Further insights into the genetic causes of autism spectrum disorders

childhood disability LINK

Summary

Autism spectrum disorders (ASD) are highly heritable and include a range of symptoms. They are characterized by impaired social interaction and repetitive behaviours; however, cognitive abilities associated with ASD range from above average to intellectual disability (ID). Studies in twins and families suggest that these disorders are highly heritable. It seems that multiple rare deletions and duplications within portions of genes, known as copy number variations (CNVs), are important to the variation and heritability in ASD. This study investigates the CNVs implicated in ASD to further clarify the genetic basis of this spectrum of disorders.

Several rare, intragenic copy number variations (CNV) are implicated in ASD For this study, single nucleotide polymorphism (SNP) microarrays were used to genotype 966 individuals with ASD and 1,287 matched control individuals. All study subjects were of European ancestry. The total number of CNVs, their approximate sizes, and the total number of genes affected by CNVs were compared between case and control subjects. While neither of the two former attributes differed between groups, rare, genic CNVs occurring with less than 1% frequency were 1.19 fold more frequent in ASD subjects. Furthermore, individuals with ASD harboured CNVs previously implicated in ASD or ID 1.69 times more frequently than control subjects. This analysis also revealed four novel genetic loci significantly associated with ASD: SHANK2, SYNGAP1, DLGAP2, and DDX53-PTCHD1. Other CNVs were identified in genes important for neuronal development and GTPase/Ras signalling.

What families should know

This study highlights some of the genetic explanations for the heritability of ASD. However, this study also found that 5.7% of individuals with ASD also had at least one de novo, or uninherited CNV, indicating that sporadic genetic events are also important. The wide variation in CNVs found here and in other studies accounts in part for the wide variation in symptoms found in patients with ASD. Hopefully, continuing investigations will help to draw

links between particular CNVs and developmental symptoms, enabling improved genetic testing and counselling, and more targeted treatment.

What practitioners should know

This study provides further evidence that common genetic variation cannot explain a majority of ASD cases. Instead, multiple combinations of variations lead to a wide range of ASD phenotypes. This study also confirms the involvement of CNVs previously implicated in ASD and suggests that some CNVs implicated in ID are also important in ASD. Importantly, studies of CNVs in ASD can provide insight into the molecular mechanisms that are disrupted in these disorders. The SHANK2, SYNGAP1, and DLGAP2 loci are involved in synapse function, which seems to be a common target of gene disruption in ASD. This study showed the novel finding of disrupted genes involved in GTPase/Ras signalling. Continuing genetic analysis of patients with ASD will facilitate a deeper understanding of these disorders and allow practitioners to better target therapies to optimize long-term outcome in patients with ASD.

Reference

Pinto, D., Pagnamenta, A., Klei, L., Anney, R., Merico, D., Regan, R., et al. (2010). Functional impact of global rare copy number variation in autism spectrum disorder. Nature, 466(7304), 368-372.

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