

# Neuroimaging Findings in Neurodevelopmental Copy Number Variants: Identifying Molecular Pathways to Convergent Phenotypes

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## ABSTRACT

Genomic copy number variants (CNVs) are associated with a high risk of neurodevelopmental disorders. A growing body of genetic studies suggests that these high-risk genetic variants converge in common molecular pathways and that common pathways also exist across clinically distinct disorders, such as schizophrenia and autism spectrum disorder. A key question is how common molecular mechanisms converge into similar clinical outcomes. We review emerging evidence for convergent cognitive and brain phenotypes across distinct CNVs. Multiple CNVs were shown to have similar effects on core sensory, cognitive, and motor traits. Emerging data from multisite neuroimaging studies have provided valuable information on how these CNVs affect brain structure and function. However, most of these studies examined one CNV at a time, making it difficult to fully understand the proportion of shared brain effects. Recent studies have started to combine neuroimaging data from multiple CNV carriers and identified similar brain effects across CNVs. Some early findings also support convergence in CNV animal models. Systems biology, through integration of multilevel data, provides new insights into convergent molecular mechanisms across genetic risk variants (e.g., altered synaptic activity). However, the link between such key molecular mechanisms and convergent psychiatric phenotypes is still unknown. To better understand this link, we need new approaches that integrate human molecular data with neuroimaging, cognitive, and animal model data, while taking into account critical developmental time points. Identifying risk mechanisms across genetic loci can elucidate the pathophysiology of neurodevelopmental disorders and identify new therapeutic targets for cross-disorder applications.

<https://doi.org/10.1016/j.biopsych.2022.03.018>

Neurodevelopmental disorders involve a wide spectrum of neuropsychiatric symptoms as a result of abnormal development of the central nervous system (1). Recent advances in gene discovery have substantially improved our understanding of the genetic architecture of these highly heritable disorders. Clinical phenotypes have been associated with cumulative effects of common variants of small effect (single nucleotide polymorphisms), as well as with rarer, highly penetrant copy number variants (CNVs) whose effect can be further modulated by common variants (2). Several recurrent CNVs were shown to have the highest individual risk for neurodevelopmental disorders in well-powered genome-wide association studies, with odds ratios (ORs) ranging from 2 to 60 for schizophrenia (3–5), compared with  $OR < 1.5$  observed in single nucleotide polymorphisms (6–8). Collectively, single nucleotide polymorphisms carry the greatest fraction of genetic risk for neuropsychiatric disorders (30%–50%) (9), and CNVs contribute to a minority of cases (<10%) (5,10). However, owing to their high penetrance, CNVs have gained considerable interest and are thought to provide the most tractable inroads to better understand the neurobiology of neurodevelopmental disorders.

Several CNVs have been consistently associated with risk of schizophrenia: these include deletions at 1q21.1, 2p16.3 (*NRXN1*), 3q29, 15q11.2, 15q13.3, and 22q11.2 and duplications at 1q21.1, 7q11.23, 15q11.2–q13.1, 16p13.11, and proximal 16p11.2 (4,5,11). Many of these CNVs, as well as others, also increase risk for intellectual disability, autism spectrum disorder (ASD), and attention-deficit/hyperactivity disorder. For example, ASD has been associated with deletions at 1q21.1, 2p16.3 (*NRXN1*), 15q13.3, 22q11.2, and 3q29 and duplications at 1q21.1 and 16p11.2 (12). Notably, 1) different CNVs lead to the same clinical condition (genetic heterogeneity), and 2) the same CNV can be associated with different conditions (pleiotropy). This leads to two central questions: 1) how can different risk genes lead to the same diagnosis, and 2) what factors contribute to the development of one specific disorder rather than the other? We will focus on the first question by addressing the study of convergent disease mechanisms.

The search for convergence can occur on multiple levels, including molecular pathways, neural circuits, and cognitive and brain phenotypes. Systems biology approaches allow us to treat genes as interactive networks, where convergent

molecular pathways have been identified across genetic risk variants and across neurodevelopmental disorders. In recent years, magnetic resonance imaging (MRI) studies on CNV cohorts have led to important discoveries on genetic drivers of altered brain structure and function. However, identifying convergent brain effects and linking cellular mechanisms to these changes has proved more challenging. With growing initiatives of data-sharing and large-scale collaborations across research groups, exciting opportunities are emerging to combine multidimensional data from neuroimaging, cognitive, and bioinformatics studies to identify key pathogenic mechanisms in the path from genome to clinical phenotypes.

In this narrative review, we provide an overview of biological findings on CNVs and neurodevelopmental disorders, placing a special focus on both convergent and locus-specific brain abnormalities across CNVs from human and animal studies. We further discuss the need to develop integrated approaches combining multiomics databases (e.g., transcriptomics, proteomics, and metabolomics) with neuroimaging and clinical data to identify relevant disease mechanisms that can be targeted using novel therapies.

### CONVERGENCE IN CNVs AND NEURODEVELOPMENTAL DISORDERS

Early studies showed that schizophrenia-associated CNVs affect genes involved in synaptic activity (3,13). Kirov *et al.* (14) showed that schizophrenia-associated CNVs were enriched for genes involved in postsynaptic density, which was associated with an enrichment of components of NMDA receptor and neuronal activity-regulated cytoskeleton-associated protein complexes. Further studies showed additional enrichments of mutations in targets of the fragile X mental retardation protein (15,16). In the largest genome-wide analysis of neuropsychiatric CNVs published to date, the Psychiatric Genomics Consortium showed that pathway enrichment is more pronounced in deletions than duplications and that deletions are enriched within a highly connected network of synaptic proteins (11). Other studies by this group showed a significant overlap between genes affected by rare and common variants associated with schizophrenia, both converging in genes related to abnormal glutamatergic synaptic function and calcium channel function (7,17). These findings provide strong evidence that disruptions of synaptic functional networks are relevant disease mechanisms underlying schizophrenia. Similarly, ASD-associated CNVs were shown to converge on networks related to synapse development and function, fragile X mental retardation protein targets, and chromatin and transcription regulators (18–20).

Although they are presently characterized as separate clinical conditions, genetic overlap between schizophrenia and ASD has been well documented. Several CNVs implicated in ASD overlap with those found in schizophrenia, and significant overlap was found in several biological pathways, including synapse/neuron projection, cell adhesion/junction, small GTPase signaling, and MAPK (mitogen-activated protein kinase) signaling (21). Forsyth *et al.* (22) examined convergence of common and rare variants in both schizophrenia and ASD, using transcriptomic data from the developing human brain, and found overlapping enrichment in modules involved in

synaptic transmission and neuronal excitability (highly expressed in the postnatal brain) and RNA processing and binding (highly expressed during early fetal development). ASD risk variants additionally showed specific enrichment (not seen in schizophrenia) in modules involved in neuronal differentiation and regulation of both chromatin organization and gene transcription during fetal development. Although these findings suggest a common genetic etiology that may explain the comorbidity of ASD and schizophrenia (23), the distinct association of ASD risk variants with neuronal differentiation during fetal development may explain the earlier onset of ASD relative to schizophrenia, but more studies are needed to validate this hypothesis.

Altogether, these findings suggest that multiple genetic risk variants are likely to converge mechanistically in the path from genome to clinical phenotypes. This leads us to our central question in this review: can such convergence across neurodevelopmental CNVs also be observed at the level of brain and cognition? Recent reviews have highlighted the importance of studying convergent brain (24) and cognitive (25) phenotypes in CNV carriers, while also noting that CNV-specific effects exist. In this review, we will describe emerging findings from cross-CNV studies on convergent cognitive and brain phenotypes and an overview of neuroimaging studies on individual CNV cohorts. We focus on white matter changes from diffusion tensor imaging (DTI) studies and the link between imaging studies and animal models, since morphometric studies have recently been comprehensively reviewed (26).

### CONVERGENT TRAITS IN CNV CARRIERS

Cognitive studies using data from the UK Biobank, a volunteer middle-aged population study where most participants are unaffected by a neurodevelopmental disorder, showed that schizophrenia-associated CNVs lead to significant impairments in cognition and measures of function (e.g., academic qualifications) (27,28). These deficits were modest and varied between CNVs but suggest that carrying a CNV can lead to significant disadvantages in educational achievement, even in carriers who escaped neurodevelopmental conditions.

Chawner *et al.* (29) investigated mainly clinically ascertained children carrying one of 13 neurodevelopmental CNVs. CNV carriers were impaired across all neurodevelopmental, cognitive, and psychopathological traits compared with control subjects. Neurodevelopmental traits were strongly impaired across CNVs, whereas the magnitude of effect was weaker in mental health and cognitive comorbidities across genotypes. Overall, different CNVs had a broadly similar effect on phenotypic outcomes, where distinct effects across CNV groups only accounted for a small proportion of variance (5%–20%, depending on trait) [see Table 3 in Chawner *et al.* (29)]. A recent study by the same author compared autism profiles of both deletions and duplications at 22q11.2 and 16p11.2 loci. Greater variability in autistic traits was found between individuals with the same CNV (74%–97% of the variance) than across CNVs (1%–21% of the variance) (30). These findings suggest that carrying a pathogenic CNV predisposes to a generic neurodevelopmental syndrome with features of intellectual disability, autism, and other psychopathological traits, but that considerable phenotypic variability exists within CNV

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groups. This variability highlights the importance of investigating additional factors (genetic or environmental) that could contribute to variation in clinical phenotypes within the same CNV.

