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Response to the letter "Haptoglobin phenotype and Parkinson disease risk" by Delanghe et al.

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We would like to thank Delanghe et al. for their thoughtful comments regarding our previously published articles [1,2]. We essentially agree with Delanghe et al. view of the results of association of haptoglobin (Hp) 2-1 phenotype with Parkinson disease (PD) [1]. The heterosis that we observed, in which the heterozygous Hp 2-1 phenotype was associated

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Conflicts of interest

No conflicts of interest.

with elevated risk of PD more strongly than both homozygous phenotypes (Hp 1-1 and Hp 2-2), may be due to the combination of multiple effects conferred by the different Hp phenotypes, not just the modulation of serum iron levels. We have previously observed that Hp 2-1 phenotype is associated with PD risk [1], and with relatively low blood iron among PD patients [2]. Since lower blood iron has been proposed as a risk factor for PD [3], it is likely that the blood iron abnormality is one of multiple contributing factors to the observed association of Hp 2-1 with PD. In addition to iron metabolism, contributing factors to the association of Hp 2-1 phenotype with PD could potentially be due to Hp 2-2 phenotype having higher angiogenic potential, as angiogenesis may be a protective factor for neurodegeneration, and to the lower levels of free hemoglobin associated with Hp 2-2 phenotype. And, on the other hand, the apparently protective effect of Hp 1-1 might be explained by the higher levels of Vitamin C associated with this phenotype, as illustrated by Delanghe et al. in Table 1 of their letter. The greater efficiency of Hp 2-2 molecules in eliciting angiogenesis than either Hp 2-1 and Hp 1-1 molecules may be potentially relevant to the protective effect of Hp 2-2 on PD risk, insofar as angiogenesis can lead to dopaminergic neurons survival. In fact, promoters of angiogenesis such as vascular endothelial growth factor (VEGF) have been shown to be neuroprotective for dopaminergic neurons both *in-vitro* and *in-vivo* in a mouse model of PD [4].

It is noteworthy that heterosis was observed with respect to Hp phenotype regarding association with other diseases in addition to PD. Notably, an excess of Hp 2-1 phenotype as compared to both Hp 1-1 and Hp 2-2 phenotypes was previously observed by Fröhlander and Forsgren [5] among patients with motor neuron disease, another neurodegenerative disorder.

As a final note, Delanghe et al. cite our article (Costa-Mallen et al., 2008), reference [4] in their Letter, regarding a study in an animal model of PD: “In an animal model of PD, a sustained increase of Hp in both plasma and cerebrospinal fluid, as observed in Hp-1 allele carriers, has been detected before the onset of degeneration of dopaminergic neurons [4]”. This citation of our article in the letter of Delanghe et al. was in error since our article did not describe the animal model study.

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