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The *TM6SF2* rs58542926 T allele is significantly associated with non-alcoholic fatty liver disease in Chinese

To the Editor:

A recent study has identified that a missense variant in *TM6SF2* gene (rs58542926: C>T, NP_001001524.2:p. E167K) is significantly associated with non-alcoholic fatty liver disease (NAFLD) [1]. Further analyses suggested that this variant is also significantly associated with NAFLD disease progression [2,3]. However, most of the studies thus far were performed in non-Asian populations, leaving out the question as to whether this variant also confers a risk of NAFLD in Asians (particularly East Asians), the largest population in the world. A most recent study led by Wong and colleagues examined the impact of *TM6SF2* variant on NAFLD in a Chinese cohort, where the *TM6SF2* 167K allele was concluded to have a limited effect on NAFLD [4]. This was deemed to be attributed to the low minor allele frequency (MAF = 7% in their study) as well as the confounding effect of the *PNPLA3* I148M variant, another significant risk factor for NAFLD that are replicated among all major human populations [5]. In order to further verify the effect of this newly discovered allele in NAFLD, we conducted a case-control study in a community-based Han Chinese population.

The rs58542926 polymorphism was genotyped in blood DNA samples from NAFLD patients (n = 384) and healthy controls (n = 384) that were collected in the health examination center of Shanghai Jiao Tong University Affiliated First People's Hospital (Shanghai, China). Genotyping was conducted using a Taqman-based assay (Life Technologies, CA, USA). Both the case and control groups consisted of 229 males and 155 females, with a mean age of 45 ± 13 years. The NAFLD diagnosis was made based on ultrasonographic examinations according to the guideline defined by the Chinese National Consensus Workshop on NAFLD [6]. The examination was performed by one experienced operator who was blinded to both clinical and biochemical evaluations of the patients. No histological data based on liver biopsy were available for these patients. For each individual, detailed data for ultrasonographic examination of the upper abdominal organs, clinical data for a comprehensive physical examination as well as a questionnaire for demographic, disease history, family history, smoking and alcohol intake information were all collected. The NAFLD patients were selected by excluding the cases with other known causes of steatosis, including heavy alcohol intake (>20 g/day), the use of medications known to contribute to hepatic steatosis, and hepatitis B and C virus infection. Patients with a high likelihood to have other known liver diseases were also excluded. Randomly selected healthy volunteers from the same population with normal liver enzymes, liver ultrasound and without any major illnesses were chosen as controls. The cases and controls were 1:1 matched according to their gender and age information. All enrolled individuals are self-reported Han Chinese and reside in the Shanghai metropolitan area. Informed consent was obtained from all participants. The study was approved by the ethical committees of the Shanghai Jiao Tong University and strictly conforms to the principles of the Declaration of Helsinki.

Consistent with Wong's results, the *TM6SF2* 167K allele has a similarly low frequency in our dataset (MAF = 6.6%). However, we still observed a significant association between *TM6SF2* 167K allele and NAFLD ($p = 0.0007$) after adjustment for age, sex, body mass index and status of diabetes (Table 1). Furthermore, to clarify the independent effect of the *TM6SF2* allele on NAFLD, we controlled the *PNPLA3* rs738409 polymorphism, which was significantly associated with NAFLD in our data ($p = 0.0002$, data not shown). Our analysis showed that rs58542926 remained to be associated with NAFLD ($p = 0.0004$) after conditioning on rs738409 (Table 1). Moreover, several genome-wide association studies have shown that a variant in *NCAN* (rs2228603), whose locus is near *TM6SF2*, is strongly associated with NAFLD [7,8]. However, rs2228603 is not significantly associated with NAFLD in our samples ($p = 0.1$, data not shown). After conditioning on this variant, the *TM6SF2* rs58542926 variant still remains significant ($p = 0.001$) in our data (Table 1).

In summary, we demonstrated that in a Han Chinese population cohort, the *TM6SF2 167K* allele has a similar allele frequency as reported in Caucasian populations (~7%) [1–3] but higher than that in African-Americans (3.4%) [1], Hispanic-Americans (4.7%) [1], and Argentinians (5.5%) [9]. Our data suggests that this variant significantly contributes to increased NAFLD risk in Chinese population, independent of the *PNPLA3* rs738409 and *NCAN* rs2228603 polymorphisms. This observation further highlights the independent and potentially causal role of rs58542926 in the disease biology of NAFLD. However, further investigation is needed in East Asian populations to test whether it is also involved in NAFLD disease progression and severity, especially using biopsy-characterized samples.

Conflict of interest

The authors declared no conflict of interest in relation to this manuscript.

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Table 1. Association between *TM6SF2* rs58542926 variant and NAFLD.

Genotype count			
Genotype	CC	CT	TT
Control	333	33	0
Case	302	65	0

Statistical analysis*					
Unconditioned		Condition on rs738409		Condition on rs2228603	
OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
2.2 (1.4-3.4)	0.0007	2.3 (1.4-3.6)	0.0004	2.1 (1.4-3.4)	0.001

*Associations were tested using logistic regression with adjustment for age, sex, BMI and status of diabetes.

OR, odds ratio; CI, confidence interval.

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Is it worthy of switching to PegIFN alfa-2a in patients achieving virological suppression with entecavir?

To the Editor:

We read with great interest the article "Switching from entecavir to PegIFN alfa-2a in patients with HBeAg positive chronic hepatitis B: A randomized open-label trial (OSST trial)" [1]. This elegant study assessed the rates of HBeAg seroconversion and HBsAg loss in patients with well-controlled HBV DNA replication and serum HBeAg <100 PEIU/ml on long-term entecavir (ETV) therapy after switching to a finite course of PegIFN alfa-2a. Qin Ning *et al.* [1] demonstrated that switching to a finite course of PegIFN alfa-2a significantly increased rates of HBeAg seroconversion and HBsAg loss and concluded this is a potential alternative to indefinite nucleos(t)ide analogue (NA) therapy.

Many chronic hepatitis B patients are treated with ETV in China. Some of them hope to stop this infinite treatment if a finite course of treatment can give similar or better outcomes with a reasonable cost and minimal adverse effects. In Shenzhen, patients receiving sequential therapy with NA and PegIFN are not rare. However, there are several concerns about this article and its approach. First, the absolute difference in HBeAg seroconversion rate was only 8.8%. In other words, the number to treat for one HBeAg seroconversion is 11. All these patients have to suffer the adverse effects of PegIFN. It is well known that hepatic decompensation and even death has been reported during IFN treatment. We should also pay special attention to the adverse effect of stopping of ETV. Hepatic decompensation or liver failure was not recorded in the study given the sample size. Recently, one of my patients developed acute on chronic liver failure during PegIFN treatment after stopping ETV and adefovir (ADV) which was reported on in a local hepatology meeting. The effect of an overlapping period of ETV and PegIFN on safety and efficacy