WriteClick: Editor's Choice

Editors' Note: Wu et al. argue that, in certain races, the *SMPD1* p.L302P mutation does not play an important role in Parkinson disease risk. Orr-Urtreger et al. are not surprised, since this is a founder Ashkenazi mutation. They suggest sequencing of the entire *SMPD1* gene, in a much larger cohort of patients and controls, to examine the possible effects of rare *SMPD1* mutations in non-Ashkenazi populations. Silvestri et al. and St. Louis et al. compare their findings in studies of sleep disorders in patients with myotonic dystrophy type 2 (DM2) and try to explain differences in their results, especially regarding obstructive sleep apnea. They agree on the necessity of prospective large-scale studies in patients with DM2 looking objectively at sleep abnormalities.

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

THE p.L302P MUTATION IN THE LYSOSOMAL ENZYME GENE *SMPD1* IS A RISK FACTOR FOR PARKINSON DISEASE

Ruey-Meei Wu, Chin-Hsien Lin, Han-I Lin, Taipei, Taiwan: Gan-Or et al.[1] replicated data on a large number of patients with Parkinson disease (PD) in 2 Ashkenazi Jewish cohorts. We would suggest that the authors obtain data from other populations to support the pathogenic role of *SMPD1* in the risk of PD. We have genotyped *SMPD1* p.L302P using TaqMan Genotyping Assays on the StepOnePlus Real-Time PCR machine (Applied Biosystems, Foster City, CA) in 1,139 participants. This group comprised 579 patients with PD and 560 control subjects in a Taiwanese population. Among the PD group, 199 patients were young onset (<50 years). We did not identify any p.L302P mutation in patients or control subjects. The *SMPD1* p.L302P mutation is unlikely to play a major role in PD risk in our ethnicity.[2–4] Different demographics and region-specific genetic and environmental interactions may contribute to the differences in results.[5]

Author Response: Avi Orr-Urtreger, Ziv Gan-Or, Tel-Aviv, Israel: Wu et al. analyzed their PD cohort and controls from Taiwanese origin for the *SMPD1* p.L302P mutation and no carriers of this mutation were identified. The *SMPD1* p.L302P is a founder mutation causing Niemann-Pick type A disease among Ashkenazi Jews and a risk factor for PD in this population.[1] In contrast, this specific mutation was never described in the Taiwanese population. Until 2009, no Niemann-Pick patients with *SMPD1* mutations were identified in Taiwan, and then only one patient with compound heterozygous genotype (p.P330R/p.A451D) was described.[6] To reach statistical significance, we analyzed 938 patients with PD and compared them to more than 10,000 controls. Lin et al. analzyed only 579 patients with PD and 560 controls. It is not reasonable to expect the replication of the effect of a founder Ashkenazi mutation in a small population in which the *SMPD1* p.L302P was never described and in which other *SMPD1* mutations are very rare. To examine the possible effects of rare *SMPD1* mutations on this population, sequencing of the entire *SMPD1* gene is required in a much larger cohort of patients and controls.

1. Gan-Or Z, Ozelius LJ, Bar-Shira A, et al. The p.L302P mutation in the lysosomal enzyme gene *SMPD1* is a risk factor for Parkinson disease. Neurology 2013;80:1606–1610.
2. Farrer MJ, Stone JT, Lin CH, et al. Lrrk2 G2385R is an ancestral risk factor for Parkinson's disease in Asia. Parkinsonism Relat Disord 2007;13:89–92.
3. Lin CH, Chen ML, Chen GS, Tai CH, Wu RM. Novel variant Pro143Ala in HTRA2 contributes to Parkinson's disease by inducing hyperphosphorylation of HTRA2 protein in mitochondria. Hum Genet 2011;130:817–827.
4. Lin CH, Tan EK, Chen ML, et al. Novel ATP13A2 variant associated with Parkinson disease in Taiwan and Singapore. Neurology 2008;71:1727–1732.
5. Ross CA, Smith WW. Gene-environment interactions in Parkinson's disease. Parkinsonism Relat Disord 2007;13 (suppl 3):S309–S315.
6. Lan MY, Lin SJ, Chen YF, et al. A novel missense mutation of the SMPD1 gene in a Taiwanese patient with type B Niemann-Pick disease. Ann Hematol 2009;88:695–697.

