypic convergence vs divergence between different GDDs.

Phenotypic Measurement

While it is intuitively appealing to compare GDDs for observed rates of different psychiatric diagnoses, this approach is fundamentally challenged by the limitations of diagnostic nosology in psychiatry.[55] First, the diagnostic criteria codified in *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*, and *DSM-5* can allow a given diagnostic category to be assigned to wildly different clinical presentations.[56] Second, because individuals often meet criteria for several diagnostic constructs,[45] diagnostic status is more of a combinatorial profile than a binary assignment, complicating analysis of diagnostic convergence between different GDDs. Third, patients can show significant levels of psychopathology while remaining below diagnostic thresholds, and these subthreshold clinical features, which can be meaningful predictors of outcome,[57] are lost by focusing on diagnoses alone. Finally, the developmental patterning of clinical features (eg, ASD features typically emerge in childhood and mood disorders typically emerge after puberty)[58] and the challenges of diagnosing childhood-onset disorders in adulthood[59] make the timing of assessment an important potential modulator of observed diagnostic convergence vs divergence between different GDDs. It is possible to counter these potential measurement issues through methodological choices, but the ideal study design (Box)—prospective and longitudinal collection of deep phenotypic dimensional and diagnostic data in a standardized manner across multiple GDD groups—is hard to execute.

Box. Methodological Recommendations When Assessing Phenotypic Convergence vs Divergence Across Different Gene Dosage Disorders (GDDs)

Value of GDDs for Mapping Genetic Influences on the Human Brain
- Known gene content (compared with functional annotation for common intergenic SNVs)
- Large effect sizes on brain and behavior (compared with smaller effects of individual common SNVs)
- Prevalence of aneuploidies and recurrent CNVs permits phenotyping of individual variants at the group level
- Risks of ascertainment bias and phenotypic complexity can be addressed as detailed below

Prospective Studies to Compare GDD Phenotypes
- Recruit GDDs from large population-based or cross-disorder sampling frame to acquire homogeneous phenotypes across GDDs
- Multidisciplinary teams with domain expertise in diverse GDDs and phenotypes
- Include proband and family advocates
- Create a data resource with the scientific community

Minimize Ascertainment Bias While Maximizing Sample Size per GDD Cohort
- Truly random sampling requires large population-based genetic screens where the number to be screened is dependent on the prevalence of the GDD
- Including first-degree relatives of GDD probands minimizes some aspects of ascertainment bias
- Such screens require international consortia

Gather Deep Phenotypic Data Standardized Across GDDs
- Clinical complexity necessitates comprehensive diagnostic interviews
- Questionnaire-based rating scales validated across development and cognitive abilities
- Multisite consortia including neuroimaging require matched controls at each scanning site
- Apply homogenous data quality assessment and control practices across GDD cohorts

Tailor Statistical Analyses to Resolve Phenotypic Convergence vs Divergence
- Use metrics that resolve phenotypic similarities and differences across GDDs (eg, η^2, cross-phenotype correlation between GDDs)
- Dimension reduction methods must be robust to stratification by GDD
- Directly compare GDDs across phenotypic layers (eg, psychiatric diagnosis, cognition, brain anatomy, and gene expression)
- Develop convergence and divergence benchmarks (eg, how does the effect size of GDD subtype compare with that for age or psychiatric diagnosis)

Recognize Annotational Gaps When Testing for Mechanistic Convergence
- Bioinformatic approaches are limited by the depth and breadth of annotational resources, limiting inference

Abbreviations: CNV, copy number variation; SNV, single-nucleotide variant.

Statistical Modeling and Interpretation

The intrinsic interdependence among different behavioral,[60] cognitive,[61] and neuroimaging-derived traits[62] means that questions regarding phenotypic convergence and divergence between

different GDDs are ultimately multivariate in nature. Thus, it is more meaningful to assess convergence and divergence by examining the profile of alterations across multiple behavioral measures (or their principal components) rather than conducting mass univariate comparison for individual behavioral measures. Consequently, the degree of phenotypic similarity between 2 GDDs is best thought of as a continuous variable, and there is unlikely to be a single objective threshold for defining convergence vs divergence that is universally applicable across different research and clinical settings.

Potential Biological Bases of Phenotypic Convergence and Divergence

Our consideration of specific biological mechanisms for phenotypic convergence and divergence between different GDDs is framed by the following 3 broad models: (1) diverse coding and regulatory components of the human genome work together as modules to shape biological features, such as gene coexpression networks,[63] cell-types,[64] cellular circuits,[65] and large-scale brain networks,[66] (2) individual neuropsychiatric disorders show distributed alterations across several elements of this lower-dimensional space (ie, molecular pathways[67] and macroscale brain networks[68]), and (3) some of these disruptions represent intermediate phenotypes (or endophenotypes[69]) that translate genetic variation into disease-related outcomes (eFigure 1 in the Supplement). Although these models include assertions that can be hard to test in humans,[70] they nevertheless offer a helpful framework to ask: do different genetic risks for psychopathology converge on common intermediate phenotypes?

