De novo mutations in synapse-related genes show importance in causing autism spectrum disorders and schizophrenia

childhood disability LINK

Summary

De novo mutations are important genetic causes of several diseases. De novo genetic mutations are acquired by chance as DNA is replicated to be passed on to offspring. On average, newly formed embryos have 2 de novo mutations. These mutations can cause disease when they disrupt genes coding for important proteins. Autism spectrum disorders (ASD) and schizophrenia are neurological disorders with heterogeneous characteristics and reduced reproductive fitness, and are thus likely to be influenced by de novo mutations. Indeed, recent studies demonstrate that some such mutations are more frequent in individuals with ASD or schizophrenia than in unaffected individuals. This study further characterizes de novo mutations that are associated with these two neurodevelopmental conditions.

Disrupted protein function is associated with ASD and schizophrenia. For this study, 401 synaptic genes were sequenced in 142 individuals with ASD and 143 individuals with schizophrenia and their parents. Sequences were compared to a subset of 39 synaptic genes sequenced in 285 control individuals and their parents. Individuals with ASD or schizophrenia were recruited in the Synapse-to-Disease (S2D) project, and most had no family history of either disorder. Individuals with ASD or schizophrenia were five times more likely than control individuals to exhibit de novo mutations that affected protein function. In total, 15 de novo mutations were detected, with 14 found in individuals with ASD or schizophrenia. These 14 mutations were found in the SHANK3, GSN, FLI16237, MAP2K1, GRIN2B, BSN, ATP2B4, NRXN1, IL1RAPL1, KLC2, KIF5C, and KIF17 genes.

What families should know

While ASD and schizophrenia are highly heritable, this study indicates that uninherited, de novo mutations are also important in the development of these disorders. De novo mutations are especially important in cases where no family history exists. The prevalence of such mutations may also explain the increased risk for these disorders among children with parents of greater age.

What practitioners should know

This study supports previous findings that de novo mutations contribute to the etiology of ASD and schizophrenia. De novo mutations may partially explain the high global incidences of ASD and schizophrenia despite varying environmental factors and the reduced reproductive fitness of affected individuals. De novo mutations were not only more frequent, but also had greater deleterious potential, measured as the nonsense: missense ratio, in individuals affected by ASD or schizophrenia. This study identified important mutated genes in ASD and schizophrenia, including SHANK3, a synapse protein coding gene, which has previously been implicated in ASD. These genes may provide clues to the molecular pathways disrupted in ASD and schizophrenia.

Reference

Awadalla, P., Gauthier, J., Myers, R., Casals, F., Hamdan, F., Griffing, A., et al. (2010). Direct measure of the de novo mutations rate in autism and schizophrenia cohorts. The American Journal of Human Genetics, 87, 316-324.

Link to article : https://www.ncbi.nlm.nih.gov/pubmed/20797689