### NEUROIMAGING FINDINGS IN CNV COHORTS

#### Morphometric MRI Findings on Individual CNV Cohorts

The Enhancing Neuro Imaging Genetics through Meta Analysis (ENIGMA) consortium uses meta- and mega-analyses of psychiatric disorders and associated genetic risk variants, gathering large multicenter cohorts. This consortium has provided valuable information on how 22q11.2, 16p11.2 distal, 15q11.2, and 1q21.1 CNVs affect cortical and subcortical brain morphology (Table 1) (31). Morphometric MRI findings from 76 studies on 20 pathogenic CNVs have also been summarized in a recent systematic review (26). This review highlights the moderate to large effects observed across CNV loci on global and regional brain measures, which contrasts with milder effects observed in ASD and schizophrenia (24). Concerning global measures (brain volume, cortical thickness, and surface area), almost all CNVs showed impact on these measures, but the direction of effect was variable across genotypes. For 1q21.1 and 16p11.2, dosage-dependent effects were observed in total brain volume and surface area, which reflect the known associations with head size (Figure 1). The same effects were not seen in global cortical thickness. In regional neocortical measures, effects were variable across CNVs. Finally, in the basal ganglia, limbic system, and cerebellum, duplications mostly led to reductions in volume, whereas deletions had a more variable effect (26).

#### Diffusion-Weighted Imaging Findings on Individual CNV Cohorts

Microstructural changes in white matter tracts can be investigated using DTI (Figure 2A, B). In Table 2, we provide an overview of DTI findings in individual CNV cohorts. The 22q11.2 deletion has been the most studied, with studies reporting lower fractional anisotropy (FA) (32–34), higher FA (35–37), and mixed findings across white matter tracts (38–41); more consistent findings were reported for diffusivity measures (axial diffusivity [AD], radial diffusivity [RD], and mean diffusivity [MD]), with general decreases across studies. ENIGMA-22q conducted the largest DTI study to date on 22q11.2 and found widespread increased FA in deletion carriers compared with healthy control subjects, primarily in the internal capsule, callosal, and corticothalamic tracts, but also lower FA in the fornix-stria terminalis region, superior longitudinal fasciculus, and external capsule (38). Carriers of the 22q11.2 deletion with psychosis showed overall lower AD, RD, and MD compared with 22q11.2 deletions without psychosis. A recent study found opposite effects in DTI measures in 22q11.2 deletion and duplication carriers (higher FA in deletion and lower FA in duplication) (42). Using advanced DTI methods, the authors found that increased FA in deletion carriers was accompanied by higher fractions of primary and secondary fiber populations (F1 and F2, reflecting dominant and nondominant fiber orientation, respectively) and lower extracellular space and was

associated with enlarged cerebrospinal fluid volume and reduced white matter volume. Conversely, lower FA in duplication carriers was accompanied by lower F1 and F2 but was not associated with volumetric changes. This suggests that higher FA in deletion carriers may arise from abnormally densely packed white matter fibers.

Increased FA has also been reported in 15q11.2, 16p11.2, and 7q11.23 (Williams syndrome) deletions. In patients with Williams syndrome, findings are heterogeneous across studies (43–47); the most consistent findings are increased FA in the superior longitudinal fasciculus and decreased FA in the posterior limb of the internal capsule. Similar to observations regarding 22q11.2, the 15q11.2 and 16p11.2 CNVs also showed dosage-dependent effects in white matter (26). Overall, 16p11.2 proximal deletion carriers showed increased FA and AD and decreased RD, and duplication carriers showed opposite effects (48–50) compared with noncarriers. Increased FA in deletion carriers (and lower FA in duplication carriers) was found in the body of the corpus callosum and in the internal and external capsule (48,50). DTI studies on 15q11.2 (BP1-BP2) from our group (51,52), comprising carriers with no clinical diagnoses, found increased FA in deletion carriers in the internal capsule and cingulum, as well as dosage-dependent effects.

One important question is how white matter changes in CNV carriers relate to findings in idiopathic neuropsychiatric disorders. Most large-scale DTI studies have reported decreased rather than increased FA in neurodevelopmental disorders, such as schizophrenia (53), bipolar disorder (54), and ASD (55). In a meta-analysis, ENIGMA-Schizophrenia reported widespread reductions in FA and higher MD and RD in patients with schizophrenia. Lower FA was found in many white matter tracts that connect frontal, parietal, temporal, and limbic areas (53). A mega-analysis from the Japanese Cognitive Genetics Collaborative Research Organization consortium showed similar alterations across neurodevelopmental disorders: schizophrenia, bipolar disorder, and ASD showed lower FA in the body of the corpus callosum, and both schizophrenia and bipolar disorder showed lower FA in tracts of the limbic system (e.g., fornix and cingulum) (55). Both 15q11.2 and 22q11.2 deletions are associated with schizophrenia, although with very different odds [OR = 1.3–2.2 and >28, respectively (5,11)]. The increased FA observed in these CNVs is distinct from the widespread decreased FA observed in idiopathic schizophrenia (Figure 2C). Although there is some convergence in DTI findings across CNVs (generally increased FA), these findings do not match with those in general ASD and schizophrenia populations, which may point to different pathophysiological mechanisms in neurodevelopmental disorders associated with these CNVs. These considerations bring us to two main questions: 1) how does increased FA in CNV carriers relate to cognition and risk for psychosis, and 2) what are the underlying mechanisms of FA changes in CNV carriers and neurodevelopmental disorders?

In our recent study, we assessed how white matter changes in 15q11.2 CNV carriers mediated cognitive performance (52). Deletion carriers showed lower performance across several cognitive tests. These effects were partially mediated by lower FA in the posterior thalamic radiation, whereas increased FA in the anterior limb of the internal capsule and the hippocampal

**Table 1. Summary of Morphometric Magnetic Resonance Imaging Findings From ENIGMA CNV Studies**

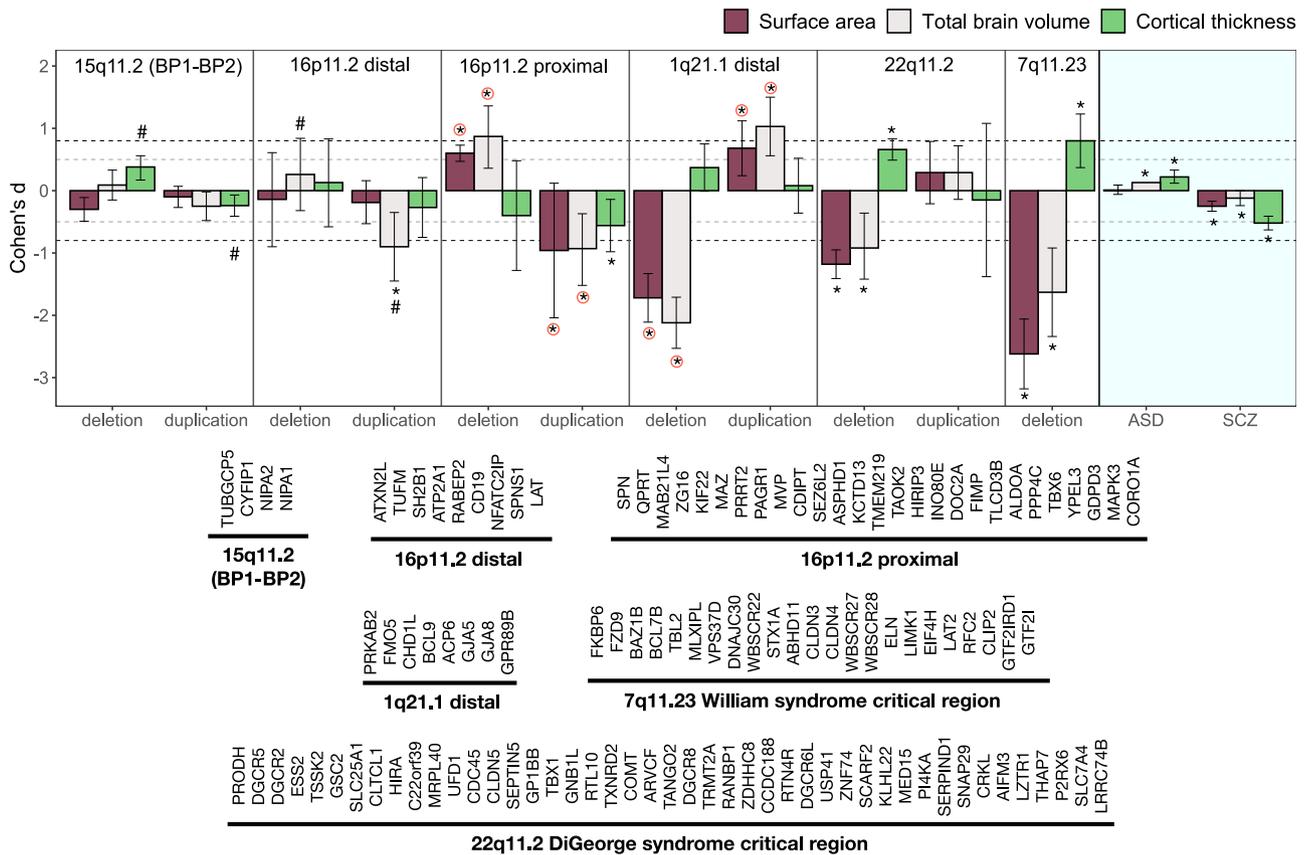
CNV Region	Author, Year	n	Age, Years, Mean (SD)	Global Measures	Subcortical Volumes	Summary Findings
15q11.2 (BP1-BP2)	Van Der Meer <i>et al.</i> , 2020 (56)	Main: 146 del/192 dup/44,266 HC Replication: 57 del/114 dup/981 HC	Main: del = 55.4 (19.3); dup = 55.6 (18.3); HC = 56.1 (18.4) Replication: del = 45.2 (13.9); dup = 46.3 (12.1); HC = 46.9 (13.9)	ICV: NS SA: Del < HC CT: Del > HC > dup	Del < HC NAC	Del carriers showed lower total SA, thicker cortices, and lower NAC volume than HCs. In the replication sample, smaller SA was also seen in del carriers compared with HCs, and meta-analysis of the two samples showed the same pattern of alterations. Differences in CT were more evident in the frontal lobe, anterior cingulate, and precentral and postcentral gyri. Dosage-dependent effects were seen in CT in these regions using linear regression, where dup carriers showed opposite patterns, but with smaller effect sizes than seen in del carriers. In an exploratory analysis, mediation effects of total SA and CT were observed on fluid intelligence.
16p11.2 Distal	Sonderby <i>et al.</i> , 2020 (94)	Main: 12 del/12 dup/6882 HC Replication: 3 del/6 dup/832 HC	Main: del = 27.8 (20.4); dup = 31.2 (19.6); HC = 43.5 (20) Replication: del = 48.7 (24); dup = 47 (15); HC = 46.2 (12)	ICV: Del > HC > dup SA: NS CT: NS	Del > HC > dup NAC, caudate, pallidum, and putamen	Using linear regression, mirrored dosage effects (del > HC > dup) were found on ICV and regional NAC, caudate, pallidum, and putamen volumes. In the replication sample, the same significant dosage effect was observed in the pallidum. Apart from cortical SA, the same direction of effect was observed in both samples.
1q21.1 Distal	Sonderby <i>et al.</i> , 2021 (95)	Main: 28 del/22 dup/37,088 HC Replication: 2 del/5 dup/1150 HC	Main: del = 41.7 (19); dup = 55.4 (12.7); HC = 61.1 (12.8) Replication: del = 53.5 (2.1); dup = 46.4 (16.5); HC = 44.8 (12.4)	ICV: Del < HC < dup SA: Del < HC < dup CT: NS	Del > HC > dup caudate and hippocampus	Using linear regression, mirrored dosage effects (del < HC < dup) were found for ICV and cortical SA. An opposite effect (del > HC > dup) was found in the caudate and hippocampal volumes. The dosage effect on cortical SA was primarily driven by del carriers, and the dosage effect on the caudate and hippocampus was primarily driven by dup carriers. A meta-analysis including the replication sample strengthened these findings and revealed additional significant between-group differences in the NAC, caudate and putamen. Differences in cortical surface were more evident in the frontal lobe, cingulate cortex, and some regions of parietal and temporal lobes. Regionally, differences in CT were found in the superior temporal region (del > HC > dup) and in the pericalcarine region (del < HC < dup). Decreases in cortical SA and ICV contributed to poorer cognitive performance in del carriers.

