

**Reply to: *GNPAT* variant is associated with iron phenotype in healthy Taiwanese women:
A population without the *HFE* C282Y mutation**

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Abbreviations:

glyceronephosphate O-acyltransferase (GNPAT)

Transferrin saturation (TS)

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To the Editor,

We read with interest the report by Hsiao et al. that Taiwanese women not selected for iron phenotypes, who were heterozygous or homozygous for the glyceronephosphate O-acyltransferase (*GNPAT*) p.D519G (rs11558492) polymorphism, had higher serum iron levels than *GNPAT* wild-type subjects. Women with *GNPAT* p.D519G also had higher levels of serum iron and transferrin saturation (TS) after a test dose of oral iron. The response to oral iron was not significantly different in Taiwanese women with or without *TMPRSS6* rs855791, a polymorphism associated with reduced activity of the enzyme matriptase-2, an inhibitor of hepcidin transcription.¹ Moreover, the association of *GNPAT* p.D519G with baseline serum iron levels was independent of *TMPRSS6* rs855791, age, and amount of menstrual blood loss. In our exome sequencing study, *GNPAT* p.D519G was also associated with high-iron phenotypes in Caucasian men with *HFE* p.C282Y homozygosity.² The important results of Hsiao et al. provide further support for a role of *GNPAT* in the regulation of iron metabolism in a population in which *HFE* p.C282Y is rare.

The allele frequency of *GNPAT* p.D519G in the Taiwanese cohort was 12%, similar to that in the general population of the 1000 Genomes Project (14%). Thus, *GNPAT* p.D519G is a relatively common determinant of the higher baseline serum iron levels and response of serum iron/TS measures to oral iron among Taiwanese women. In non-anemic young Caucasian women with hypoferritinemia, test doses of oral iron ≥ 60 mg increased circulating hepcidin levels and decreased fractional iron absorption on the subsequent day.³ Taken together, these observations suggest that *GNPAT* p.D519G alters hepcidin regulation and iron absorption in response to oral iron, although this is unproven. At present, there are no published observations of the possible effects of *GNPAT* p.D519G on hepcidin expression or iron absorption in Caucasian women with or without p.C282Y.

In our paper,² we did not propose that *GNPAT* p.D519G is a “*HFE* modifier,” but rather that it is a modifier of iron status in *HFE* p.C282Y homozygotes. Hsiao et al. suggest that *GNPAT* p.D519G acts independently of *HFE* on hepcidin regulation, and their results indicated that the effect of the *GNPAT* p.D519G allele does not involve interaction with matriptase-2. However, their observations do not exclude a possible interaction of *GNPAT* p.D519G with wild-type *HFE* protein or any other upstream regulator of hepcidin transcription. We observed that siRNA-mediated knockdown of *GNPAT* in HepG2/C3A cells markedly reduced *HAMP* mRNA expression but had no demonstrable effect on the BMP/SMAD pathway.³ Thus, taken together, our results and those of Hsiao et al. are consistent with the possibilities that *GNPAT* p.D519G either affects a gene or genes upstream of *HAMP*, or alters hepcidin expression directly. Elucidating *GNPAT*'s putative role in regulating hepcidin requires further study.

References:

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