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De novo POGZ mutations in sporadic autism disrupt the DNA-binding activity of POGZ

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Abstract

Background: A spontaneous de novo mutation is a new mutation appeared in a child that neither the parent carries. Recent studies suggest that recurrent de novo loss-of-function mutations identified in patients with sporadic autism spectrum disorder (ASD) play a key role in the etiology of the disorder. POGZ is one of the most recurrently mutated genes in ASD patients. Our laboratory and other groups have recently found that POGZ has at least 18 independent de novo possible loss-of-function mutations. Despite the apparent importance, these mutations have never previously been assessed via functional analysis.

Methods: Using wild-type, the Q1042R-mutated, and R1008X-mutated POGZ, we performed DNA-binding experiments for proteins that used the CENP-B box sequence in vitro. Data were statistically analyzed by one-way ANOVA followed by Tukey-Kramer post hoc tests.

Results: This study reveals that ASD-associated de novo mutations (Q1042R and R1008X) in the POGZ disrupt its DNA-binding activity.

Conclusions: Here, we report the first functional characterization of de novo POGZ mutations identified in sporadic ASD cases. These findings provide important insights into the cellular basis of ASD.

Keywords: Autism spectrum disorder, Recurrent mutation, De novo mutation, POGZ, DNA-binding activity

Background

The genetic etiology of autism spectrum disorder (ASD) remains poorly understood. A spontaneous de novo mutation is a new mutation appeared in a child that neither the parent carries. Recent next-generation sequencing studies have demonstrated that de novo mutations greatly contribute to the risk of ASD and often produce large effects [1–5]. In particular, genes with highly recurrent de novo possible loss-of-function mutations play key roles in the etiology of this disorder. De novo mutations in multiple (≥3) unrelated patients have been identified in several such high-confidence ASD risk genes, including *CHD8*, *ARID1B*, *SYNGAP1*, *DYRK1A*, *SCN2A*, *ANK2*, *ADNP*, *DSCAM*, *CHD2*, *KDM5B*, *SUV420H1*, *GRIN2B*, *ASH1L*, and POGZ [5]. Among these 14 genes, POGZ is one of the most recurrently mutated genes in ASD patients [4, 5]. Our laboratory and other groups have recently found that POGZ has at least 18 independent de novo possible loss-of-function mutations (Fig. 1, upper) [4–8]. Therefore, de novo mutations in POGZ can be strongly associated with ASD risk; however this association requires experimental validation. Despite the apparent importance, these mutations have never previously been assessed via functional analysis. Here, we report that ASD-associated de novo mutations in the POGZ disrupt the DNA-binding activity of POGZ. These findings provide insight into the cellular basis of ASD. In addition, de novo POGZ mutations are frequently found also in patients with intellectual

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