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Disparate Diseases Due to Copycat Copy Number Variations

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Copy Number Variation (CNV) is the new catchphrase in a number of disparate neuropsychiatric disorders. Thanks to new DNA microarray technology, these small microdeletions or microduplications that could not be detected by traditional chromosomal analysis are all the rage. While independent studies of neuropsychiatric disorders such as autism, schizophrenia, and mental retardation have identified many CNVs that may be rare causes of each, many of these CNVs have been identified in more than 1 disorder. A recent study by Guilmatre and colleagues is among the first to systematically address the overlap in CNVs across autism, schizophrenia, and mental retardation. This study confirms previous studies suggesting that a single CNV, often affecting only a single gene, can be linked to risk for more than 1 of these neuropsychiatric disorders, without being observed at significant rates in control subjects.

The investigators identified 28 candidate CNVs from the literature found using array-based comparative genomic hybridization that had been associated with autism, schizophrenia, or mental retardation. These 28 candidate regions were examined for CNVs in 4 case-control groups using advanced quantitative polymerase chain reaction protocols on short fluorescent fragments. They simultaneously examined 247 cases with mental retardation, 260 cases with autism, 236 cases with schizophrenia, and 236 controls for each of these 28 CNVs.

Of the 28 CNVs studied, the investigators identified 11 CNVs associated with at least 1 of the 3 disorders in their cases. Interestingly, while most of these CNVs were absent from the control population, all but 1 of the genetic CNVs were found in multiple disease states.

This finding is quite interesting given that most of these disease-associated CNVs are involved in synaptic transmission, synaptic function, or synaptic modulation. Subtle alterations in synaptic function may be a strong risk factor for all 3 neuropsychiatric disorders, with the genetic context in which the CNV occurs, perhaps in concert with environmental or other genetic influences, playing a major role in determining the final affected symptom domains.

Of the 4 most prevalent CNVs identified in cases, the synaptic cell adhesion molecule neurexin 1 (encoded by *NRXN1*) was unique because it is not flanked by segmental duplications that would make it more susceptible to homologous recombination mechanisms that commonly generate CNVs. *NRXN1* is part of a family of cell adhesion molecules that bridge the synaptic cleft, bringing the presynaptic axon terminal in minimal molecular contact with the postsynaptic dendritic spine. Neurexins are largely found on the presynaptic terminal while their binding partners, neuroligins, are found largely on the postsynaptic side, completing the second half of this “synaptic bridge.” Neuroligins and neurexins have

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previously been associated with human autism, mental retardation, and schizophrenia, and this new study confirms these findings.

The future of genetic risk in mental health is made both more promising and more complex by these novel findings of genetic overlap among disparate neuropsychiatric disorders. The challenge for neuroscientists for years to come will be examining how such genetic mutations affect brain function and behavior, both in humans and in genetic animal models of autism, schizophrenia, and mental retardation.