Editors' Note: Kuhlentbauer critiques the study by Wu et al. on a rare *FUS* gene variant and essential tremor (ET), pointing out its weaknesses and stressing the need for replication of the results before assuming any definite conclusion. As a result of this WriteClick exchange, the editors are establishing a policy that studies reporting a novel mutation as the cause of a neurologic disease must include an adequately powered verification sample. Should propofol be avoided in patients with mitochondrial disorder? Parness and Savard et al. explain their opposite views.

Chafic Karam, MD, and Robert C. Griggs, MD

IDENTIFICATION OF A NOVEL RISK VARIANT IN THE *FUS* GENE IN ESSENTIAL TREMOR

Gregor Kuhlentbauer, Kiel, Germany: Wu et al.¹ described the association between a novel rare variant in the *FUS* gene (Met392Ile) and ET. They claimed that they observed “a consistent trend” and a “2 times increased risk” in the replication sample based on the finding that 2/250 patients—yet only 1/250 controls—showed the allele in question. The *p* value in the replication sample is 1.0 and the 95% confidence interval of the odds ratio 0.18 to 22.29. This is a negative and not a positive finding in the replication sample and the interpretation by the authors is misleading. The conclusion that the joint analysis of both samples is positive is also of limited importance because the number of controls in the first sample is 24 times larger than in the replication sample. Therefore, the whole association rests on 6/347 patients carrying the associated allele in the first sample. Replication is needed before considering this variant as a risk variant for ET.

Author Response: Eng-King Tan, Singapore; Yih-Ru Wu, Taipei, Taiwan: We thank Dr. Kuhlentbauer for his interest in our study. The frequency of the *FUS* variant was twice that in cases compared to controls in the second case control set. We agree that due to the rarity of the variant, the second sample set was inadequate to verify the result in our much larger discovery set. As we mentioned, further replication in different populations will be of interest.

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1. Wu YR, Foo JN, Tan LCS, et al. Identification of a novel risk variant in the *FUS* gene in essential tremor. *Neurology* 2013;81:541–544.

PROPOFOL-RELATED INFUSION SYNDROME HERALDING A MITOCHONDRIAL DISEASE: CASE REPORT

Jerome Parness, Pittsburgh: Savard et al.¹ described a case of propofol-infusion syndrome (PRIS) heralding an occult case of mitochondrial disease. The authors stated: “Our observations support the recommendation to avoid using propofol in patients with known mitochondrial diseases.” Au contraire!

In the practice of pediatric anesthesia, propofol (2–3 mg/kg) is primarily used as a single-dose induction agent, and sometimes in an infusion for surgical cases lasting a few hours. Recent reviews of anesthetic outcomes of patients with mitochondrial disorders did not reveal adverse anesthetic outcomes.^{2,3} This is remarkable since many of the modern anesthetic agents—parenteral or inhaled—adversely affect mitochondrial function.⁴

Since all cases of PRIS result from prolonged (i.e., days) use of high-dose propofol infusion, it seems unlikely that this syndrome is due to a classic drug-receptor second-messenger interaction. Something must accumulate: the parent drug, a metabolite, a component of the lipid carrier, or some combination of the above. Propofol can affect the mitochondrion by at least 4 different mechanisms,⁴ yet it is remarkably safe when used in a bolus, with or without a short infusion.

Categorically banning propofol in such a heterogeneous group of patients⁵ is unwarranted.

Author Response: Martin Savard, Alexis F. Turgeon, Quebec City, Canada: We thank Dr. Parness for his interest and commentary. PRIS is an uncommon but potentially catastrophic clinical syndrome and no therapeutic alternatives exist aside from the withdrawal of the drug and supportive care. Our limited knowledge on the etiology and pathophysiology of PRIS preclude effectively preventing its occurrence. High doses and long-term infusion are the main risk factors. However, even with the same risk factors, some individuals experience PRIS while others do

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Identification of a novel risk variant in the *FUS* gene in essential tremor

Gregor Kuhlenbaumer, Eng-King Tan and Yih-Ru Wu

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