**Table 1. Continued**

CNV Region	Author, Year	n	Age, Years, Mean (SD)	Global Measures	Subcortical Volumes	Summary Findings
22q11.2	Sun <i>et al.</i> , 2018 (96)	474 del/315 HC	del = 18 (9.2); HC = 18.2 (8.6)	ICV: NA SA: Del < HC CT: Del > HC <sup>a</sup>	NA	Del carriers showed widespread reductions in SA and globally thicker cortex. <sup>a</sup> The most prominent SA reductions were found bilaterally in the medial occipital and anterior cingulate cortex. Overall, 22q11.2 del carriers with psychosis showed thinner cortices compared with del carriers without psychosis. Effect sizes from these comparisons correlated with those found in the ENIGMA-schizophrenia case-control study. The larger 3-Mb 22q11.2 deletion (LCRA-LCRD) had significantly reduced cortical SA compared with the smaller 1.5-Mb deletion (LCRA-LCRB).
	Ching <i>et al.</i> , 2020 (97)	533 del/330 HC	del = 17.85 (8.6); HC = 18.14 (9.24)	ICV: Del < HC SA: NA CT: NA	Mixed	Del carriers showed lower total ICV and lower thalamus, putamen, hippocampus, and amygdala volumes. Del carriers also showed increased lateral ventricle, caudate, and NAC volumes. Subcortical shape analysis revealed complex spatial patterns of morphometric differences. The larger 3-Mb 22q11.2 deletion (LCRA-LCRD) led to more pronounced subcortical alterations than the smaller 1.5-Mb deletion (LCRA-LCRB). Del carriers with psychosis showed smaller hippocampus, amygdala, and right thalamus volumes and ICV compared with del carriers without psychosis. Effect sizes for these comparisons correlated with those from ENIGMA-schizophrenia, major depressive disorder, bipolar disorder, and obsessive-compulsive disorder case-control studies but did not correlate with effect sizes from ENIGMA ASD and ADHD case-control studies.

ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; BP, breakpoint; CNV, copy number variant; CT, cortical thickness; del, deletion; dup, duplication; ENIGMA, Enhancing Neuro Imaging Genetics through Meta Analysis; HC, healthy control subject; ICV, intracranial volume; LCR, low copy repeat; NA, not applicable; NAC, nucleus accumbens; NS, nonsignificant; SA, surface area.

<sup>a</sup>With exception of a focal thickness reduction in the parahippocampal and superior temporal gyri and left caudal anterior cingulate cortex.

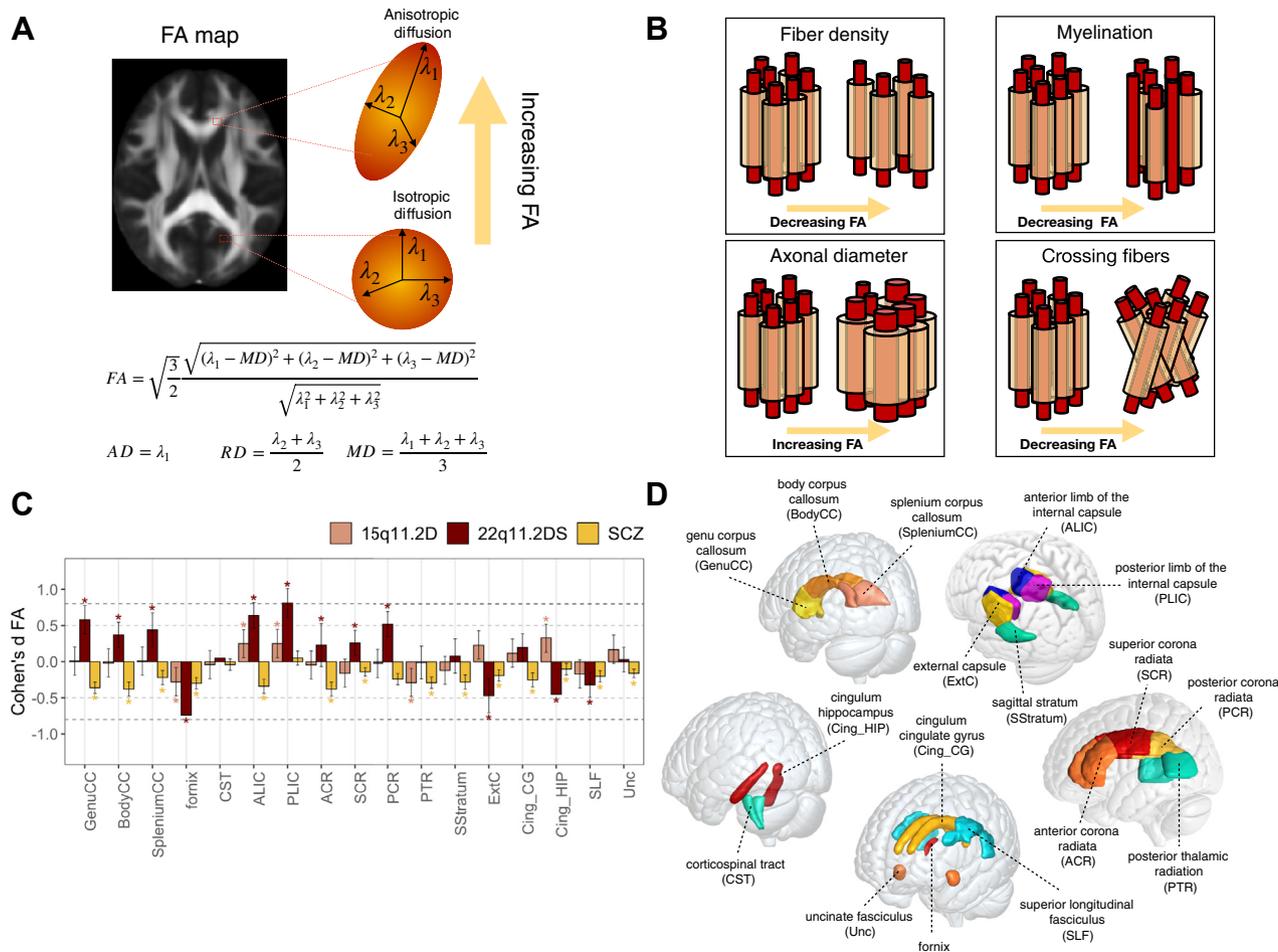


**Figure 1.** Effects of 15q11.2 (BP1-BP2), 16p11.2 distal, 16p11.2 proximal, 1q21.1 distal, 22q11.2, and 7q11.23 CNVs on global cortical surface area, total brain volume, and cortical thickness. For the 16p11.2 distal CNV, intracranial volume was used instead of total brain volume. Effects of idiopathic ASD and SCZ are also shown for comparison. Effects sizes and 95% confidence intervals were obtained from a recent meta-analysis (26) and represent the summary estimates of the effect size of each CNV including all neuroimaging studies reporting total brain volume, cortical surface area, and thickness. Data for idiopathic ASD and SCZ were also represented in this meta-analysis and were obtained from the largest studies to date. Statistically significant effects from the meta-analysis are represented by an asterisk (\*). Circled asterisks represent measures where reciprocal effects were observed for deletions and duplications in each genomic region. Hash symbol (#) represents reciprocal effects that were observed in ENIGMA CNV studies when performing a dose response analysis using linear regression (Table 1). For 1q21.1 distal and 16p11.2 proximal CNVs, dosage-dependent effects were observed in intracranial volume and surface area, which reflect the known associations with head size (1q21: increased for duplication, decreased for deletion; 16p11.2: increased for deletion, decreased for duplication). Carriers of the 1q21.1 distal, 22q11.2, and 7q11.23 deletions show similar effects on global measures (decreased surface area and total brain volume and increased cortical thickness), whereas 16p11.2 proximal deletion carriers show opposite effects. Genes within each CNV region are also shown. ASD, autism spectrum disorder; CNV, copy number variant; ENIGMA, Enhancing Neuro Imaging Genetics through Meta Analysis; SCZ, schizophrenia.

