

## CORRESPONDENCE

## Intestinal-Cell Kinase and Juvenile Myoclonic Epilepsy

**TO THE EDITOR:** With regard to the article by Bailey et al. (March 15, 2018, issue)<sup>1</sup> on the potential role of variants in the gene encoding intestinal-cell kinase (*ICK*) in genetic generalized epilepsies, including juvenile myoclonic epilepsy: We attempted replication by rechecking for enrichment of *ICK* variants in two previously published analyses of mainly familial cases of genetic generalized epilepsy,<sup>2,3</sup> which included a total of 1149 cases of genetic generalized epilepsy and 5911 ethnically matched controls. We analyzed the burden of single-gene rare variants with the use of whole-exome sequencing data, applying population stratification and both sample and variant quality control. We found no evidence of an enrichment of *ICK* variants in genetic generalized epilepsies or juvenile myoclonic epilepsy. Specifically, we did not detect a nonsynonymous variant in 357 persons with juvenile myoclonic epilepsy at a minor allele frequency at or below 0.1%. Although we cannot exclude the possibility that *ICK* variants may be population-specific risk factors for juvenile myoclonic epilepsy, the lack of validation in our cohorts does not support a true disease association but rather suggests that the authors' results may be due to chance, possibly owing to methodologic issues (see the Supplementary Appendix, available with the full text of this letter at NEJM.org).

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No potential conflict of interest relevant to this letter was reported.

1. Bailey JN, de Nijs L, Bai D, et al. Variant intestinal-cell kinase in juvenile myoclonic epilepsy. *N Engl J Med* 2018;378:1018-28.
2. Epi4K Consortium, Epilepsy Phenome/Genome Project. Ultra-rare genetic variation in common epilepsies: a case-control sequencing study. *Lancet Neurol* 2017;16:135-43.
3. May P, Girard S, Harrer M, et al. Rare coding variants in genes encoding GABA<sub>A</sub> receptors in genetic generalised epilepsies: an exome-based case-control study. *Lancet Neurol* 2018;17:699-708.

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**THE AUTHORS REPLY:** We thank Lerche et al. for sharing their data and respectfully disagree with their suggestion that the association between variant *ICK* and juvenile myoclonic epilepsy that we described is due to chance, given our reliance on guidelines from the National Human Genome Research Institute in establishing causality of sequence variants.<sup>1</sup> We also applied guidelines from the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG–AMP) when we weighed and scored evidence for the pathogenicity of *ICK* variants, although we acknowledge that the ACMG–AMP guidelines were formulated, in the main, to determine the pathogenicity of new variants in genes previously established as pathogenic when variant. However, the multiple lines of evidence that we obtained contributed to inferences at the level of both variant and gene<sup>1,2</sup> and thus implicate *ICK* variants as pathogenic in persons with juvenile myoclonic epilepsy from Latin America and Japan.<sup>1</sup>

There is overwhelming evidence that both locus and allelic heterogeneity is high in epilepsy. In our view, this is the most likely explanation for the negative findings in the European and North American data sets cited by Lerche et al.

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Since publication of their article, the authors report no further potential conflict of interest.

1. MacArthur DG, Manolio TA, Dimmock DP, et al. Guidelines for investigating causality of sequence variants in human disease. *Nature* 2014;508:469-76.
2. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med* 2015;17:405-24.

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