Prevalence of the *TM6SF2* variant and non-alcoholic fatty liver disease in Chinese

To the Editor:

Non-alcoholic fatty liver disease (NAFLD) is currently the most common chronic liver disease worldwide and may progress to cirrhosis and hepatocellular carcinoma [1–3]. A recent exome-wide association study identified the *TM6SF2* variant (encoding p.Glu167Lys) as a novel locus associated with higher liver fat level [4]. The variant is associated with decreased hepatic secretion of very-low-density lipoprotein and higher risk of myocardial infarction [4,5].

Since Asians were underrepresented in the exome-wide association studies [4,5], here we report the prevalence of the *TM6SF2* variant in a well-characterized Chinese cohort. In the HK-MRS Study, 922 randomly selected community subjects underwent non-invasive assessment of liver fat and fibrosis by proton-magnetic resonance spectroscopy and transient elastography, respectively [3]. All subjects were ethnic Chinese. Genotyping was performed using a TaqMan assay (dbSNP rs58542926; Applied Biosystems, C_89463510_10) in 920 subjects with adequate blood samples.

Overall, the *TM6SF2* variant was detected in 4 subjects (0.4%, 95% CI 0–0.9%). Subjects carrying the variant had significantly lower total cholesterol and low density lipoprotein-cholesterol levels than those without (Table 1). None of them were taking lipid-lowering drugs at the time of assessment. Though limited by small numbers, subjects carrying the variant also tended to have higher liver fat. Two of the 4 subjects had NAFLD with intrahepatic triglyceride contents of 13.9% and 21.1% suggestive of moderate to severe steatosis. These 2 subjects were carrying the GG and CG genotypes at the patatin-like phospholipase 3 gene (*PNPLA3* rs738409, encoding p.Ile148Met), which is another major genetic determinant of NAFLD [6]. On the other hand, none of the subjects with the *TM6SF2* variant had increased liver stiffness measurement by transient elastography indicative of advanced fibrosis or cirrhosis [7]. Furthermore, *TM6SF2* heterozygotes did not have increased liver fat and fibrosis compared to the homozygotes for the allele encoding Glu167 (Table 1).

Our data suggest that the *TM6SF2* variant is rare in the Chinese population and probably does not cause severe liver injury from NAFLD. The impact of this genetic variant at the population level is thus limited. However, its discovery sheds light on the pathogenesis of NAFLD and may unravel new treatment targets.

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Table 1. Clinical characteristics of community Chinese subjects with different *TM6SF2* genotypes.

Characteristics	EE[a]	EK[a]	KK[a]	*p* value
n	794	122	4	
Age (yr)	48 ± 11	50 ± 11	39 ± 10	0.062
Female sex, n (%)	455 (57.3)	73 (59.8)	3 (75.0)	0.68
Body mass index (kg/m^2)	22.9 ± 3.5	22.4 ± 3.5	21.5 ± 4.1	0.23
Waist circumference (cm)	82 ± 10	80 ± 10	80 ± 10	0.28
Alanine aminotransferase (IU/L)	21 (17-31)	22 (16-27)	29 (13-49)	0.73
Aspartate aminotransferase (IU/L)	19 (17-23)	20 (16-23)	22 (15-27)	0.85
Fasting glucose (mmol/L)	5.1 ± 0.9	5.2 ± 0.8	5.1 ± 0.8	0.87
Total cholesterol (mmol/L)	5.2 ± 1.0	5.1 ± 1.2	3.6 ± 1.1	0.009
HDL-cholesterol (mmol/L)	1.5 ± 0.4	1.6 ± 0.4	1.2 ± 0.4	0.18
LDL-cholesterol (mmol/L)	3.0 ± 0.9	3.0 ± 1.0	2.0 ± 0.8	0.049
Triglycerides (mmol/L)	1.1 (0.8-1.7)	0.9 (0.7-1.2)	1.2 (0.4-1.7)	0.002
Diabetes, n (%)	31 (3.9)	7 (5.8)	0	0.58
Hypertension, n (%)	123 (15.5)	18 (14.8)	1 (25.0)	0.85
Intrahepatic triglyceride content (%)	2.1 (0.9-6.0)	2.1 (0.9-6.0)	7.5 (0.8-19.3)	0.73
Intrahepatic triglyceride content ≥5.0%, n (%)	222 (28.0)	39 (32.0)	2 (50.0)	0.42
Liver stiffness measurement (kPa)[b]	4.6 ± 1.7	4.9 ± 1.8	4.7 ± 0.8	0.27
Liver stiffness ≥9.6 kPa, n (%)[b]	11 (1.7)	4 (4.3)	0	0.22

