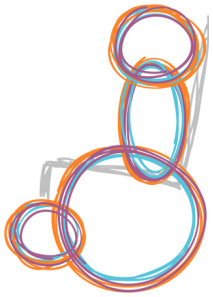
Mutations in the foxp1 gene may be associated with language impairments that accompany intellectual disability and autism

childhood disability LINK



Summary

Developmental language disorders occur frequently and are often inherited between generations. However, little is known about the genes that cause these disorders. Previous studies indicate that mutations in the FOXP2 gene are associated with language impairments. Close similarities and functional interactions between the FOXP2 and FOXP1 genes suggest that the latter may also be involved. However, one previous study demonstrated that FOXP1 mutations are not involved in the same language impairments as caused by FOXP2 mutations. Thus, the present study examined whether FOXP1 mutations may be implicated in other developmental conditions that are associated with language impairment, such as intellectual disability (ID) and autism spectrum disorders (ASD).

For this study, the genetic sequence of the FOXP1 gene was analyzed in individuals with non-inherited ASD and ID. In particular, copy number variant (CNV) mutations were assessed in 53 individuals with ASD, 30 individuals with ID, and 27 with both conditions. Complete mutation analysis was performed on all exons and intron-exon boundaries in 84 individuals with ASD, 110 individuals with ID, and 51 with both ASD and ID. The CNV and exon analyses were compared to 570 healthy control individuals.

One CNV and one de novo nonsense mutation was found in affected individuals but not in healthy controls. A test called a luciferase assay conducted in human embryonic kidney (HEK) cells confirmed that the nonsense mutation disrupted the function of the FOXP1 protein.

What families should know

This study reports on two individuals with mutations in the FOXP1 gene and strikingly similar impairments in language development. One patient was diagnosed with ID and the other with both ASD and ID. The former started speaking at 3 years of age and the latter at 6 years of age. In late childhood and adolescence, the patients displayed limited expressive language abilities but better receptive language abilities. In addition, both showed stereotyped and obsessive behaviors along with irritability and hyperactivity. It may be

possible that the particular features of ASD and ID observed in these two patients are partly attributable to disruptions in the FOXP1 gene.

What practitioners should know

The FOXP1 and FOXP2 genes code for transcriptional repressor proteins. Heterozygous FOXP2 mutations have previously been shown to be sufficient for causing verbal dyspraxia; in the present study, a heterozygous nonsense mutation in FOXP1 also seems to be associated with language impairments. Notably, the specific verbal dyspraxia phenotype was not apparent in the two subjects described here; however, developmental testing confirmed that they both had severely impaired language development along with moderate ID and, in one case, ASD. This suggests that FOXP1 mutations may have a more global effect than FOXP2 mutations. FOXP1 mutations have been previously reported in two other individuals with delayed speech, corroborating the involvement of this gene in language development. The FOXP1 and FOXP2 genes provide interesting genetic targets for further investigation into the molecular mechanisms underlying neurodevelopmental disorders like ID, ASD, and language impairment.

Reference

Hamdan, F., Daoud, H., Rochefort, D., Piton, A., Gauthier, J., Langlois, M., et al. (2010). De novo mutations in FOXP1 in cases with intellectual disability, autism, and language impairment. American journal of Human Genetics, 87(5), 671-678.

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