CORRESPONDENCE

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The Exact Mechanism by Which Hepatic Transmembrane 6 Superfamily Member 2 Modulates Triglyceride Metabolism Is Still Uncertain

Dear Editors:

The rs58542926 C>T variant of transmembrane 6 superfamily member 2 gene (*TM6SF2*), which encodes an E167K (p.Glu167Lys) amino acid substitution, has been associated with reduced total plasma cholesterol (TC) levels, cardiovascular disease (CVD) ,[1] and nonalcoholic fatty liver disease (NAFLD) , [2] but in opposite directions. Specifically, the rs58542926-T allele confers protection against CVD at the expense of higher risk for NAFLD.[3]

The pioneer genome-wide association studies on CVD[1] and liver triglyceride (TG) accumulation[2] were subsequently replicated in different populations around the world in both adults and children, as reviewed in a recent meta-analysis.[3] We read with great interest the elegant study by Fan and coworkers,[4] which described a liver-targeted human *TM6SF2* transgene in mice elevating plasma TC and LDL-C and enhancing cholesterol biosynthesis in hepatocytes, thus confirming previous studies by the same group with transient elevated gene expression.[1] Inversely, loss of *TM6SF2* in a *Tm6sf2* knock-out (KO) mice decreased plasma TC and LDL-C. The role of TM6SF2 in liver cholesterol metabolism was further supported by the regulation of cholesterol metabolism-related genes. Fan and coauthors[4] suggested that TM6SF2 increases cholesterol biosynthesis and the E167K variant may result in partial loss-of-function. Accordingly, we have found decreased TM6SF2 protein expression in liver biopsies of NAFLD patients.[5] Furthermore, in subjects heterozygous for the E167K variant, we were able to show decreased gene expression of the 167K (rs58542926- T) allele assessed by an allele-specific PCR.[5] Hence, it is interesting to note that the K variant may not only represent an isoform with "lower biochemical function," but a less stable mRNA or protein. This observation opens the intriguing possibility that studies of over expression—even allele specific—could not provide a proper answer to this novel putative functionality of rs58542926. In fact, the rs58542926 is linked (D'>0.999) to several *TM6SF2* upstream gene variants—that are putatively regulatory—including rs735273 (T/C, minor allele frequency [MAF]: 0.47), rs8103496 (A/G, MAF: 0.47), rs11882123 (A/G, MAF:0.47), rs8107974 (A/T, MAF: 0.12 in perfect linkage disequilibrium with the rs58542926 variant and rs10401969 (T/C, MAF: 012), data extracted from 1000 genomes, phase_3:eur. Of note, rs11882123, rs8107974, and rs10401969 are also located in the downstream UTR (untranslated) or intronic region (with non sense-mediated effect) of the *SUGP1* locus, a gene of the multi locus complex *TM6SF2/SUGP1/NCAN* recently associated with NAFLD.[6]

On the other hand, differences in the effect of TM6SF2 on lipid metabolism between species are worthy of being highlighted. First, while in humans the 167K (rs58542926-T) allele is associated with decreased plasma TG levels and fatty liver,[3] in mice, *tm6sf2* gain-of-function unexpectedly induced liver steatosis without changes in plasma TG and *tm6sf2* loss-of-function increased plasma TG levels but had a minor effect on liver TG accumulation even under exposure of a high-fat diet (HFD). Second, the absence of histological changes associated with disease severity (either inflammation or liver fibrosis) along with unchanged levels in liver enzymes would indicate that deregulation of *tm6sf2* in mice may not induce progression of NAFLD from steatosis to steatohepatitis, which arguably is seen in humans. This differential effect could be species-specific or, as Fan et al[4] discussed, explained by a number of factors including duration of HFD feeding (a presumed mild insult), other protective mechanisms, or simply the absence of an effect of TM6SF2 on inflammation.

Taken together, while the role of TM6SF2 in cholesterol and VLDL secretion seems to be straightforward, the mechanisms by which TM6SF2 regulates TG metabolism are still unclear. Certainly, more experiments are needed to shed light on the biological role of TM6SF2 in TG and TG–related pathways, and its effect on liver disease progression independent of liver fat if any. Therefore, data from animal models complement current knowledge of pathophysiological mechanisms of NAFLD and CVD but should be taken with caution in terms of suggesting new avenues of treatment. The dual and opposite effect of the *TM6SF2* E167K variant on plasma and liver lipid profiles is an example of the complexity of operating on one gene product and the difficulty to implement Precision Medicine by modulating, in this case, just one target.

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References

1. Holmen OL, Zhang H, Fan Y, et al. Nat Genet 2014; 46:345–351.
2. Kozlitina J, Smagris E, Stender S, et al. Nat Genet 2014; 46:352–356.