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Editors' Note: Mawer et al. address the 2 issues that were raised in Tomson and Klein's editorial regarding their study. They clarify the gestational timing of antiepileptic drug dose and the conflicting conclusions about the influence of folic acid supplementation on the IQ of children. Dickson et al. believe that grouping hippocampal sclerosis regardless of whether transactive response DNA binding protein pathology is present weakens the *TMEM* genotype association to hippocampal sclerosis of the elderly. Schneider et al. agree and reanalyze their data accordingly but the results show that the relationship between *TMEM* genotype and hippocampal sclerosis was not masked by the inclusive definition.

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

FINE-TUNING RISK ASSESSMENT WITH ANTIEPILEPTIC DRUG USE IN PREGNANCY

George Mawer, Rebecca Bromley, Manchester; Gus A. Baker, Liverpool, UK; Kimford J. Meador, Stanford, CA; Jill Clayton-Smith, Manchester, UK: We would like to address 2 issues raised in Drs. Tomson and Klein's[1] editorial regarding our study.[2] They noted that we failed to adequately define the gestational timing of drug dose in our report on the IQ of children exposed to antiepileptic drugs in utero. We regret this omission. For each drug, the dose quoted is prescribed before conception. The choice of 800 mg/day as an upper limit to low dose of valproate was based on the distribution of doses in the valproate-treated group.

Drs. Tomson and Klein noted that there were conflicting conclusions about the influence of folic acid supplementation on the IQ of the child. In the UK study,[2] we found no difference in the IQ of children between those whose mothers had received preconceptual folic acid and those who had not. The Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study,[3] however, reported higher IQ levels in those children whose mothers had received periconceptual folic acid.

Policy in the UK study actively encouraged folic acid supplementation in women with epilepsy (WWE). As a result, 80% of the WWE who were not receiving folate before conception were doing so by 12 weeks gestation. This may have masked any adverse effects on IQ arising from a lack of folate supplementation.

1. Tomson T, Klein P. Fine-tuning risk assessment with antiepileptic drug use in pregnancy. Neurology 2015;84:339–340.
2. Baker GA, Bromley RL, Briggs M, et al. IQ at 6 years after in utero exposure to antiepileptic drugs: a controlled cohort study. Neurology 2015;84:382–390.
3. Meador KJ, Baker GA, Browning N, et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Lancet Neurol 2013;12:244–252.

THE *TMEM106B* LOCUS AND TDP-43 PATHOLOGY IN OLDER PERSONS WITHOUT FTLD

Dennis W. Dickson, Rosa Rademakers, Alexandra M. Nicholson, Jacksonville, FL: Yu et al.[1] investigated the association of TMEM106B variants with TAR-DNA binding protein 43 (TDP-43) pathology in elderly individuals without frontotemporal lobar degeneration (FTLD-TDP). They also examined whether these associations were independent of comorbid pathologic processes, such as Alzheimer disease (AD) and hippocampal sclerosis (HS). The results confirmed earlier findings that TMEM106B variants are an important TDP-43 pathology risk factor in FTLD-TDP, sporadic amyotrophic lateral sclerosis, AD, tangle predominant dementia, and Lewy body disease.[2–4] The authors also reported a lack of association between TMEM106B variants and HS after adjusting for the presence of TDP-43 pathology. This likely reflects lack of specificity in the HS diagnostic criteria.

Evidence suggests that HS in the elderly is a degenerative process that can be distinguished from hippocampal neuronal loss associated with anoxic-ischemic injury or epilepsy by the presence of TDP-43 pathology.[5] Grouping HS of the elderly with HS due to other etiologies confounds the results and weakens the TMEM106B association with HS of the elderly. Current evidence suggests the strongest genetic determinant of HS in the elderly is TMEM106B and more precise neuropathologic criteria for HS should be used when assessing genetic risk factors for HS.

Author Response: Julie A. Schneider, Lei Yu, David A. Bennett, Chicago: We thank Dickson et al. for their comments on our article.[1] They expressed concern that by including HS without TDP pathology in the definition of HS we may have masked an association of the TMEM variant with HS. In our study, 13% (n = 70) of 544 subjects had HS pathology. Of these, TDP was present in 60 (86%; HS+TDP) and absent in 10 (14%; HS-TDP). To address their concern, we excluded HS-TDP and revised our logistic regression model using HS+TDP as the outcome. We did not find a significant association of TMEM with HS+TDP (odds ratio 1.183, 95% confidence interval 0.799–1.752, $p = 0.402$).

To ensure results were not confounded by TDP, we repeated the model by further controlling for TDP and results were unchanged ($p = 0.512$). Overall, while we agree that HS with and without TDP may reflect differing disease processes, these analyses show that a relationship between TMEM and HS was not masked by our inclusive definition and support that TMEM is related specifically to the pathology of TDP. However, results might vary with larger numbers of HS cases, especially if one considers HS+TDP as the outcome. Further studies of the TMEM variant, HS, and TDP pathology in community-based cohorts are warranted.

1. Yu L, De Jager PL, Yang J, et al. The TMEM106B locus and TDP-43 pathology in older persons without FTLD. Neurology 2015;84:927–934.
2. Aoki N, Murray ME, Ogaki K, et al. Hippocampal sclerosis in Lewy body disease is a TDP-43 proteinopathy similar to FTLD-TDP Type A. Acta Neuropathol 2015;129:53–64.
3. Rutherford NJ, Carrasquillo MM, Li M, et al. TMEM106B risk variant is implicated in the pathologic presentation of Alzheimer disease. Neurology 2012;79:717–718.
4. Nelson PT, Wang WX, Partch AB, et al. Reassessment of risk genotypes (GRN, TMEM106B, and ABCC9 variants) associated with hippocampal sclerosis of aging pathology. J Neuropathol Exp Neurol 2015;74:75–84.
5. Lee EB, Lee VM, Trojanowski JQ, Neumann M. TDP-43 immunoreactivity in anoxic, ischemic and neoplastic lesions of the central nervous system. Acta Neuropathol 2008;115:305–311.

CORRECTION

Poor early relapse recovery affects onset of progressive disease course in multiple sclerosis

In the article "Poor early relapse recovery affects onset of progressive disease course in multiple sclerosis" by M. Novotna et al. (*Neurology*® 2015;85:722–729), there is an error in the disclosures. Dr. Lucchinetti's disclosures should read: "C.F. Lucchinetti has received research support from the Department of Defense, NIH, Novartis, Biogen, Alexion, and Sanofi; holds a patent re: Aquaporin-4- associated antibodies for diagnosis of neuromyelitis optica; and receives royalties from the publication of *Blue Books of Neurology: MS 3* (Saunders Elsevier, 2010)." The authors regret the error.

Author disclosures are available upon request (journal@neurology.org).