To date, most data on mechanistic convergence in neuropsychiatry have come from studies of behaviorally defined psychiatric disorders. Convergence between psychiatric disorders has also been observed at genetic,[71,72] molecular,[67] cellular,[73] and macroanatomical[74] levels. In particular, meta-analysis of multiple psychiatric genome-wide association study have identified hundreds of pleiotropic loci that may contribute to the shared genetic architecture of psychiatric disorders.[73,75] Pleiotropic genes appear to be enriched for those involved in excitatory neurons, chromatin regulation, and neural communication.[76] The expression of these genes peaks during mid-gestation, suggesting that this period is critical for many psychiatric disorders.[73,75-77] Similar functional enrichments have been demonstrated for genes harboring an excess of de novo rare variants in ASD and ID.[5,78] Thus, despite the genetic heterogeneity and allele frequency spectrum, genetic risk factors associated with psychiatric disorders and cognitive abilities may converge on a refined set of molecular functions and developmental epochs. It remains unknown if these points of convergence are also relevant for GDDs. We therefore profiled developmental expression trajectories and cellular expression signatures of genes located in CNVs enriched in neurodevelopmental and psychiatric disorders (ie, ASD and/or schizophrenia) (eMethods and eTable in the Supplement).

We compared genes in CNVs associated with ASD and schizophrenia with genes that harbor de novo rare SNVs in ASD,[5] developmental disorder,[79] and schizophrenia[80] (**Figure 4**). Despite heterogeneity, SNV-implicated ASD, developmental disorder, and schizophrenia risk genes showed heightened expression in prenatal development and neurons. On the contrary, genes within CNVs displayed remarkably heterogeneous developmental and cellular expression signatures without signs of convergence. In addition, we did not detect any specificity that distinguishes recurrent CNVs from nonrecurrent CNVs. This is in line with previous studies showing that recurrent and nonrecurrent CNVs matched for intolerance scores (eg, loss-of-function observed/expected upper bound fraction) confer similar risk for ASD.[81]

This striking difference may stem from the methods used to establish association between psychiatric conditions and the 2 classes of variants (SNVs vs CNVs). Whereas rare SNVs were identified using de novo paradigms (ie, variants and genes with extreme effect sizes on fitness), most CNVs were identified thanks to their recurrence in unrelated individuals. As a result, recurrent CNVs with moderate or even mild effect size on neurodevelopment could reach significant association with a disease. CNV genes may not show the same convergence as SNV genes because (1) CNVs achieve pathogenicity through combined effects of dosage abnormalities in multiple genes that operate across diverse developmental stages and cell types or (2) CNVs achieve pathogenicity through the action of a subset of their constituent genes that do show biological convergent with SNV-implicated genes, but this signal is obscured by the full CNV gene set.

Expanded biological annotation of CNV genes would help to structure hypotheses regarding subsets of genes within each locus that may be especially pertinent for brain-related phenotypes (eg, highly expressed in brain and/or involved in neurodevelopmental pathways[82]). Such annotation would also help to specify potential pathway convergences and divergences between different GDDs. Some axes of brain organization are already amenable to improved annotation with existing technologies (eg, spatial patterns of gene expression in the human brain[83,84] or cell type–specific chromatin architecture[85,86]), while others may remain out of reach for some time to come (eg, interindividual variation in cell type proportions or microcircuit configuration). The observation that most common SNVs associated with psychiatric conditions are in noncoding regions[76] raises the idea that such regulatory architecture may also contribute to the pathogenicity of CNVs.

Summarizing the Path Traveled and Considering the Road Ahead

Beyond the importance of individual GDDs as medical disorders in their own right, comparative research across multiple different GDDs has an immense untapped potential to advance our understanding of psychiatric disease mechanisms more broadly. Such comparative GDD research represents a key accompaniment to comparative research across behaviorally defined patient cohorts.

To date, the most mature body of comparative research across GDDs relates to behavioral phenotypes.[9] However, there has been a rapid recent expansion of theoretical interest in and technical capacity for expanded deep phenotypic comparisons between different GDDs that encompass clinical, neuroimaging, and genomic data. Early findings from this new research suggest that the degree of phenotypic convergence between different GDDs varies substantially across different outcomes, being

