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Correspondence

Transmembrane-6 superfamily member 2 (TM6SF2) E167K variant increases susceptibility to hepatic steatosis in obese children

Dear Editor,

The global rise in prevalence of childhood obesity is associated with an increase of obesity-related metabolic disorders including hepatic steatosis. In Italy, the overweight/obesity prevalence mirrors European proportions, with the highest prevalence (≥37%) of paediatric obesity in Southern Italy [1]. In children/adolescents Non-alcoholic fatty liver disease (NAFLD), defined as fat accumulation that exceeds 5% of liver weight, is considered a complication arising from obesity.

A genetic background is recognized to contribute significantly to the susceptibility to hepatic steatosis. Recent studies have identified a sequence variant at residue 167 (E167K) of the *Transmembrane 6 superfamily member 2* (*TM6SF2*) gene, a novel genetic determinant of NAFLD [2], and very recently the association between *TM6SF2* E167K variant and liver fat content was reported in obese children [3]. As for any genetic association study, a confirmatory study is warranted. Thus, the aim of this study was to investigate the effect of the *TM6SF2* E167K genetic variant on hepatic steatosis in a large cohort of 878 overweight/obese Italian children (mean SDS-BMI of 1.9 ± 0.5) recruited from the Pediatric Endocrine Unit, Hospital for Microcitaemia in Cagliari, Italy. Anthropometric, demographic and clinical data were described before [4].

A total of 423 children/adolescents underwent ultrasonographic liver evaluation to assess the presence or absence of steatosis, as previously reported [4]. The *TM6SF2* rs58542926 gene variant was genotyped by TaqMan® assay.

47% of the 878 overweight/obese subjects) were of male gender, 70% were pre-pubertal and 12% had hepatic steatosis according to ultrasound imaging.

The *TM6SF2* E167K minor allele frequency was 0.06. *TM6SF2* 167K carriers (11%) showed lower mean total cholesterol (EE vs. EK+KK: 169 ± 33 mg/dl vs. 161 ± 28 mg/dl; $P = 0.029$) and lower median triglycerides (EE vs. EK+KK: 55 mg/dl (39–78) vs. 51 mg/dl (36–66), $P = 0.007$). No differences were detected in glucose metabolism or liver enzymes between the two groups.

TM6SF2 167K carriers showed a higher prevalence of hepatic steatosis ($P = 0.002$, Fig. 1). In multivariate analysis (Supplementary Table 1), *TM6SF2* 167K carriers had a >3-fold increased risk for hepatic steatosis (O.R. 3.6, C.I. 1.6–8.0, P value 0.002) independently from the confounding risk factors (age, gender, SDS-BMI, Tanner's stage and *PNPLA3* I148M genotype).

In summary we found the *TM6SF2* 167K variant is associated with a higher prevalence of hepatic steatosis. Carriers of the *TM6SF2* 167K allele showed a greater than 3-fold increased risk for hepatic steatosis, independently from other risk factors including the presence of *PNPLA3* I148M variant, which has not been reported in previous studies [3].

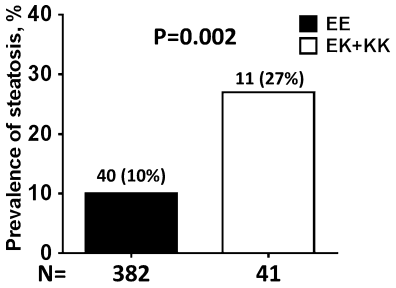

Fig. 1. Transmembrane-6 superfamily member 2 (TM6SF2) rs58542926 associates with higher steatosis prevalence in overweight/obese children. Prevalence of steatosis stratified by *TM6SF2* 167EE and 167EK+KK genotypes. Steatosis presence was defined as steatosis grade ≥ S1. *P*-value was calculated by chi-square under a dominant genetic model. Steatosis presence data were available for 423 individuals of those 382 were EE and 41 were EK+KK. Number and proportion of individuals with hepatic steatosis are reported above the bars. *Abbreviations*: *N*, number; *TM6SF2*, *Transmembrane 6 superfamily member 2 gene*; EE, individuals with two 167E alleles; EK, heterozygotes; KK, individuals with two 167K alleles.

In line with previous literature [2], fasting triglycerides were lower in *TM6SF2* 167K carriers. The E167K aminoacidic substitution induces a loss of function of TM6SF2 and a consequent increased fat accumulation in the liver [2].

We did not observe any differences in aminotransferases, at variance with the study of Grandone [3]. Geographical differences or selection bias (we had 10% liver steatosis vs. 50% in Ref. [3]) may be responsible for these dissimilar observations.

Although hepatic steatosis is closely related to systemic insulin resistance, we did not observe any association of the E167K variant with fasting indices of insulin resistance, consistent with previous studies in adults [5].

A limitation of this study is that hepatic fat content was determined by ultrasound, a technique with low sensitivity. On the other side, the fact that we detected a difference in hepatic fat, even with a low sensitivity method, could strengthen our results.

In conclusion, we show for the first time that *TM6SF2* 167K carriers have a 3-fold increased risk to develop hepatic steatosis, which appears early in life. Future studies are needed to confirm these data and to address the usefulness in a clinical setting.

Conflict of interest

None declared.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.dld.2015.10.003.

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