The distribution of rs12979860 genotypes in our dataset was similar to the population described by Petta *et al.*, and typical for a Caucasian population with 48.72% of the subjects homozygous for the C allele, 41.54% heterozygous, and 9.74% homozygous for the T allele.

However, in contrast to Petta *et al.*, we did not find a significant role of *IL28B* in relation to histological characteristics of NAFLD (Table 1A). Results did not change substantially when the analysis was adjusted for age, gender, DMdx, BMI and recruitment site. The adjusted model, however, confirmed the expected role for BMI and diabetes mellitus in regard to histological features of NAFLD (Table 1B).

Importantly, the trend for inflammation was reversed. While 64% of patients with increased inflammation in the study by Petta *et al.* had the CC genotype, less than 40% of patients with severe inflammation in our study had the CC genotype. Furthermore, the NAFLD Activity Score, which showed borderline significance in the adjusted model ($p = 0.0937$), became less significant when an additive model (CC>CT>TT) was used ($p = 0.2243$). Similar to the trend observed with inflammation, the NAS tended to be lower in patients with rs12979860 CC genotype, and therefore in the opposite direction to the observation by Petta *et al.*

Thus, in summary, our data do not show a significant association of *IL28B* and histological features in North American Caucasian patients with NAFLD.

However, almost all of our patients were obese, while only 40% of the patients in Petta *et al.*'s study were obese (BMI >30). It would, therefore, be interesting to know if the association reported by Petta *et al.* change when stratifying their cohort according to BMI group, <25, 25–30, and >30 BMI.

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Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript. The underlying research reported in the study was funded by the NIH Institutes of Health.

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Reply to: "*IL28B* rs12979860 is not associated with histologic features of NAFLD in a cohort of Caucasian North American patients"

***IL28B* rs12979860 genotype and liver damage in NAFLD: An obesity-modulated effect?**

To the Editor:

We recently reported a link between interleukin 28B (*IL28B*) rs12979860 genotype and severity of liver disease, in a cohort of 160 biopsy-proven non-alcoholic fatty liver disease (NAFLD) patients, forty percent of them with obesity, and with a mean age of 45.6 years [1]. In particular, we observed that the *IL28B* CC genotype, associated in chronic hepatitis C (CHC) with a higher rate of sustained virological response after antiviral therapy [2], in NAFLD patients was independently associated with a higher prevalence of moderate-severe liver lobular inflammation and fibrosis [1]. Our results were in line with other data on CHC patients suggesting a link, even if not confirmed in other studies, between *IL28B* CC genotype and severity of liver disease [3,4].

In this complex picture, we read with great interest data reported by Garrett and colleagues [5] on the association between *IL28B* genotype and severity of histological features in NAFLD patients. Specifically, the authors did not identify any association among *IL28B* status and steatosis, inflammation, ballooning and fibrosis in their cohort of NAFLD patients [5]. However, as correctly highlighted by the same authors, they enrolled a cohort of severe obese NAFLD patients evaluated for bariatric surgery [5], and therefore very different from our enrolled cohort [1]. In particular, it should be possible to assume that the genetic background

probably discriminating the "normal" from to the "morbidly obese" NAFLD patient, could *per se* explain the different results observed. In other words, it is plausible to state that "morbidly obese NAFLD" is a disease different from "normal NAFLD". Beyond these considerations, the results by Garret and colleagues [5] could suggest an obesity-dependent effect of the *IL28B* genotype on liver damage in NAFLD patients. Accordingly, we analyzed separately non-obese (n = 94) and obese (n = 66) NAFLD patients, observing that the association between *IL28B* genotype and severity of liver damage was maintained only in non-obese NAFLD patients. In particular, among obese patients, a moderate-severe liver lobular inflammation was observed in 17/28 *IL28B* CC, compared to 16/38 *IL28B* TT/TC NAFLD patients ($p = 0.13$). By contrast, the prevalence of moderate-severe lobular inflammation was significantly higher in non-obese *IL28B* CC, compared to non-obese *IL28B* TT/TC NAFLD patients (28/46 *vs.* 9/48; $p < 0.001$). The protective role of *IL28B* TT/TC genotype against moderate-severe lobular inflammation was maintained at multivariate logistic analysis (OR 0.171, 95% C.I. 0.058–0.507, $p = 0.001$). As observed with lobular inflammation, the association between liver fibrosis and *IL28B* genotype was present only in non-obese patients. Specifically, in obese NAFLD patients, the prevalence of F2-F4 liver fibrosis was not significantly different between *IL28B* CC and *IL28B* TT/TC patients (17/28 *vs.* 22/38; $p = 0.81$). By contrast, the prevalence of F2-F4 was significantly higher in non-obese *IL28B* CC, compared to non-obese *IL28B* TT/TC NAFLD patients (25/46 *vs.* 14/48; $p = 0.01$).

These data overall seem to suggest an effect of *IL28B* CC genotype only in patients at lower metabolic risk, and not in obese patients, were the impact of metabolic alterations on NAFLD severity probably overcomes the pathogenic role of genetic background. However, due to small sample of obese patients in our cohort, a further validation is needed.

Finally, the lack of association between *IL28B* genotype and severity of steatosis in our NAFLD group, which was instead observed in CHC patients (protective role of *IL28B* C/C against steatosis) [6] is not surprising. In fact, first, we evaluated a population where all patients have steatosis, mostly moderate-severe, and second, differently from NAFLD patients, it is plausible to suppose a strong interaction among HCV, *IL28B* genotype and metabolic factors in the genesis of steatosis in CHC.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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