portion of the cingulum contributed to better cognitive scores. Duplication carriers performed similarly to control subjects as previously reported (56,57). Although these findings in 15q11.2 indicate potential compensatory mechanisms associated with increased FA, studies on other CNVs suggest a rather negative impact of increased FA. In patients with Williams syndrome, higher FA in the superior longitudinal fasciculus was negatively correlated with visuospatial scores (43); in 22q11.2 deletion carriers, higher FA in the cingulum was associated with more positive symptoms (41), higher FA in the inferior fronto-occipital fasciculus was associated with more prodromal symptoms (36), and overall higher FA and lower AD, RD, and MD were associated with ultra-high risk status for schizophrenia, whereas low baseline IQ and prematurity were associated with lower FA and higher AD, RD, and MD (37). Furthermore, increased FA was associated with cognitive

decline in young participants with 22q11.2 deletion (58). These findings suggest that abnormal increased FA in both 22q11.2 and 7q11.23 deletion carriers may be associated with impaired cognitive function.

The underlying mechanism of FA changes in CNV carriers is unclear. The most recent DTI study on 22q11.2 associates higher FA in deletion carriers with volumetric changes (42). Similar studies in other CNVs are needed, although substantial research is still needed to confidently relate DTI data to underlying cellular changes (59). Animal models can provide a more in-depth investigation of underlying cellular causes (see Insights From Animal Models). Longitudinal studies can help us determine how changes in white matter microstructure occur during development and how these relate to volumetric abnormalities. A recent longitudinal study showed that 22q11.2 deletion carriers (age = 5–35 years) had consistently



**Figure 2.** Microstructural changes in white matter tracts can be investigated using DTI. **(A)** Schematic representation of DTI-derived measures. The most widely reported measure from this tensor model is FA, which reflects the degree to which diffusion is directly constrained. FA values are close to 0 in isotropic diffusion (no constraints) and close to 1 in anisotropic diffusion (restricted diffusion). MD is the average diffusion across all directions, which reflects the average molecular motion irrespective of direction. AD and RD represent movement of molecules parallel (main direction of movement) and perpendicular to axons, respectively (102). **(B)** Representation of microstructural changes that can affect FA. **(C)** White matter microstructure alterations, found in the largest DTI studies in deletion carriers of 15q11.2 (BP1-BP2) (15q11.2D) and 22q11.2 (22q11.2DS), and in patients with idiopathic SCZ (38,52,53,103). Effect sizes on 15q11.2 deletion were extracted from a UK Biobank (population-based) study (102 15q11.2D and 28,951 HC; mean age: 15q11.2D = 55.4 [range: 40–68] and HC = 54.8 [range: 40–70]), and effect sizes on 22q11.2 deletion (334 22q11.2DS and 260 HC; mean age: 22q11.2DS = 16.88 and HC = 16.55, range: 6–52) and patients with SCZ (1963 SCZ and 2359 HC; mean age: SCZ = 36.22 [range: 18–77] and HC = 36.14 [range: 18–86]) were extracted from ENIGMA consortium studies. Statistically significant effects are represented by an asterisk (\*). Effect sizes are larger in 22q11.2 deletion. Both copy number variants led to higher FA in the internal capsule, contrasting with lower FA in patients with SCZ. Similar effects are found in the fornix, with decreased FA across the three groups. Opposite effects are found in the hippocampal portion of the cingulum between both copy number variants, where 22q11.2 deletion carriers showed decreased FA, similar to patients with SCZ, but 15q11.2 deletion carriers showed increased FA in this tract. Both 15q11.2 deletion carriers and patients with SCZ showed lower FA in the posterior thalamic radiation, but no changes were found in 22q11.2 deletion carriers. There were no significant age-by-diagnosis interaction effects in both 15q11.2 and 22q11.2 studies. In patients with SCZ, average FA skeleton reduced faster with age when compared with HC subjects. **(D)** Anatomical representation of white matter tracts defined by the JHU White Matter Atlas (ICBM-DTI 81), which was used in these studies to define white matter regions. 22q11.2DS, 22q11.2 deletion syndrome; AD, axial diffusivity; DTI, diffusion tensor imaging; ENIGMA, Enhancing Neuro Imaging Genetics through Meta Analysis; FA, fractional anisotropy; HC, healthy control; MD, mean diffusivity; RD, radial diffusivity; SCZ, schizophrenia.

increased FA and decreased AD, RD, and MD in all ages compared with control subjects, and white matter developmental trajectories were similar to control subjects (37). This suggests that white matter anomalies appear early on, possibly during prenatal or early childhood development, but it is still unclear how higher FA relates to onset of psychiatric symptoms in 22q11.2 deletion carriers.

### Convergent Neuroimaging Findings in Cross-CNV-Studies

Individual cohort studies suggest some similarities, but also distinct effects, across CNVs. However, variation in samples, ascertainment methods (e.g., population-based vs. clinical samples), and differences in imaging acquisition and

**Table 2. Summary of Previously Published DTI Studies on Individual CNV Cohorts**

CNV Region	Author, Year	Field Strength	Direction b-Value	n	Age, Years, Mean (SD)	DTI Measures	Summary Findings
15q11.2 (BP1-BP2)	Silva <i>et al.</i> , 2019 (51)	1.5T	17 800 s/mm <sup>2</sup>	30 del/27 dup/ 19 HC	Del = 42.8 (12.5) Dup = 43.5 (13.5) HC = 38.9 (10.6)	FA: Del > HC > dup AD: Mixed RD: Del < HC < dup MD: Del < HC < dup	Whole-brain TBSS: higher FA, lower AD, RD, and MD in del carriers compared with dup carriers. Regional analyses: del carriers had higher FA in ILF_L, PCR_L, PTR_R, Cing_CG_L, ALIC_L, and PLIC; lower AD in BodyCC and SpleniumCC; higher AD in PLIC_L; lower RD in BodyCC, SpleniumCC, SLF, ACR_R, SCR_R, Cing_CG_L, ALIC_L, and PLIC; and lower MD in BodyCC, SpleniumCC, SLF, ACR_R, SCR, PCR_R, and Cing_CG_R compared with dup carriers. HCs showed intermediate values between the two carrier groups.
	Silva <i>et al.</i> , 2021 (52)	3T	50 1000 s/mm <sup>2</sup>	102 del/113 dup/ 28,951 HC	Del = 55.4 (7.3) Dup = 54.8 (7.2) HC = 54.8 (7.4)	FA: Mixed AD: Mixed RD: Mixed MD: Mixed	Regional analyses: del carriers showed higher FA in ALIC_L, PLIC_L, Cing_HIP_L, and lower FA in PTR_R; decreased AD in BodyCC and SpleniumCC; higher AD in ALIC_R and PLIC_L; lower RD in Cing_HIP; higher RD in fornix and PTR_R; lower MD in BodyCC and Unc_L; and higher MD in fornix compared with HCs. Dup carriers showed lower FA in Cing_CG_R and Cing_HIP and higher RD in Cing_HIP_R compared with HCs. FA changes in ALIC_L, PTR_R, and Cing_HIP_L partially mediated cognitive performance in del carriers. Lower FA in PTR_R contributed to worse cognitive scores, whereas higher FA in ALIC_L and Cing_HIP_L contributed to better cognitive scores in del carriers.
16p11.2 (BP4-BP5)	Owen <i>et al.</i> , 2018 (58)	3T	30 1000 s/mm <sup>2</sup>	22 del/23 HC	Del = 11.6 (2.1) HC = 12.5 (2.2)	FA: Del > HC AD: Del > HC RD: NS MD: Del > HC	Whole-brain TBSS: del carriers showed extensive regions of higher FA, MD, and AD compared with HCs: higher FA in BodyCC, SCR, and PLIC; and higher AD and MD throughout the supratentorial WM and some brainstem tracts (corticospinal and pontine crossing fibers). When STV was added as a nuisance regressor, only higher AD remained significant. Tractography-based analysis showed higher FA and AD bilaterally in the IntC and ExtC. After STV regression, the higher FA in the ExtC was no longer significant.