Values are mean ± standard deviation or median (interquartile range), the latter for variables not following normal distribution.
HDL, high density lipoprotein; LDL, low density lipoprotein.
[a]EE, homozygotes for the allele encoding Glu167; EK, heterozygotes; KK, homozygotes for the allele encoding Lys167.
[b]Including 758 subjects with valid and reliable liver stiffness measurement by transient elastography.

Conflict of interest

Vincent Wong, Grace Wong, and Henry Chan have served as speakers for Echosens. Henry Chan is a consultant of Furui Medical Science.

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Vincent Wai-Sun Wong
Grace Lai-Hung Wong
Chi-Hang Tse
Henry Lik-Yuen Chan*

Institute of Digestive Disease, The Chinese University of Hong Kong, Hong Kong
State Key Laboratory of Digestive Disease, The Chinese University of Hong Kong, Hong Kong
Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong
*Corresponding author.
E-mail address: hlychan@cuhk.edu.hk

Bacterial translocation in liver cirrhosis: Site and role in fibrogenesis

To the Editor:

I read with great interest the comprehensive review by Wiest and colleagues [1] on pathological bacterial translocation in liver cirrhosis. They remarkably analyzed the compartments involved and their influencing factors. My concern regards the possible site(s) of bacterial translocation (BT), and the role of BT in the progress of both precirrhotic chronic liver damage, particularly fibrosis, and installed liver cirrhotic lesions themselves.

Regarding the site of bacterial translocation in cirrhosis, the authors rightly outline that, whereas small intestinal bacterial overgrowth has the greatest potential for promoting BT and bacteria causing spontaneous infections are most frequently exactly those overgrowing in the small intestine [2,3], studies of experimental liver injury in mice revealed that the cecum and the colon might be the sites with largest rate of BT and increase in intestinal permeability [1]. Data in humans were lacking. A recent *in vivo* human study, not referenced in the Wiest's review [1], has reported that colonic permeability was increased in patients with compensated liver cirrhosis, as compared to matched controls using a multisugar test, whereas gastroduodenal and small intestine permeability were not altered [4]. Whether or not these changes preceded alterations of the gut microbiome is not known.

A second point of increasing importance, not discussed in the review [1], regards the experimental role of inflammasomes at the colonic level in both local microbiota taxonomy and potential translocation associated with chronic precirrhotic liver disease, namely non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). There is suggestive evidence that a deficiency in components of two inflammasomes (NLRP6 and NLRP3) – which are large multiprotein complexes that sense intracellular danger signals via NOD-like receptors (NLRs), the sensor, NLR, forming a complex with the effector molecule, procaspase-1, with or without the contribution of an adapter molecule, such as the apoptosis-associated speck like CARD-domain containing protein (ASC) – normally acting as sensors of endogenous or exogenous pathogen-associated molecular patterns (PAMPs) and regulators of the colonic microbiota, leads to dysbiosis associated with aggravation of NAFLD and progression to NASH [5]. Thus, members of the altered colonic microbiota in inflammasome-deficient mice may promote a signalling cascade in the liver upon translocation, resulting in progression to NASH in susceptible animals. Toll-like receptors (TLRs) have a major role in NAFLD pathophysiology due to the liver's exposure to relatively large amounts of PAMPs derived from the intestine and delivered *via* the portal circulation. Intact bacteria or bacterial products derived from the intestine trigger TLR4 and TLR9 activation, which results in an increased rate of chronic liver disease progression in mice that house a colitogenic gut microbiota associated with inflammasome deficiency [5]. Indeed bacterial overgrowth, including in colon [7], is particularly important in patients with a leaky gut because it increases the luminal amount of PAMPs. It is noteworthy that mice deficient in sensing PAMPs or downstream signaling are resistant to NASH [6].

Finally, the consequences of intestinal dysbiosis or bacterial overgrowth associated with gut leakage may not be limited to infectious complications, as spontaneous bacterial peritonitis, due to translocation. Animal studies have clearly pointed that