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CORRESPONDENCE

PNPLA3 I148M Variant Is Associated With Metabolic Stress-Response Phenotype in Patients With Nonalcoholic Fatty Liver Disease

To the Editor:

We read with great interest the article by Smagris et al.[1] showing the impact of *PNPLA3*-rs738409 on the morphology and physiology of liver lipid droplets. The authors used a remarkable knockin/knockout mice with a methionine codon at position 148 of the *Pnpla3* gene, and showed that the effect of the *PNPLA3*-mutation on hepatic fat content seems to be diet-dependent.[1] Notably, an *in vitro* study in Huh-7 cells demonstrated that *PNPLA3* might modulate liver metabolism beyond its classical participation in triacylglycerol remodeling.[2] In fact, Met148 *PNPLA3* overexpression was associated with a significant increase in lactate levels, suggesting a shift to anaerobic metabolism.[2] We replicated this finding in patients with nonalcoholic fatty liver disease (NAFLD) showing a significant association between the rs738409 and the lactate-to-pyruvate (L:P) ratio, confirming the complex liver metabolic regulatory pathway in which *PNPLA3* is involved. Lactate and pyruvate were measured in serum samples from controls (n = 13) and patients with histopathologic evidence of NAFLD, either fatty liver (NAFL) n = 16 or nonalcoholic steatohepatitis (NASH) n = 17, by high-performance liquid chromatography / mass spectrometry; homozygous Ile148 or Met148 subjects were represented equally in each group.

We compared the L:P ratio in subjects homozygous for the risk Met148 variant (genotype GG) versus homozygous Ile148 (genotype CC) according to the disease status (controls, NAFL, and NASH), and we observed that among those homozygous for the risk Met148 variant, the L:P ratio was significantly increased (1.25-fold) in NAFLD patients (either NAFL or NASH) as compared to controls (Fig. 1). Conversely, no differences in the L:P ratio were observed between subjects homozygous for the Ile148 variant, either in the control or NAFLD group (Fig. 1). A significant interaction between the risk GG genotype and NAFLD on the L:P ratio was detected ($P < 0.03$).

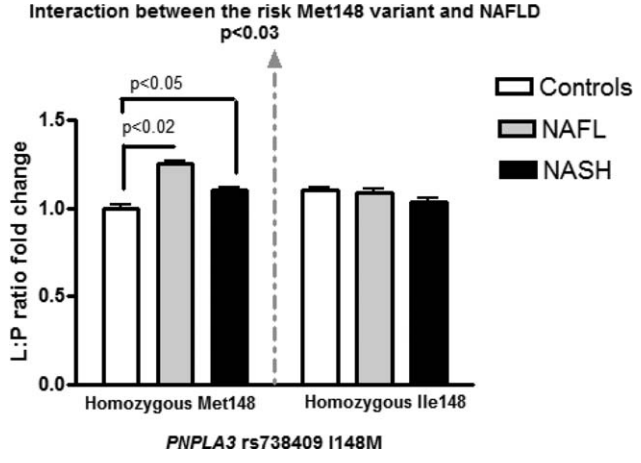

Fig. 1. Fold changes in lactate-to-pyruvate ratio (L:P) in the whole population according to disease status and *PNPLA3* rs738409 genotypes. NAFLD patients with two copies of the risk allele of rs738409 (homozygous GG) as compared to control subjects carrying the same genotype had a significantly greater L:P ratio. On the other hand, the L:P ratio did not change in subjects homozygous for the Ile148 variant (the CC genotype), including patients with NAFLD. These findings suggest a possible synergistic effect of NAFLD with the *PNPLA3*-rs738409 on the general metabolic stress response. *P* values were obtained by analysis of variance (ANOVA) after logarithmic (log) transformation of the L:P ratios.

The L:P ratio reflects the redox state of the cytosolic compartment suggesting hypoxia, mitochondrial dysfunction, and oxidative stress[3]; the L:P ratio in the circulation mirrors the substrate pair ratio of the liver.[4] Our clinical observation suggests that rs738409 modulates the metabolic response of the liver to environmental insults; hence, the variant seems to influence the metabolic adaptation of the liver to energetic imbalance. Homozygous for the risk Met148 variant appears to have a "metabolic adaptive disadvantage" once they are exposed to metabolic stress (fatty liver) compared with homozygous Ile148. Collectively, these findings suggest that *PNPLA3* is not simply a key determinant of the genetic architecture of NAFLD but also modulates a complex metabolic network involving an energy metabolism regulated tightly by gene/environmental interactions.

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