Table 2. Continued

CNV Region	Author, Year	Field Strength	Direction	<i>n</i>	Age, Years, Mean (SD)	DTI Measures	Summary Findings
			b-Value				
	Berman <i>et al.</i> , 2015 (98)	3T	DTI: 30 1000 s/mm <sup>2</sup> HARDI: 64 3000 s/mm <sup>2</sup>	36 del/45 HC	Del = 11.6 (2.3) HC = 12.2 (2.9)	FA: NS AD: Del > HC RD: Del > HC MD: Del > HC	Fiber tractography to delineate two WM tracts known to be implicated in language processing: the auditory radiation (HARDI data) and arcuate fasciculus (DTI data). Del carriers had higher MD and RD in the arcuate fasciculus, in both the right and left hemispheres, and higher AD in the right arcuate fasciculus. Del carriers showed higher MD and AD in the auditory radiation.
	Chang <i>et al.</i> , 2016 (49)	3T	30 1000 s/mm <sup>2</sup>	Pediatric: 30 del/13 dup/34 HC Adult: 7 del/22 dup/28 HC	Pediatric: del = 11.6 (2.3); dup = 11.2 (2.8); HC = 12.2 (2.7) Adult: del = 39.6 (9.3); dup = 38.4 (9.8); HC = 38.3 (10.1)	FA: Del > HC > dup AD: Del > HC < dup RD: Dup > HC MD: Del > HC, dup > HC	Pediatric del carriers showed extensive higher FA, AD, and MD throughout the supratentorial WM relative to HCs. Pediatric dup carriers showed opposite changes, with lower FA and higher RD and MD. Adult del carriers showed increased AD in association, limbic, and projection tracts relative to HCs, similar to what was seen in the pediatric del cohort. Similar to the pediatric dup cohort, adult dup carriers showed lower FA and higher RD relative to HCs and additional decreases in AD.
	Ahtam <i>et al.</i> , 2019 (99)	3T	30 1000 s/mm <sup>2</sup>	21 del/18 HC	Del = 10.91 (2.09) HC = 12.58 (1.99)	FA: NS AD: Del > HC RD: Del > HC MD: Del > HC	Tractography study of bilateral dorsal language pathways. Del carriers showed higher AD and RD in the bilateral anterior segment of the arcuate fasciculus, increased MD and RD in the right long segment of the arcuate fasciculus, and higher AD in Unc.
	Villalón <i>et al.</i> , 2021 Abstract only (48)	3T (pooled data)	Multishell acquisitions (Consortium data)	59 del/62 dup/ 192 HC	Del = 14 (7.3) Dup = 27.9 (13.9) HC = 28.8 (15.5)	FA: Del > HC > dup AD: Del > HC > dup RD: Del > HC < dup MD: NA	Mirror gene dosage effects of del and dup at the global level for FA, AD, RD, ND, and ICVF. Del carriers showed higher FA in the CR, IntC, ExtC, cingulum, and BodyCC compared with HCs, whereas dup carriers showed mirror effects in many of the same regions. Del carriers showed lower RD and higher AD, whereas dup carriers showed higher RD and lower AD. NODDI measures showed lower ND in del carriers, whereas dup carriers showed higher ND and lower ICVF compared with HCs.

Table 2. Continued

CNV Region	Author, Year	Field Strength	Direction		Age, Years, Mean (SD)	DTI Measures	Summary Findings
			b-Value	n			
7q11.23 (WS)	Hoeft <i>et al.</i> , 2007 (43)	3T	6 815 s/mm <sup>2</sup>	20 WS/10 DD <sup>a</sup> / 10 HC	WS = 26.8 (7.5) DD = 23.2 (5.5) HC = 27.8 (9.5)	FA: Mixed AD: NA RD: NA MD: NA	Compared with HCs, patients with WS showed higher FA in SFOF_R, SLF, ExtC, Unc, IFO, ILF/IFOF, and forceps major and lower FA in SpleniumCC, PLIC, corticopontine tract, CST, and STR. Compared with DD individuals, patients with WS showed higher and lower FA in the same regions. Greater FA in SLF_R was negatively correlated with visuospatial construction scores.
	Arlinghaus <i>et al.</i> , 2011 (44)	3T	32 1000 s/mm <sup>2</sup>	16 WS/16 HC	WS = 24 (5.5) HC = 23 (4)	FA: Mixed AD: NA RD: NA MD: NA	Subjects with WS had lower FA in SpleniumCC, CR, ExtC, PLIC, Unc/IFOF, and SLF (some regions) and higher FA in IFOF/ILF, SLF (some regions), and Unc. Tract-based analysis revealed that different portions of the Unc had increased and decreased FA in patients with WS.
	Avery <i>et al.</i> , 2012. (45)	3T	32 1000 s/mm <sup>2</sup>	8 WS/9 HC; Note: HC group also had high nonsocial fear	WS = 22 (3.5) HC = 25 (6.4)	FA: Mixed AD: WS > HC RD: Mixed MD: NA	Subjects with WS showed lower FA bilaterally in the ventral amygdalofugal pathways, Unc, ILF, and IFOF_R. In these regions, patients with WS had higher RD and AD. Patients with WS had higher FA in IFOF_R (connected to the amygdala), with lower RD and higher AD in this region. TBSS analysis showed lower FA in subjects with WS in ventral amygdalofugal pathway, Unc_R, GenyCC, BodyCC, SpleniumCC, anterior commissure, PLIC, ExtC, IFOF_L, and CST_L.
	Faria <i>et al.</i> , 2012 (46)	3T	32 700 s/mm <sup>2</sup>	8 WS/8 HC	WS = 18.6 (4.4) HC = 16.6 (3.2)	FA: Mixed AD: WS < HC RD: Mixed MD: NA	Patients with WS showed higher FA in the SLF_R, SFOF_L, cingulum, and caudate and lower FA in CST, CP, and PLIC. Patients with WS also had higher RD in CP_R and CST_L and lower RD in the left cingulum and ALIC_R. Patients with WS showed lower AD in the ExtC_L and right amygdala.
	Haas <i>et al.</i> , 2014 (100)	3T	23 850 s/mm <sup>2</sup>	18 WS/18 HC	WS = 11.88 (4.2) HC = 11.06 (2.92)	FA: WS > HC AD: WS > HC RD: WS < HC MD: WS < HC	In the TBSS analysis, subjects with WS showed higher FA in the IFOF_R and Unc and lower RD and MD and higher AD in these regions. Atlas-based analysis showed that subjects with WS had higher FA in the fusiform gyrus, amygdala, and hippocampus on the left side and higher FA in the fusiform gyrus and amygdala on the right side. Subjects with WS showed lower MD within the right fusiform gyrus and right medial orbitofrontal gyrus.

Table 2. Continued

CNV Region	Author, Year	Field Strength	Direction	<i>n</i>	Age, Years, Mean (SD)	DTI Measures	Summary Findings
			b-Value				
	Gagliardi <i>et al.</i> , 2018 (47)	3T	2-shell acquisition	10 WS/18 HC	WS = 27.6 (6.4) HC = 23.9 (4.4)	FA: Mixed AD: NA RD: NA MD: NA	Voxelwise analysis showed clusters of lower FA in the middle and superior CP, PLIC, SpleniumCC, and the subcortical WM of the parieto-occipital region in patients with WS. Patients with WS showed higher FA in the adjacent parieto-occipital WM in the left. Patients with WS showed higher degree of connections between few parieto-occipital areas of both hemispheres and frontal areas, cingulum, and parahippocampus (most differences in the same hemisphere, whereas only a few of them were transcallosal). Most of the impaired connections originate from parieto-occipital regions and are directed to frontal areas.
22q11.2	Da Silva Alves <i>et al.</i> , 2011 (32)	3T	32 1000 s/mm <sup>2</sup>	27 del (12 SCZ+; 15 SCZ-)/31 HC/ 12 idiopathic SCZ	Del (SCZ+) = 31.17 (6.78) Del (SCZ-) = 28.80 (8.56) SCZ = 23.33 (3.47) HC = 32.35 (9.74)	FA: Del < HC <sup>b</sup> AD: NA RD: NA MD: NA	Including IQ as a covariate, del carriers (SCZ+ and SCZ-) showed lower FA in the precentral and postcentral areas bilaterally, in the right parietal subgyral, right superior frontal area, and parahippocampal area. No significant changes were found between SCZ+ and SCZ- in the del group. Patients with idiopathic SCZ had lower FA in the right frontal subgyral, right insula, and right inferior frontal area compared with HCs. In the whole del group, FA was negatively correlated with scores of the positive and negative symptoms of PANSS. Positive symptoms were associated with lower FA in areas of the frontal and right temporal areas, and negative symptoms were associated with lower FA in areas of the frontal and left temporal lobe.
	Radoeva <i>et al.</i> , 2012 (33)	1.5T	15 800 s/mm <sup>2</sup>	33 del/16 HC (unaffected siblings)	Del = 17.7 (1.8) HC = 18.0 (1.7)	FA: Del < HC AD: Del < HC RD: NS MD: NA	Del carriers showed lower FA in Unc and lower AD in PTR, PCR, RLIC, sagittal stratum, SCR, ACR, IFOF, SLF, ExtC, Cing_CG, and SCP.
	Perlstein <i>et al.</i> , 2014 (39)	1.5T	15 800 s/mm <sup>2</sup>	52 del/47 HC	Del = 18 (2.2) HC = 18.1 (1.6)	FA: Mixed AD: Del < HC RD: Del < HC MD: NA	Del carriers showed higher FA and lower RD in ALIC, lower FA and AD in fornix, and lower AD and RD in Unc. Higher positive scale of prodromal symptoms (SOPS-Positive Symptoms) were associated with higher FA in ALIC and with lower RD in Unc. The degree of increased FA and decreased RD in ALIC was related to the variation of the NOGO-66 receptor gene coded on 22q11.2. Follow-up study to (14).

