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Review article

TM6SF2: A novel target for plasma lipid regulation

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ABSTRACT

Transmembrane 6 superfamily 2 (*TM6SF2*), a gene identified at the locus 19p12, has been recognized to regulate plasma lipids. Here, we provide an overview of the roles of TM6SF2 as a novel target for plasma lipid regulation. We first review the association of TM6SF2 variant with plasma lipid traits, cardiovascular disease (CVD) and non-alcoholic fatty liver disease (NAFLD). Then, we present an overview about the *in vivo* validation of TM6SF2 as a regulator of plasma lipid levels using mice, with overexpression or knockdown/knockout of TM6SF2. Thereafter, we discuss the mechanisms underlying TM6SF2 regulation of lipid metabolism involving intestinal cholesterol absorption and hepatic cholesterol biosynthesis and transport.

In conclusion, increasing evidence suggests that TM6SF2 may be a major regulator of plasma lipid levels and become a therapeutic target in cardiovascular disease.

1. Introduction

Transmembrane 6 superfamily 2 (*TM6SF2*), a gene without any known function, was first reported in 2000 [1]. TM6SF2 is located on chromosome 19, at locus 19p12. TM6SF2 encodes a protein containing 351 amino acids (39.5-kDa) with an estimated isoelectric point (pI) of 8.29 [1]. The protein is predicted to have 7–10 transmembrane domains [2], but does not contain any known functional domains [3].

TM6SF2 is mainly expressed in the liver, intestine, kidney, and in other tissues at low levels [2,4–7]. In terms of subcellular localization, TM6SF2 is localized in the endoplasmic reticulum (ER), the ER-Golgi intermediate compartment, and Golgi of liver cells and enterocytes [2,6]. Recently, many researches have focused on the roles of TM6SF2 in lipid metabolism, and have revealed that TM6SF2 is associated with non-alcoholic fatty liver disease (NAFLD) and cardiovascular disease (CVD) [5,8,9]. The present review focuses on the genetic association of TM6SF2 with blood lipids, CVD and NAFLD. The evidence and mechanisms for TM6SF2 as a regulator of plasma lipid metabolism are also discussed.

2. Association of variant TM6SF2 with plasma lipids, CVD and NAFLD

2.1. Variant TM6SF2 and plasma lipids

Several genome-wide association studies (GWAS) have suggested that a locus in chromosome 19 is closely associated with plasma lipids [10–15]. *TM6SF2* was identified as a functional gene at the 19p12 locus [2,5]. Recent studies reported two major nonsynonymous variants of TM6SF2, including rs58542926 (E167K) and rs10401969 [2,7,16–18]. Most studies have focused on the effects of the TM6SF2 E167K variant on plasma lipid traits [4,5,7,8,18–21]. The TM6SF2 E167K variant is characterized by an adenine for guanine substitution in coding nucleotide 499, which replaces glutamate with lysine at residue 167 (rs58542926 c.499 C > T, p.Glu167Lys, E167K) [4]. The E167K variant protein is misfolded, undergoes accelerated intracellular degradation [4], and has an increased rate of protein turnover [22], leading to a reduction of TM6SF2 protein level and gene function [4,22] (Fig. 1). Expression of this minor allele of nonsynonymous variant was reported to reduce the plasma lipoprotein concentrations [4,5,7,8,18–21].

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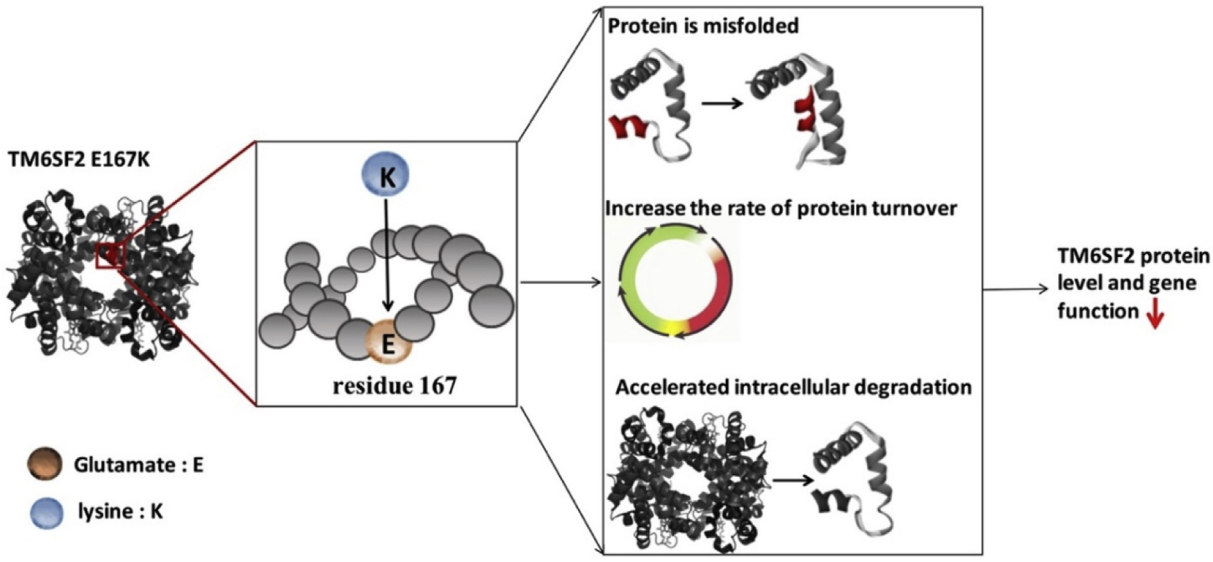

