Mapping genotype to phenotype in neurodevelopmental copy number variants

The first studies that identified an association between copy number variants (CNVs) and neurodevelopmental conditions were published over a decade ago. Several studies since then have confirmed the validity of these results, and individuals with neurodevelopmental conditions have an excess of de novo and rare CNVs compared with their siblings or the general population. These CNVs span multiple genes, but seem to converge on specific pathways—e.g., synaptic transmission, chromatin modification, and transcriptional regulation in autism. These studies typically investigate whether CNVs are enriched in specific neurodevelopmental conditions such as autism and attention-deficit hyperactivity disorder (ADHD); a phenotype-first approach. In The Lancet Psychiatry, Samuel Chawner and colleagues ask the opposite question: do CNV carriers have phenotypes that differ by genotype?

To investigate this question, the authors conducted the largest systematic investigation of phenotypic differences in 258 CNV carriers aged 6–19 years and 106 sibling controls in the IMAGINE-ID cohort. Participants were phenotyped for a range of neurodevelopmental, cognitive, and psychiatric phenotypes; a non-trivial task. Focusing on 13 CNVs associated with neurodevelopmental conditions, they first investigated if CNV carriers differed from the sibling controls for multiple psychiatric conditions and across the phenotypes measured. In line with previous research, CNV carriers had significantly higher odds of being diagnosed with a psychiatric condition (odds ratio [OR] 13.8, 95% CI 7.2–26.3), and higher impairment across all phenotypes tested, with attention-deficit hyperactivity disorder (OR 6.9, 3.2–15.1), and autism spectrum disorder traits (OR 44.1, 15.3–127.5) being particularly high. They next investigated whether CNV carriers differed in their phenotypic presentation according to their genotype. The results support a model in which CNV carriers have broadly overlapping phenotypes, with some genotype-specific effects. Notably, phenotypes associated with intelligence and conduct problems differed between CNV genotypes, whereas sleep and mood difficulties were similarly impaired across the 13 CNV genotypes.

These results support a systemic vulnerability model. According to this model, neuropsychiatric conditions and behaviour are emergent properties of complex systems. Genes disrupted by neurodevelopmental CNVs affect several neural networks leading to broad phenotypic alterations. Studies investigating common variant, rare variant, and transcriptomic overlap have identified substantial but differing shared biology between various neuropsychiatric conditions, blurring diagnostic boundaries. Together, these findings point to the immense complexity in mapping genotypes to phenotypes across neurodevelopmental and neuropsychiatric conditions. CNVs need not map onto a unique constellation of phenotypes, and substantial shared biology exists between phenotypes. Clearly, delineating the association between genotype and phenotype is non-trivial, and the challenge ahead is to

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identify the molecular and neural mechanisms that link genotype to phenotype.

The CNVs accounted for only 5–20% of the phenotypic variance in the study by Chawner and colleagues; most of the variance is attributable to other factors. Indeed, the authors report that age accounts for as much as a quarter of the variance in some phenotypes. This finding should not come as a surprise, because several of these phenotypes vary considerably with age and might be modified by interventions at crucial time periods.

The next step is to evaluate the association between developmental trajectories of these phenotypes and the CNV genotypes. Do developmental trajectories change with CNV genotype? Do specific interventions work equally well across the CNV genotypes? These are important issues that need to be investigated to provide better support to individuals with neurodevelopmental CNVs.

An inherent limitation of the study is the absence of whole-genome data. Evidence suggests that even in carriers of damaging mutations, common, inherited genetic variants might contribute to a proportion of the phenotypic variance, and, in some instances, might modify the penetrance of rare variants. Genetic variants across the allelic spectrum are associated with neuropsychiatric conditions. In light of this, will accounting for other genetic variants in CNV carriers help better delineate genotype-specific effects of these CNVs? Advances in sequencing technology and statistical methods coupled with larger sample sizes could help answer this.

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Neighbourhood and mortality in severe mental illness

People with severe mental illness have higher mortality rates, culminating in about 20 years of lost life compared with that of the general population, and momentum is growing to reduce this inequality. In the general population, neighbourhood social context is related to mortality, but whether such patterns also exist for people with severe mental illness has received little attention. Understanding this relationship could allow us to tailor social interventions for this distinctive population. The study by Jayati Das-Munshi and colleagues in *The Lancet Psychiatry* represents a welcome step in that direction, linking higher neighbourhood ethnic density to lower mortality rates among people with severe mental illness from ethnic minority backgrounds. These results raise the intriguing possibility that factors associated with ethnic density might promote longevity among people with severe mental illness.

Their study was based on a large cohort of 18 201 people with severe mental illness, identified and followed with use of electronic health registers for mortality outcomes for a median of 6.36 years in an ethnically heterogeneous location in south London, UK. Using these data, Das-Munshi and colleagues had previously observed that mortality rates were lower for some ethnic minority groups than for the white British population. In this study, they extend those findings to show that neighbourhood-level ethnic density, defined...