Table 2. Continued

CNV Region	Author, Year	Field Strength	Direction b-Value	n	Age, Years, Mean (SD)	DTI Measures	Summary Findings
	Jalbrzikowski <i>et al.</i> , 2014 (40)	3T	64 1000 s/mm <sup>2</sup>	36 del/29 HC	Del = 16.3 (4.3) HC = 15.5 (3.8)	FA: Mixed AD: Del < HC RD: Del < HC MD: NA	TBSS analysis showed higher FA and lower AD and RD throughout WM regions in del carriers. Del carriers showed higher FA in the PLIC_R, SCR_R, PCR_R, BodyCC, and SLF_L and lower AD and RD in BodyCC, SpleniumCC, ATR, SLF, and ILF. Additionally, del carriers showed lower AD in IFOF and lower RD in SCR_L and upper regions of CST. Region analysis further showed lower FA in Cing_HIP_L, anterior cingulum bundle, IFOF, ILF, SLF, Unc_L, SpleniumCC, and BodyCC and lower RD in ILF and SLF. The greatest effect size was observed for AD changes in the SLF. Decreased AD in IFOF was associated with greater severity of positive symptoms.
	Kates <i>et al.</i> , 2015 (41)	1.5T	15 800 s/mm <sup>2</sup>	51 del (No medication: 32 del/46 HC (no medication: 39 HC)	Del = 18 (2.3) HC = 18.1 (1.6)	FA: Mixed AD: Del < HC RD: Del < HC MD: NA	Del carriers showed lower FA in the left anterior cingulum and lower AD bilaterally, lower AD in the superior cingulum bilaterally and lower RD on the right side, and higher FA and lower RD in the posterior cingulum bilaterally. Del carriers without medication showed lower FA and AD in the anterior cingulum, lower FA in the superior cingulum, and higher FA in the posterior cingulum, but no differences were found in the ones who take medication. Within del carriers, SOPS-Positive Symptoms were associated with higher FA and lower RD in the superior cingulum bilaterally. Follow-up study to (14,15). Tractography study of the cingulum.
	Bakker <i>et al.</i> , 2016 (35)	3T	32 1000 s/mm <sup>2</sup>	21 del/23 UHR <sup>o</sup> / 33 HC	Del = 26.2 (3.6) UHR = 24.3 (3.1) HC = 26.2 (5.5)	FA: Del > HC AD: Del < HC RD: Del < HC MD: Del < HC	Compared with HCs, del carriers had higher FA in ATR, PTR, IFOF_L, SpleniumCC, BodyCC, and forceps major; lower AD in ILF, IFOF, SLF, forceps major, Unc, SpleniumCC, ATR_R, PTR_R, CR, and sagittal stratum; lower RD in forceps major, SLF_L, BodyCC, SpleniumCC, and CR; and higher MD in ATR (but whole-brain mean MD was lower). Compared with UHR individuals, del carriers had lower whole-brain mean MD; higher FA in ATR, SpleniumCC, BodyCC, and CR; lower AD in SLF, IFOF, SpleniumCC, and BodyCC; and lower RD in ATR_L, SpleniumCC, BodyCC, and CR. HCs showed intermediate values for MD, AD, and RD between del and UHR patient groups.

Table 2. Continued

CNV Region	Author, Year	Field Strength	Direction	<i>n</i>	Age, Years, Mean (SD)	DTI Measures	Summary Findings
			b-Value				
	Kikinis <i>et al.</i> , 2017 (101)	1.5T	15 800 s/mm <sup>2</sup>	50 del (9 del with high risk for developing psychosis)/47 HC	Del = 18.1 (2.3) Del (high-risk) = 18.8 (2.8) Del (low-risk) = 17.9 (2.2) HC = 18.0 (1.6)	FA: NS AD: Del < HC RD: Del < HC MD: Del < HC	Del carriers showed lower MD, AD, and RD in BodyCC, SpleniumCC, SLF, and CR. Del carriers with high risk for psychosis showed lower AD in SLF_L, SpleniumCC, BodyCC, SCR_R, and right IntC (retrolenticular part, PLIC and ALIC). Decreased AD in the corpus callosum were associated with an increase in positive prodromal symptoms in del carriers and remained significant after including medication as a covariate.
	Olszewski <i>et al.</i> , 2017 (36)	3T	64 700 s/mm <sup>2</sup>	57 del/30 HC (12 unaffected siblings)	Del = 28.87 (2.29) HC = 20.97 (1.46)	FA: Del > HC AD: Del < HC RD: Del < HC MD: NA	Del carriers showed higher FA and lower RD in IFOF_L, right cingulum, and right thalamofrontal tract; lower RD in ILF_R and Unc_R; and higher FA in IFOF_R. Prodromal symptoms and psychosis were related to higher FA and lower RD in IFOF in del carriers.
	Roalf <i>et al.</i> , 2017 (34)	3T	64 1000 s/mm <sup>2</sup>	39 del (27 del with psychosis)/39 HC	Del = 19.99 (1.7) HC = 19.83 (4.25)	FA: Del < HC AD: Del < HC RD: Del > HC MD: Del < HC	Del carriers showed lower FA in Cing_CG and Cing_HIP; lower MD in ILF; lower AD in Cing_CG, forceps major, IFOF, and SLF; and higher RD in Cing_HIP compared with HCs. Exploratory analysis showed that del carriers with psychosis had lower mean FA in Cing_CG and Unc compared with del carriers without psychosis.
	Villalón-Reina <i>et al.</i> , 2020 (38)	Multisite (10 sites): 3T (9 sites), 1.5T (1 site)	Different directions and b-values in each site	334 del/260 HC	Del = 16.88 (6.4) HC = 16.55 (8.01)	FA: Mixed AD: Del < HC (One tract del > HC) RD: Del < HC MD: Del < HC	Using harmonization protocols developed by ENIGMA-DTI, this study performed meta- and mega-analyses of data across multiple sites. Results were nearly identical between both analyses. 22q11.2 del carriers had lower diffusivity values (MD, AD, and RD) in most tracts and mixed changes in FA. Del carriers showed higher FA in the tapetum, GenuCC, BodyCC, SpleniumCC, ALIC, PLIC, PCR, and SCR, with moderate to large effect sizes, and lower FA in the SLF, fornix/stria terminalis, and ExtC compared with HCs. Del carriers had lower MD in almost all tracts, with greatest effects in PCR and PTR; lower AD in most tracts with exception of the PLIC that showed higher AD in del carriers relative to HCs; and lower RD in most tracts, with largest effects in the corpus callosum and PCR. Del carriers with psychosis showed overall lower diffusivity values, with lower AD in ALIC, PTR, Cing_CG, SLF, and sagittal stratum; lower RD in GenuCC; and lower MD in GenuCC and PLIC compared with del carriers without psychosis.

Table 2. Continued

CNV Region	Author, Year	Field Strength	Direction b-Value	<i>n</i>	Age, Years, Mean (SD)	DTI Measures	Summary Findings
	Bagautdinova <i>et al.</i> , 2020 (37)	3T	30 1000 s/mm <sup>2</sup>	101 del (39 del for assessing the impact of clinical risk factors)/100 HC	Del = 5–35 (range) HC = 5–35 (range)	FA: Del > HC AD: Del < HC RD: Del < HC MD: Del < HC	Longitudinal study looking at WM development in 22q11.2 del carriers. Similar developmental trajectories were found in del vs. HCs (no age × group interaction effects were detected). FA followed increasing quadratic or linear developmental curves. Del carriers showed higher FA in ATR, Cing_CG, SLF (parietal bundle), forceps minor, and forceps major. AD followed linear decreasing developmental curves. Del carriers showed lower AD in Unc, ILF, SLF_R (parietal bundle), SLF (temporal bundle), and left cingulum-angular bundle. RD followed decreasing quadratic developmental curves. Del carriers showed lower RD in ATR, Unc, Cing_CG, ILF, SLF (parietal bundle), SLF (temporal bundle), forceps minor, and forceps major. MD followed decreasing quadratic or linear developmental curves. Del carriers showed lower MD in ATR, Unc, Cing_CG, ILF, SLF (parietal bundle), SLF (temporal bundle), forceps minor, forceps major, and left cingulum-angular bundle. Partial least squares correlation between WM measures and risk factors of psychosis revealed that UHR status was associated with a pattern of decreased MD, AD, and RD and increased FA, whereas low baseline IQ and prematurity were associated with an opposite pattern of increased MD, AD, and RD and decreased FA.

Table 2. Continued

CNV Region	Author, Year	Field Strength	Direction		Age, Years, Mean (SD)	DTI Measures	Summary Findings
			b-Value	<i>n</i>			
	Seitz-Holland <i>et al.</i> , 2021 (42)	3T	Multishell	26 del/19 dup/ 18 HC	Del = 20.47 (8.8) Dup = 22.24 (14.41) HC = 19.51 (10.91)	FA: Del > HC > dup AD: NA RD: NA MD: NA	Del carriers showed widespread increased FA and dup carriers showed reciprocal decreases in FA compared with HCs. Additional imaging and processing methods were used to further investigate the underlying causes of higher FA in del carriers. Del carriers showed increased FA, even after accounting for extracellular FW, and showed lower FW values than HCs. Del carriers showed higher fraction of both the primary (F1) and secondary (F2) fiber populations and lower fractional volume of the isotropic compartment (Fiso), when compared with HCs. In contrast, dup carriers showed reciprocal changes in all measures. Higher FA in del carriers was associated with enlarged cerebrospinal fluid and smaller WM volumes, suggesting that WM tracts are abnormally densely packed. In contrast, lower FA in dup carriers was not associated with volumetric changes.

We used PubMed to find these neuroimaging studies. Search keywords included the name of genomic loci known to be associated with neurodevelopmental disorders or name of the syndrome and were used in combination with the following words: “Diffusion tensor imaging” OR “white matter” OR “white matter microstructure” OR “white matter diffusion”. For 15q11.2, 16p11.2, and 7q11.23 CNVs, all DTI studies found are described. For 22q11.2, because literature is more extensive, we only selected studies from 2010 with more than  $n = 20$  carriers. For a summary of additional earlier DTI studies on 22q11.2 deletion, see Supplementary Table S1 in Villalón-Reina *et al.* (38).

