Overlap of polymicrogyria, hydrocephalus, and Joubert syndrome in a family with novel truncating mutations in *ADGRG1/GPR56* and *KIAA0556*

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Abstract

Genetic mutations associated with brain malformations can lead to a spectrum of severity and it is often difficult to determine whether there are additional pathogenic variants contributing to the phenotype. Here, we present a family affected by a severe brain malformation including bilateral polymicrogyria, hydrocephalus, patchy white matter signal changes, and cerebellar and pontine hypoplasia with elongated cerebellar peduncles leading to the molar tooth sign. While the malformation is reminiscent of bilateral frontoparietal polymicrogyria (BFPP), the phenotype is more severe than previously reported and also includes features of Joubert syndrome (JBTS). Via exome sequencing, we identified homozygous truncating mutations in both *ADGRG1/GPR56* and *KIAA0556*, which are known to cause BFPP and mild brain-specific JBTS, respectively. This study shows how two

independent mutations can interact leading to complex brain malformations.

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Keywords

- **Polymicrogyria**
- **Hydrocephalus**
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- **Lissencephaly**