LETTER

P413L *CHGB* is not associated with ALS susceptibility or age at onset in a Dutch population

Gros-Louis and colleagues (1) performed a classical candidate gene case-control study on *Chromogranin B* (*CHGB*) variations in ALS patients of French, French-Canadian, and Scandinavian origin. They found a significant association between a missense variation in exon 4 (rs742710) and ALS susceptibility conferring an ≈3.3-fold increased risk of ALS in the French/French-Canadian population studied. This missense variation is comparable to the *APOE-ε4* allele in Alzheimer's disease (2). In addition, this P413L *CHGB* variant also acts as a modifier of disease onset by decreasing the median age at onset by 7 years in patients with sporadic ALS and by as much as 11 years in familial ALS.

The impact of such a difference in disease susceptibility and modification is striking; in the largest (genomewide) association study performed thus far in almost 5,000 ALS patients and over 14,000 controls, only two loci were found that increased the risk of ALS 1.2-fold (3). The probe for the variation studied by Gros-Louis and colleagues is not present on the 317K Illumina array used in that genome-wide association study nor properly tagged by any other SNP. This makes *CHGB* an interesting candidate to fill the gap of missing genomic variations that can (partly) explain the heritability of ALS.

Given the impact of this finding, we sought to determine how this SNP is distributed in a population of 1,028 sporadic ALS patients, 60 familial ALS cases, and 1,812 age- and sex-matched controls from The Netherlands using a Taqman assay (Applied Biosystems). Our replication study had 80% power to detect an odds ratio of ≥1.65 given the known allele frequency and a significance cutoff of 0.05.

We observed little difference in minor allele frequencies between the control (0.035), sporadic ALS (0.034), and familial ALS (0.033) groups, and no statistically significant differences were found in sporadic ALS [odds ratio (OR) = 0.98; 95% confidence interval (CI) = 0.7–1.3; $P = 0.84$] and familial ALS (OR = 0.8; 95% CI = 0.3–2.2; $P = 0.94$). When looking at the age at onset, carriers of the P413L variant did not show an earlier disease onset in our population. Median age at onset in P413L carriers was 60.56 years versus 60.70 years in non-P413L carriers (hazard ratio = 1.02; 95% CI = 0.80–1.30; $P = 0.88$).

Replication association studies do not tend to be very successful when it comes to confirming initial published associations for various reasons: for instance, lack of power (inflated type I results), inappropriate controls, or differences in population structures (4). Although Gros-Louis et al. did observe an association trend in the additional Scandinavian cohort of patients and controls (1), the pooled OR of the French, French-Canadian, and Swedish samples was less (OR = 2.4) compared to the initial French and French-Canadian finding (OR = 3.7). The P413L variant is relatively rare, and so large numbers of patients and controls are needed to avoid type I errors or inflation of risk estimates (4). Finally, population-specific effects, as exemplified in familial ALS (5), could explain these conflicting results.

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1. Gros-Louis F, et al. (2009) Chromogranin B P413L variant as risk factor and modifier of disease onset for amyotrophic lateral sclerosis. *Proc Natl Acad Sci USA* 106: 21777–21782.
2. Strittmatter WJ, et al. (1993) Apolipoprotein E: High-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. *Proc Natl Acad Sci USA* 90:1977–1981.
3. Van Es MA, et al. (2009) Genome-wide association study identifies 19p13.3 (UNC13A) and 9p21.2 as susceptibility loci for sporadic amyotrophic lateral sclerosis. *Nat Genet* 41:1083–1087.
4. Ioannidis JP (2008) Why most discovered true associations are inflated. *Epidemiology* 19:640–648.
5. Van Es MA, et al. (2009) Large scale SOD1 mutation screening provides evidence for genetic heterogeneity in amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry*, in press.

Author contributions: P.W.J.v.V., J.H.V., and L.H.v.d.B. designed research; P.W.J.v.V. performed research; P.W.J.v.V. and J.H.V. analyzed data; and P.W.J.v.V., J.H.V., and L.H.v.d.B. wrote the paper.

The authors declare no conflict of interest.

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