ACR, anterior corona radiata; AD, axial diffusivity; ALIC, anterior limb of the internal capsule; BodyCC, body of the corpus callosum; BP, breakpoint; Cing\_CG, cingulum (cingulate gyrus); Cing\_HIP, cingulum (hippocampus); CNV, copy number variant; CP, cerebral peduncle; CR, corona radiata; CST, corticospinal tract; DD, developmentally delayed; del, deletion; DTI, diffusion tensor imaging; dup, duplication; ENIGMA, Enhancing Neuro Imaging Genetics through Meta Analysis; ExtC, external capsule; FA, fractional anisotropy; FW, free-water; HARDI, High Angular Resolution Diffusion Imaging; HC, healthy control subject; ICFV, intracellular volume fraction; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; IntC, internal capsule; L, left hemisphere; MD, mean diffusivity; ND, neurite dispersion; NS, nonsignificant; PANSS, Positive and Negative Syndrome Scale; PCR, posterior corona radiata; PLIC, posterior limb of the internal capsule; PTR, posterior thalamic radiation; R, right hemisphere; RD, radial diffusivity; SCR, superior corona radiata; SCZ+, with schizophrenia; SCZ-, without schizophrenia; SFOF, superior fronto-occipital fasciculus; SLF, superior longitudinal fasciculus; SOPS, Scale of Prodromal Symptoms; SpleniumCC, splenium of the corpus callosum; STR, superior thalamic radiation; STV, supratentorial volume; TBSS, tract-based spatial statistics; UHR, ultra-high risk; Unc, uncinate fasciculus; WM, white matter; WS, Williams syndrome.

<sup>a</sup>Participants with DD did not carry the CNV but were compared to patients with WS (carrying the 7q11.23).

<sup>b</sup>Without including IQ as a covariate, deletion carriers (SCZ+ and SCZ-) showed additional higher FA in the anterior cingulate; deletion carriers (SCZ+) showed higher FA in the left anterior cingulate and left frontal subgyral; and deletion carriers (SCZ-) showed higher FA in the right frontal subgyral.

<sup>c</sup>UHR participants did not carry the 22q11.2 CNVs but were compared to 22q11.2 deletion carriers.

processing can lead to variable results. In a single cohort study from the UK Biobank, clinically unaffected carriers of 12 schizophrenia-associated CNVs had smaller volumes in the thalamus, hippocampus, and nucleus accumbens compared with noncarriers (60). A recent follow-up study, also using data from the UK Biobank, reported smaller cortical surface area (overlapping with findings in schizophrenia) and increased cortical thickness (contrasting with findings in schizophrenia) in carriers of schizophrenia-associated CNVs (61). Carriers of the 22q11.2 deletion (who were not present in these UK Biobank studies) also showed reductions in surface area and widespread thicker cortex in previous studies. Deletion carriers with psychosis had thinner cortices than carriers without psychosis, with no differences in surface area (38). This suggests that cortical thickness may be associated with illness progression, and surface area may be a more valid risk marker for schizophrenia. The largest cross-CNV neuroimaging study to date, including eight neuropsychiatric CNVs, identified the cingulate gyrus, insula, supplementary motor cortex, and cerebellum as regions showing more shared alterations across CNVs (62). However, the largest proportion (about two thirds) of effects on brain morphology were distinct across CNVs.

Drakesmith *et al.* (63) investigated whether brain changes in CNV carriers were associated with their degree of pathogenicity, which was based on penetrance scores calculated by Kirov *et al.* (4) and reflect the probability of manifesting a given phenotype. The penetrance of a CNV for schizophrenia and developmental delay was associated with changes in the curvature of the dorsal cingulum bundle and structural measures of the corpus callosum (63). Although this study had a small sample (21 carriers and 15 noncarriers), these findings suggest common neurodevelopmental abnormalities in white matter microstructure contributing to risk for schizophrenia and developmental delay.

Studies have also explored similarities in functional connectivity patterns across CNVs. A magnetoencephalography study investigated resting-state oscillatory connectivity and reported decreased connectivity between occipital, temporal, and parietal areas in CNV carriers (64). Moreau *et al.* (65) combined functional MRI data from 16p11.2 and 22q11.2 CNV carriers; individuals with idiopathic ASD, schizophrenia, and attention-deficit/hyperactivity disorder; and respective control subjects to look for convergent patterns of functional connectivity alterations. Individually, 16p11.2 deletion carriers showed increased connectivity in the ventral attention, motor, and frontoparietal networks, whereas 22q11.2 deletion carriers showed decreased connectivity of the default mode network and limbic network. Dosage-dependent effects were observed for both CNVs. When looking at similarities between dysconnectivity measures, hyperconnectivity between thalamus and sensory-motor, auditory, and visual networks was common across CNVs and also observed in patients with ASD and schizophrenia.

### INSIGHTS FROM ANIMAL MODELS

To interpret alterations in structural and microstructural MRI data from humans, comparison with MRI, histological, and histochemical data from animal models is crucial. Several laboratories have succeeded in recapitulating neuropsychiatric

CNVs in mouse models. A recent review provides an overview of schizophrenia-related phenotypes in five CNV mouse models (66), and a current opinion touches upon important issues in construct and face validity of these models (67).

Advances in small animal imaging protocols have increased the translational validity of these models by allowing comparisons between human and animal imaging findings. A functional MRI study showed reduced prefrontal functional connectivity in both humans and mice with a 16p11.2 deletion (68). Mice with a 16p11.2 deletion and duplication showed mirrored effects on the volume of several brain structures, including the basal forebrain, fornix, hypothalamus, mammillothalamic tract, medial septum, midbrain, and periaqueductal gray (69). Similarities were also found between a 22q11.2 deletion mouse model and human deletion carriers, particularly in volumetric changes in corticocerebellar, corticostriatal, and corticolimbic circuits (70).

Models of individual genes can help dissect single-gene contributions to brain phenotypes seen in CNV carriers. The 15q11.2 (BP1-BP2) region comprises only four genes, facilitating examination of individual genes and their interactions. *CYFIP1* is considered a likely contributor to 15q11.2-associated phenotypes. Using a rat model, we showed that *Cyfp1* haploinsufficiency leads to decreased FA, myelin thinning, and abnormal myelin basic protein distribution in oligodendrocytes (71); myelin thinning was also observed by another group in *Cyfp1*-heterozygous mice (72). A recent study also identified myelin thinning in the striatum of 16p11.2 deletion mice, accompanied by lower expression of myelin genes and reduced levels of key lipid components of myelin (73). The selective deletion of *Gtf2i* (deleted in Williams syndrome) in excitatory neurons of the forebrain led to reduced myelin-related gene transcripts and oligodendrocyte cell number, myelin thinning, and impaired axonal conductivity. Administration of a remyelinating drug rescued abnormal social behaviors in this mouse-mutant line (74). Mice heterozygous for *Tbx1*, a gene encoded within the 22q11.2 locus, showed reduced myelin in the fimbria and reduced mRNA levels of *Ng2*, a gene required to produce oligodendrocyte progenitor cells (75). Increasing evidence suggests a key role of myelin and oligodendrocytes in neurodevelopmental disorders (76,77), and studies have related myelin plasticity to higher cognitive function and learning (78,79). Abnormal myelination may thus be a convergent phenotype across neurodevelopmental CNVs. Less myelin is associated with decreased FA in DTI studies, which is a common finding across neurodevelopmental disorders but not across pathogenic CNVs. However, myelin changes have a modest impact on DTI signal (80) and may be masked by other cellular events (e.g., changes in fiber density as seen in 22q11.2 deletion). More studies are needed to distinguish myelin from axonal changes in human CNV cohorts. This could be done by combining DTI with other MRI modalities, such as magnetization transfer imaging, relaxometry, and quantitative susceptibility mapping (81).

Most mouse models were developed using different background strains, which may influence phenotypes (67). We highlight the parallel generation of three CNV mouse models with the same background strain (1q21.1, 15q13.3, and 22q11.1 deletions), allowing direct comparison between these

models. Recently, a transcriptomics network study using these models showed that genes involved in a neuronal mitochondrial module were downregulated across CNVs, and the same genes were also downregulated in schizophrenia and ASD (82). These findings suggest that convergence is also present in these mouse models, at least in gene expression. In contrast, a study using structural and functional MRI data showed very distinct brain connectivity profiles across these three models (83). Studies using these mouse lines and combining neuroimaging with histological, transcriptomics, and proteomics data could be useful in identifying convergent mechanisms associated with specific shared phenotypes.

## DISCUSSION

Overall, bioinformatics, cognitive, and neuroimaging studies have revealed some convergent findings across CNVs. Bioinformatics studies suggest convergence in genes involved in synaptic activity. Findings from two studies independently looking at brain morphometry and cognitive data across CNVs, respectively, suggest that regional morphometry changes are more CNV-specific (>60% variability across CNVs) (62) than clinical and cognitive effects (5%–20% variability across CNVs) (29). Future cross-CNV studies analyzing both cognitive and neuroimaging data from the same cohort are needed to more confidently link these two independent findings. One possibility is that although convergence of morphometric findings may be low at a level of spatial resolution, similar mechanisms of neuronal change operate across CNVs, albeit across a variety of brain areas. Of particular interest are the dosage-dependent effects seen in some CNVs; both 16p11.2 proximal deletion and duplication are associated with ASD [OR = 11 and 14, respectively (84)] and showed opposite changes in neuroimaging studies. However, only the duplication is associated with schizophrenia, and therefore phenotypes that are specifically associated with the duplication (but not with the deletion) could be related to genetic liability for schizophrenia.

