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REFRESHMENT

Copy number variants in the context of evolving psychogenomic understanding†

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SUMMARY

There are well-established links between recurring copy number variants (CNVs) (ubiquitous structural variations within chromosomes) and many psychiatric diagnoses. This article considers potential advances that enhanced understanding of CNVs might offer psychiatry – a scientifically rigorous footing for the discipline and personalised prescribing based on genetic data that would benefit patients from pre-diagnosis to treatment.

KEYWORDS

Genetics; aetiology; epidemiology; autism spectrum disorders; depressive disorders.

The future of psychiatry is a fertile academic space. In a period of rapidly enhancing understanding of psychiatric disease processes there are a number of expanding research domains, including improved understanding of prodromal conditions, neuroplasticity and brain microstructure, and pharmacogenetic optimisation.

Linking all of these areas are copy number variants (CNVs). CNVs are ubiquitous intergenomic structural variations within chromosomes; they result in deletions, duplications, inversions or translocations of large DNA segments, affecting gene expression (Kirov 2015). CNVs therefore provide a basis for wider genetic heterogeneity.

Pathogenic CNVs in psychiatry

There are now well-established links between recurring CNVs and many psychiatric diagnoses. Pathogenic CNVs are highly correlated with autism spectrum disorder (ASD), intellectual disability and attention-deficit hyperactivity disorder (ADHD) as well as other, less prevalent neurodevelopmental disorders such as Prader–Willi, Smith–Magenis and velocardiofacial syndromes (Thapar 2013). The penetrance of CNVs in these disorders has so far been shown to be higher than for other psychiatric diseases.

Schizophrenia has several associated CNVs which are consistent regardless of geographical or ethnic population. Interestingly, spontaneous CNVs are of higher frequency in sporadic cases, whereas inherited CNVs are prevalent in cases with familial risk (Levy 2012).

These findings have rapidly enhanced our understanding of the pathogenesis of specific psychiatric morbidity, but excitingly, CNVs are now being identified in other psychiatric spaces; recent research shows CNVs linked with risk of depression, as well as providing new correlations with cognitive impairment (Kendall 2019; Warland 2019).

Early intervention in psychiatric illness

It is clear that CNVs are already a hugely interesting concept within academic psychiatry and their use has the potential to revolutionise patient care. Enhanced knowledge of CNVs offers a unique stepping-stone to several areas of interest for the future.

The identification of key CNVs may identify those at risk of early development of psychiatric disorder. This will allow more effective education for individual at-risk patients and their families and provoke access to psychiatric services.

A further benefit is the collation of evidence regarding the neurobiology and molecular mechanisms that underpin the development of psychiatric disorder. CNV studies of ASD, schizophrenia and intellectual disability have strongly implicated disordered synaptic function. Studies of ADHD have suggested derangement of nicotinic acetylcholine receptor pathways, glutamatergic transmission and genes involved in neural development.

Personalised prescribing

Perhaps most importantly, enhanced understanding of CNVs will offer a gateway to pharmacogenetic targets. This could transform the current standard of care for psychiatric patients. Enhanced understanding of CNVs ultimately offers the potential for personalised prescribing and dosing based on genetic data, a previously unthinkable benefit to psychiatrists' ability to care for patients who suffer debilitating symptoms and social stigma.

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One such example would be CNVs that are linked to the *CYP2D6* gene, which is a key gene involved in drug metabolism. It displays significant genetic variation. Identification of CNVs in *CYP2D6* could stratify patients in relation to their ability to metabolise certain drugs (Jarvis 2019). Subsequently, those who metabolised active drugs rapidly would require higher doses or multiple administrations; those who metabolise prodrugs rapidly might require a lower dose to avoid side-effects related to the transition to an active drug form.

It is still difficult to interpret CNV findings in a clinically meaningful way, however. Characteristic of all complex disease epidemiology, many carriers of risk CNVs will not display a psychiatric phenotype; not all those affected will obtain or own the risk CNVs. All psychiatric disease has multifactorial origins. The diagnostic overlap of many psychiatric disorders blurs the picture further.

The role of technology, education and research

At present there are also technical deficiencies in taking this research to the next stage. The microscopic manipulation of CNVs could be the link to proving causal pathogenic effects that are largely elusive today; the technology required for this is evolving, but remains immature.

CNVs must also find a place within educational discourse, and in the UK the turbulent political climate and the post-pandemic recovery may yet have impacts on all research activity.

Positively, as technology advances and the knowledge-base evolves, the cost of sequencing and analysis of CNVs continues to decrease. In some global academic institutions, CNVs are routinely screened for and offer clinically relevant scientific data; it is not unrealistic to expect that clinical psychiatric settings could regularly utilise genetic data to inform management pathways, especially in those areas where CNVs are strongly correlated: ASD, intellectual disability and ADHD, in particular. Novel interventions and strategies for modifying pathogenic risk will follow.

CNVs are therefore a research avenue that offers clinically appropriate genetic information to benefit patients from pre-diagnosis to treatment. Psychiatry could disproportionately benefit from such research owing to the variation in symptomatology and the difficulty in reaching optimal patient outcomes.

CNVs and wider psychogenomic research therefore not only offer psychiatry academic integrity, but also the scientifically rigorous footing it has historically sought, with innumerable benefits to the discipline.

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Declaration of interest

None.

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