Editorial: Similar Rates of Deleterious Copy Number Variants in Early-Onset Psychosis and Autism Spectrum Disorder.

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There is longstanding evidence that in adults a genetic overlap exists in risk between ASD, schizophrenia and intellectual disability (Kushima et al, 2018, Jacquemont et al, 2022). A range of recurrent copy number variants (CNV) in specific loci, and to some extent single gene mutations (Howrigan et al, 2020) appears to be responsible. The biological pathways that are impaired by the associated neurodevelopmental anomalies remain largely unidentified, but it is assumed these must include neuronal development, synaptic function and neuronal cell adhesion (Sanders, 2015). Yet, despite the considerable body of research aimed at identifying genetic anomalies that underly serious neurodevelopmental disorders, relatively little has been written on potential mechanisms underlying diversity in the age of onset of these conditions, which is for the most part consistent. Global intellectual disability (ID) is usually evident within the first year of life, with a delay in the development of key motor skills such as head control, sitting, crawling and walking. Evidence that a child is developing an autism spectrum disorder (ASD) often manifests soon after this, with a lack of interest in social communication and, in some cases, with delayed onset of language too. The origins of autism are by definition in early childhood but only a minority of those affected have an underlying ID and the trend over time is toward recovery (Elias and Lord, 2022). On the other hand, schizophrenia almost invariably has its onset in late adolescence or adulthood, is exceptionally rare in childhood, and often has a deteriorating course (Jonas et al, 2020). Studies of adults with schizophrenia have not revealed any consistent pattern of premorbid symptoms, with little evidence of features characteristic of the autism spectrum. Children with autism do not have a substantially increased risk of developing a psychotic disorder in later life. Whilst the polygenic risk factors that underly risk in both ASD and schizophreniform psychosis, as well as the majority of individuals with intellectual disability, could differ substantially, we are still left with the conundrum that rare but specific genetic anomalies are shared between conditions with markedly different periods of clinical manifestation.

Rarely, schizophrenia has an onset in childhood, and is associated with a particularly poor prognosis. Childhood onset schizophrenia (COS) begins under the age of 13 years, and affected individuals possess a greater burden of pathogenic CNV than is reported in adult-onset cohorts. To date, intensive studies into genetic risk have been seriously limited in scope because of small sample sizes, reducing the confidence with which existing findings can be generalised. Because there are equally as many children with non-schizophreniform manifestations of early onset psychosis (EOP) as there are with strictly defined COS, Brownstein and colleagues (Brownstein et al, 2022) aimed to investigate genetic risks within a broader category of children, selecting participants who were

affected by a wide range of psychotic symptoms that began before the age of 18 years in order to acquire an adequate sample size for their analyses.

The genetic architecture of EOP in general is unknown, but previous research has indicated there is shared genetic risk between ASD and COS. Accordingly, Brownstein et al aimed to investigate whether deleterious CNV (plus some SNV) that are associated with early onset psychosis could also be found in children with ASD. This raises challenging questions; if the onset of schizophreniform psychosis is usually in adulthood, and genetic parallels with ASD have been found in those adult-onset conditions, one might anticipate that any specific genetic predisposition to psychosis in EOP should differ from ASD. It could also be less strongly associated with intellectual disability; many pathogenic copy number variants (CNV) and single gene variants (SNV) that predispose to ASD also predispose to ID. That overlap in phenotype is not so marked in schizophrenia, even though there is shared genetic risk. Accordingly, this study could address the following questions: first, are EOP children also impaired intellectually and, second, are there sex differences in phenotypic expression in this early onset condition? We know that at the lower end of the IQ distribution in ASD the sex ratio becomes more equal but there is greater male risk in those with normal-range intelligence. Whilst there are limited sex differences in the predisposition to schizophrenia, the condition is somewhat more prevalent in men and with an earlier age of onset. If a genetic predisposition is shared between ASD, ID and EOP would these shared risks be distributed equally with females if ID is not a prominent feature of EOP?

The focus of their study was twofold. First, they studied 40 CNV and a set of 7 genes that had previously been associated with neurodevelopmental or neuropsychiatric disorders. The CNV were all recurrent loci, previously been shown to put carriers at high risk. Potentially, many of the CNV could have been inherited (Wolstencroft et al, 2022) but that information is not available. Secondly, in a novel twist to the investigation, they studied risk that could be attributed to non-recurrent CNVs too. Whilst recurrent CNVs share a common size and similar breakpoints, non-recurrent CNVs are defined as structural variants with dissimilar endpoints or junctions. Relative sizes differ between individuals carrying the same non-recurrent CNV, but they may nevertheless share a small region of overlap. In order to evaluate the pathogenicity of the non-recurrent CNVs, they used a novel measure of genome-wide dosage sensitivity (Huguet et al, 2018, 2021), the CNV risk score (CRS). The CRS reflects the probability of intolerance to haploinsufficiency of each gene encapsulated by every CNV across the genome, regardless of the mutation's population prevalence. The authors describe this value as being analogous to the polygenic risk score. By these means, they created a CRS pathogenicity score for every individual in the investigation, by summing the potential clinical impact of each individual's specific range of deletions and duplications.

A total sample of 137 children with EOP was recruited, of whom 101 had a psychosis that began before 13 years of age. This is a massive achievement for such a rare condition. Of these EOP, 28% had an onset before 8 years of age, and 28% had a schizophreniform disorder. 34% had comorbid ASD but only 12% of the total had ID which is particularly striking and might reflect an ascertainment bias. There were two relatively large comparison groups, one with ASD (N=5,540) as well as three pooled unselected community-based cohorts (N=16,504). They found 8% of the EOP were recurrent CNV carriers, compared with 3.5% of the ASD comparisons and 1.6% of controls. It has been reported recently that in paediatric patients referred for developmental delay, intellectual disability or ASD, the diagnostic yield of genetic tests can be as high as 30% (Sanders et al, 2019), but that

yield is much lower in autistic children with normal range IQ. Among the recurrent CNVs (all of which had previously associated with neurodevelopmental and neuropsychiatric risk) there was enrichment for three mutations – 22q11.2 proximal deletion, 16p13.11 deletion and 1q21.1 duplication. Each had previously been reported in both child onset schizophrenia and in ASD cohorts, as well as in adult-onset schizophrenia. The authors suggest this finding could provide a clue as to underlying pathobiology, but it is puzzling why similar genetic predispositions can lead to such (predominantly) consistent different ages of onset. It is also notable that these findings were made in a cohort that was not dominated by individuals with significant generalized cognitive deficits. The CRS findings for non-recurrent CNV were surprising too; in a comparison of CNV risk scores between samples, there was no significant difference between the early onset psychosis and the ASD groups, but both were significantly different from typical comparisons in terms of both the aggregate impact of deletions and of duplications.

In sum, the authors have conducted a remarkable study that has both conceptual and practical implications. The methodology used, to evaluate the aggregate impact of both recurrent and non-recurrent CNV deserves replication. The finding of shared genetic risk between conditions that have such diverse phenotypic manifestations is intriguing and challenges explanation in terms of the mechanisms underlying maturation of biological pathways. And their recommendation that children with EOS deserve genetic screening, just as much as those with suspected ASD, is clinically relevant and should be heeded immediately.

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