Large multisite and population-based cohorts, such as ENIGMA and UK Biobank, have led to important discoveries on brain alterations associated with pathogenic CNVs. These initiatives have allowed sample sizes with more than 100 carriers (e.g., 15q11.2 BP1-BP2 and 22q11.2 CNVs). However, sample sizes for other CNVs are still relatively small, making it difficult to compare effect sizes across studies. More cross-CNV studies, with larger samples and comprising a broader list of pathogenic CNVs, will be important to fully capture the proportion of convergent and distinct brain alterations across CNV carriers. Multimodal neuroimaging protocols are also needed to investigate the proportion of both convergent and CNV-specific effects on morphological, microstructural, and functional features of the brain. Although a large body of evidence points to convergence across CNVs on the synapse, early evidence from CNV rodent models also points to a possible convergence in myelin dynamics. It is possible that abnormal myelination is present in CNV carriers and could be associated with risk for psychosis. However, other cellular changes may also occur that influence DTI signal and may (or may not) be independent of the risk to develop psychosis. Therefore, we propose the inclusion of more specific myelin-

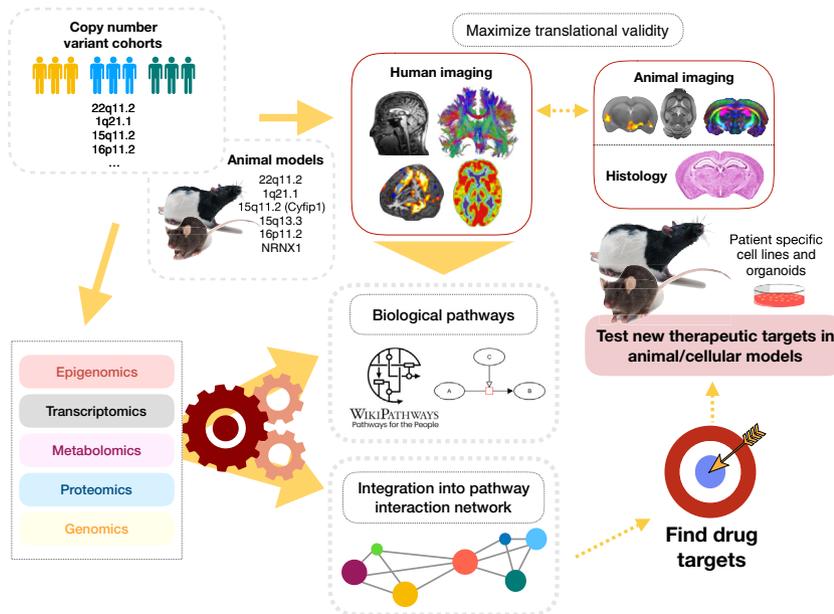
sensitive MRI protocols in CNV studies (81). Longitudinal studies are also needed to better understand the relationship between macro- and microstructural brain developmental trajectories and psychosis onset in CNV carriers.

## Bridging the Gene–Phenotype Gap

The link between neuroimaging, cognitive, and molecular findings on CNVs and neurodevelopmental disorders is still unclear. To unravel convergent biological mechanisms underlying shared brain and cognitive phenotypes, integration of different research areas is highly needed (Figure 3). This integration is possible only if we encode our biomedical knowledge into standardized machine-readable formats that can be shared, reused, and integrated across different databases.

Pathway databases, such as Kyoto Encyclopedia of Genes and Genomes, Reactome, and WikiPathways, allow the intuitive visualization of metabolic and signaling pathways of different genes and predict downstream effects on interaction partners of the affected genes (transeffects). WikiPathways (<https://www.wikipathways.org>) (85) in particular is a community database, where pathways can be created and curated by experts and rapidly accessed and reused by other researchers. With a full identifier-based and semantic annotation of nodes and interactions, WikiPathways allows high-throughput -omics data analysis, where knowledge from several prior knowledge databases can be integrated. Of interest are drug target databases to include predictions of potential interactions for drug development, gene–disease association databases, and genetic variant databases to include genetic modifier effects.

Neuroimaging findings do not specify molecular mechanisms but can be used as a guide to identify convergent effects in specific brain regions and measures. The Brain Imaging Data Structure has been created to facilitate sharing neuroimaging data through a standard machine-readable structure (86), and an extension has been added to link neuroimaging datasets to associated genetic data (87). Brain-wide expression atlases, such as the Allen Human Brain Atlas, also provide new windows to capture relationships between temporal and spatial distribution of gene expression and neuroimaging phenotypes (24,65,88,89). Large-scale initiatives, such as the Human Cell Atlas, Brain Initiative Cell Census Network, and Human Biomolecular Atlas, are also working on inclusion of single-cell transcriptomics and spatial genomics techniques to build three-dimensional reference cell atlases in humans, which will provide unprecedented cellular resolution (90). Existing MRI techniques cannot reach the same resolution for individual cell types, although efforts are being made to estimate cell-specific microstructural properties (91). Studies using CNV mouse models could provide in-depth cellular resolution, where single-cell sequencing methods could be used in combination with three-dimensional histological imaging (e.g., CLARITY) (92) but are limited in assessing phenotypes of clinical interest. Three-dimensional organoid models from human CNV carriers can be used to model fetal brain development, where transcriptomic and proteomic profiling, as well as cellular assays, can be performed. Cortical organoids from 16p11.2 CNV carriers revealed changes in 1) organoid size, recapitulating the mirrored microcephaly and macrocephaly phenotypes seen in deletion and duplication carriers; 2) several pathways involved



**Figure 3.** Finding convergent molecular mechanisms underlying shared brain phenotypes across CNVs. Identifying convergent mechanisms across pathogenic CNVs can pinpoint major disease pathways that are common across neurodevelopmental disorders. Most studies have looked at molecular and phenotypic convergence separately, making it difficult to understand how convergent cellular mechanisms lead to shared phenotypes. The collection of genomics, neuroimaging, and cognitive assessments in cross-CNV and cross-disorder cohorts can provide multilevel information that can be integrated using multivariate methods (e.g., machine learning strategies) into mathematical models that can incorporate prior biological knowledge from pathway databases to identify genomic interactions associated with different clinical outcomes (104). However, achieving sample sizes to conduct such analyses is currently challenging. We highlight the need to integrate current knowledge from multiomics (epigenomics, transcriptomics, metabolomics, proteomics, and genomics) resources with knowledge from neuroimaging and animal models to identify potential overlapping mechanisms that may lead to similar effects on the brain. Biological pathway databases, such as WikiPathways, allow the integration of knowledge from several prior

knowledge databases. Notably, WikiPathways has a dedicated rare disease portal (<http://raredisease.wikipathways.org>) with a CNV pathway section. Combining CNV pathways into interactive pathway networks can be used to identify shared molecular mechanisms across pathogenic CNVs. Neuroimaging data, in contrast, can pinpoint specific brain structures/measures where similar effects across pathogenic CNVs are observed. For example, morphometric studies suggest that deletions at 1q21.1, 7q11.23, and 22q11.2 lead to similar effects in global surface area, brain volume, and cortical thickness (Figure 1). Pathway analysis could be used to identify convergent pathways in genes across these CNV regions, as well as possible interactions with genes that are known to influence brain morphology. Therefore, if specific brain regions/measures are shown to be similarly affected across pathogenic CNVs, this could be used as a guide to restrict pathway interaction networks to only comprise genes known to influence these measures or known to be expressed in these brain regions. This approach could indicate molecular pathways leading to the imaging phenotypes observed. These networks can integrate information on predicted drug target relationships from compound databases (e.g., DrugBank or ChEMBL). These drug targets can then be tested for therapeutic value in animal models and patient-specific cell lines, as well as in patient-derived organoids. Animal and cellular models, as well as human postmortem tissue, also provide additional cellular resolution that allows the investigation of cellular causes and mechanisms leading to the brain effects seen in vivo in human carriers and further validate hypotheses formulated by imaging and pathway analysis. CNV, copy number variant. WikiPathways logo: Pico A, 2018. CC BY-SA 4.0. Available from: [https://commons.wikimedia.org/wiki/File:Wplogo\\_with\\_text\\_500.png](https://commons.wikimedia.org/wiki/File:Wplogo_with_text_500.png)

in neurodevelopment (e.g., actin cytoskeleton and neuron migration); and 3) neuronal maturation, migration, and morphology, as well as synaptic-related functions (93). Molecular analysis of patient-derived cellular models and transcriptomic analysis of postmortem brain samples of CNV carriers (in the rare cases where these are available) will be crucial for the validation of systems biology models of convergent pathways.

## CONCLUSIONS

Convergence across CNVs may provide new insights into convergent biology across neurodevelopmental disorders and pinpoint key disease mechanisms that may lead to new therapeutic targets for cross-disorder applications. We are still far from understanding how convergent molecular pathways relate to shared clinical outcomes of these genetic variants and how such biological convergence translates to risk for neurodevelopmental disorders. Integration of molecular, histopathological, clinical, and neuroimaging data, while considering crucial developmental timepoints, is needed to better understand these links.

## ACKNOWLEDGMENTS AND DISCLOSURES

This research was supported by the Medical Research Council Centre (Grant No. MR/L010305/1) and by a Wellcome Trust Strategic Award DEFINE grant (Grant No. 100202/Z/12/Z [to JH, LSW, and DEJL]).

MOU, HS, and KS are employees of deCODE genetics/Amgen. All other authors report no biomedical financial interests or potential conflicts of interest.

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Received Sep 14, 2021; revised Mar 22, 2022; accepted Mar 25, 2022.

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