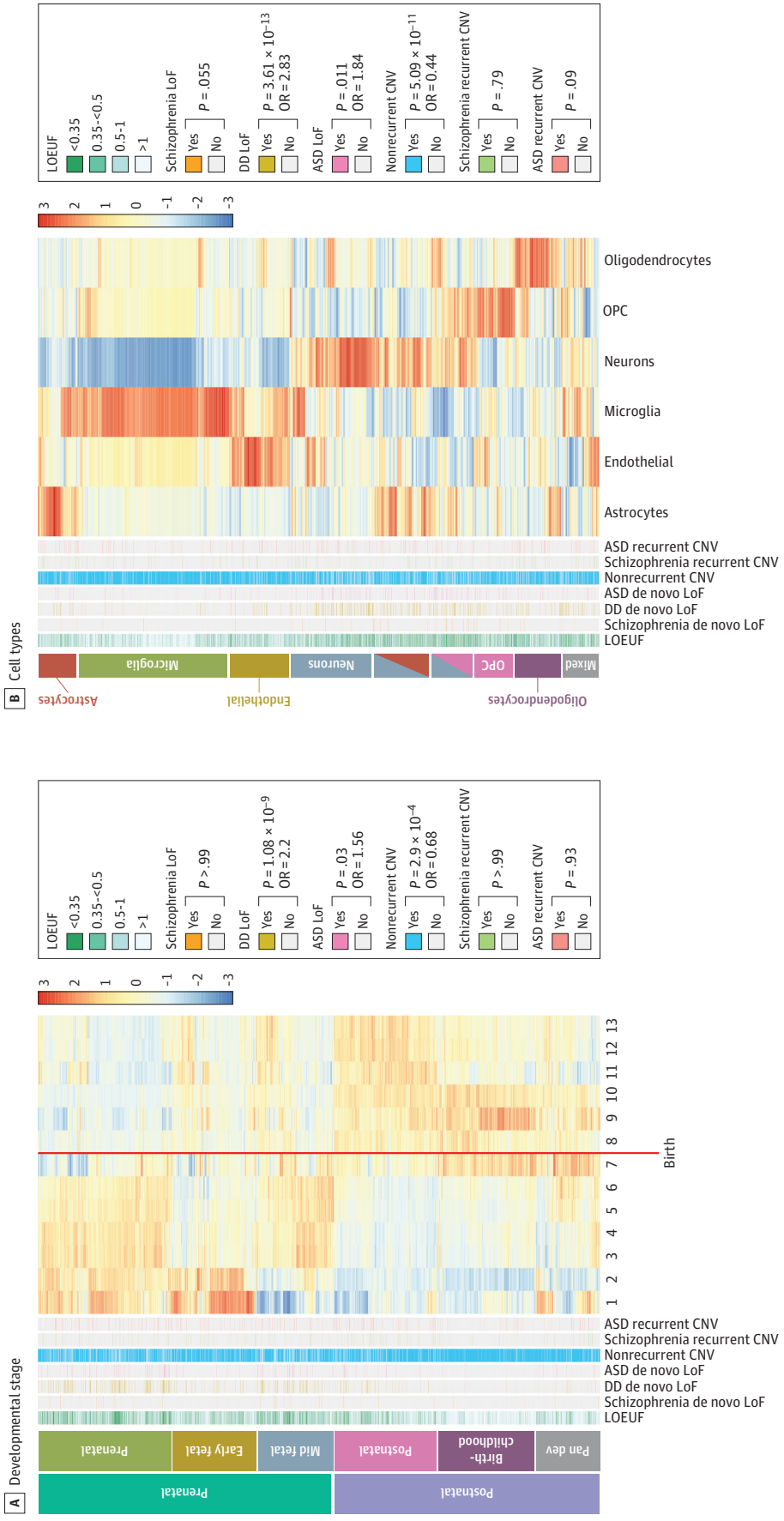


Figure 4. Developmental and Cellular Expression Profiles of Genes Affected by Rare De Novo Single-Nucleotide Variants and Recurrent or Nonrecurrent Copy Number Variants (CNVs)

Normalized scaled expression values of genes affected by rare single-nucleotide variants with large effect sizes (schizophrenia, developmental disorder [DD], and autism spectrum disorder [ASD] de novo loss-of-function [LoF] variation) and genes affected by CNVs (nonrecurrent CNVs and CNVs that are recurrent in schizophrenia and ASD) across developmental stages (A) and different cell types (B). While both single-nucleotide variant–affected and CNV-affected genes show heterogeneity in their expression pattern, single-nucleotide variant–affected genes with low loss-of-function observed/expected upper bound fraction (LOEUF) scores tend to show prenatal and neuronal enrichment (odds ratios [ORs] and *P* values from overrepresentation analysis are depicted). Methods for generation of this figure are detailed in the eMethods in the Supplement. Pan dev indicates pan developmental; OPC, oligodendrocyte precursor.

greatest for broad measures of general cognitive ability (eg, all GDDs negatively impact IQ) and least for fine-grained measures of regional brain anatomy. However, much of the existent cross-GDD research is challenged by several tenacious issues, including ascertainment bias, limited statistical power, and patchy phenotypic coverage. Tackling such limitations (Box) will require prospective funding and design of specially tailored studies. International consortia similar to those that propelled our understanding of common variants (eg, Psychiatric Genetics Consortium) are also required to reach sufficient power. The future collection of high-dimensional phenotypic data across multiple data modalities and GDD subtypes will require development of new statistical approaches for quantifying and specifying phenotypic convergence vs divergence. Alongside working toward this improved human research infrastructure, it is important to expand basic science annotation and enrichment analysis of genomic regions highlighted by GDDs. We illustrate the value of such bioinformatic approaches by systematically profiling developmental and cell type enrichments of both GDD and SNV genes. These analyses suggest that pathogenic GDDs may show less mechanistic convergence than rare pathogenic SNVs and identify several key annotational efforts that could help to test this hypothesis.

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