RESTLESS LEGS SYNDROME AND DAYTIME SLEEPINESS ARE PROMINENT IN MYOTONIC DYSTROPHY TYPE 2

Gabriella Silvestri, Maria Laura Ester Bianchi, Anna Losurdo, Giacomo Della Marca, Rome: Lam et al.[1] studied the frequency of restless legs syndrome, excessive daytime sleepiness (EDS), and fatigue in 30 patients with myotonic dystrophy type

2 (DM2). They did not find obstructive sleep apnea (OSA) or REM sleep behavior disorder. The authors concluded that EDS may also be related to an intrinsic CNS disturbance in DM2. We found that OSA is the most frequent sleep-disordered breathing (SDB) in this disorder. By home-based cardiorespiratory monitoring, we found SDB in 6 of 14 patients with DM2 (8 female, 6 male, 60.4 ± 11.9 years): 4 had OSA, 1 had central sleep apnea, and 1 had mixed features.

Interestingly, SDB indexes are inversely correlated with most respiratory parameters, suggesting polygraphic follow-up in patients with DM2 with altered pulmonary function tests. The very low prevalence of OSA found by Lam et al. could be related to estimation of the frequency of OSA only by questionnaires, which are often not sensitive enough in myotonic dystrophies.[2] It is also possible that a bias due to the higher prevalence of female subjects in their study cohort could have led to this result. Lam et al.[1] have successfully extended previous discussion[3,4] about sleep disturbances in DM2.

Author Response: Erik K. St. Louis, Erek M. Lam, Paul W. Shepard, Rochester, MN: We thank Silvestri et al. for their comments on our study of sleep disturbances in DM2.[1] We agree that polysomnography is preferable to questionnaires for evaluating SDB.

Over the past 20 years, the prevalence of polysomnographically determined moderate OSA (apnea-hypopnea index of 15 or more per hour) has increased to approximately 10%–17% in adult men and 3%–9% in adult women aged 30–70 years.[6] It is more frequent in those with comorbid type 2 diabetes, hypertension, cardiac disease, and stroke.[7] Our selection of age- and sex-matched controls makes it unlikely that confounding biases affected our findings of comparable OSA symptom frequency.

We were intrigued to learn that Silvestri et al. found relatively frequent comorbid OSA (42.8%, in 6 of 14 DM2 patients) on home sleep studies. This is slightly less than our and others' previously reported frequency of comorbid OSA in 60%–67% of patients with DM2 studied with polysomnography.[3,5] Future large-scale prospective studies of sleep disturbances in DM2 should incorporate objective sleep study data, in comparison to age- and sex-matched control subjects, to better determine the frequency of SDB and hypersomnia in DM2.

1. Lam EM, Shepard PW, St. Louis EK, et al. Restless legs syndrome and daytime sleepiness are prominent in myotonic dystrophy type 2. Neurology 2013;81:157–164.
2. Laberge L, Gagnon C, Dauvilliers Y. Daytime sleepiness and myotonic dystrophy. Curr Neurol Neurosci Rep 2013;13:340.
3. Shepard P, Lam EM, St Louis EK, Dominik J. Sleep disturbances in myotonic dystrophy type 2. Eur Neurol 2012; 68:377–380.
4. Tieleman AA, Knoop H, van de Logt AE, Bleijenberg G, van Engelen BG, Overeem S. Poor sleep quality and fatigue but no excessive daytime sleepiness in myotonic dystrophy type 2. J Neurol Neurosurg Psychiatry 2010;81:963–967.
5. Bhat S, Sander HW, Grewal RP, Chokroverty S. Sleep disordered breathing and other sleep dysfunction in myotonic dystrophy type 2. Sleep Med 2012;13:1207–1208.
6. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. Am J Epidemiol Epub 2013 Apr 14.
7. Lee W, Nagubadi S, Kryger MH, Mokhlesi B. Epidemiology of obstructive sleep apnea: a population-based perspective. Expert Rev Respir Med 2008;2:349–364.

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

Restless legs syndrome and daytime sleepiness are prominent in myotonic dystrophy type 2

Gabriella Silvestri, Erik K. St. Louis, Maria Laura Ester Bianchi, et al.

Neurology 2014;82;283-284
DOI 10.1212/01.wnl.0000443031.44463.36