Fig. 1. The association between TM6SF2 E167K variant and TM6SF2 protein.
The TM6SF2 E167K variant is characterized by an adenine for guanine substitution in coding nucleotide 499, which replaces glutamate at residue 167 with lysine (rs58542926 c.499 C > T, p. Glu167Lys, E167K). The E167K variant form is misfolded and undergoes accelerated intracellular degradation or affects the rate of protein turnover, leading to the reduction of TM6SF2 protein level and gene functions.

Grandone et al. have shown that TM6SF2 E167K is significantly associated with lower levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), and non-high-density lipoprotein cholesterol (non-HDL-C) in a group of obese children [21]. Similar results were reported by Viitasalo et al. in a group of children with a normal body weight [20]. TM6SF2 E167K variant and blood lipid traits were also determined in another cohort with 957 young obese, including African Americans (28%), Hispanics (30%), and Caucasians (42%). The results showed that TM6SF2 E167K variant is associated with lower levels of cholesterol, LDL particles, large LDL particles, small LDL particles, medium small LDL particles, and very small LDL particles in the group of Caucasians and Hispanic [18]. No association was found between TM6SF2 167 K variant and TG in those groups [18], which is in contrast with results from Grandone group's study [21].

In adult groups, Holmen et al. observed that TM6SF2 E167K variant is associated with lower plasma TC, by analyzing data from 10,437 Norwegians, including both myocardial infarction (MI) and healthy populations [5]. Furthermore, the association between TM6SF2 E167K and lower concentrations of plasma TG and LDL-C was observed in the populations from the Dallas Heart Study, Dallas Biobank and Copenhagen Study [4]. In these studies, however, plasma HDL-C levels were not associated with the TM6SF2 E167K variant [4]. The study of the Swedish Obese Subjects cohort also showed that TM6SF2 E167K variant is significantly associated with a reduction of blood TC, non-HDL-C, TG and has no relationship with HDL-C [8]. However, data from the Amish Complex Disease Research Program (ACDRP) cohort demonstrated that TM6SF2 E167K variant has association, not only with lower TG, TC and LDL-C levels, but also with higher HDL-C level [7]. It is worth noting that HDL functionality (quality) has been consistently demonstrated to be more important than HDL-C concentrations [23]. In fact, there are techniques already standardized to assess HDL quality [24]. Therefore, the relationship between TM6SF2 and HDL functionality needs further investigation.

Zhou et al. genotyped 300 Finnish subjects for TM6SF2 E167K, and then compared serum LDL-C, HDL-C and TG levels in the E167K variant carriers with those in non-carriers [25]. In contrast to other findings, no significant difference was found in serum LDL-C, HDL-C and TG concentrations between the two groups [25]. Analyses of blood samples of patients with NAFLD showed that TM6SF2 E167K variant was significantly associated with TC levels only [9]. More recently, Eslam et al. demonstrated that subjects with the E167K variant had lower levels of serum TG, but not of plasma levels of LDL-C and HDL-C [26].

In several population studies, it was found that TM6SF2 E167K variant is associated with lower TC, LDL-C and TG levels [4,5,7,8,19–21,27], but some other studies did not show significant differences [9,18,25,28]. The reasons for the discrepancy may be related to the following: (i) population structures: in three child samples, for example, two of the main samples were predominantly of the Italian population [8,21]. However, one of the complex population structures includes African Americans, Hispanics, and Caucasians [18]; (ii) population characteristics: in the adult population, some studies are based on multiethnic population-based probability samples [4], and some solely on obese people. However, it was not clear whether they had NAFLD or not [7]. In addition, some of them are based on NAFLD populations [9,26,29]; (iii) population sizes: given that the E167K variant is of low frequency variation, some studies contained only about 200 samples [9,25]. Notably, the results may not be representative when the sample size is not large enough. A meta-analysis of the association between the TM6SF2 E167K variant and lipids was carried out for six studies with about 101,326 individuals [30]. The results of this meta-analysis, by summarizing the amount of evidence, degree of replication, and absence of publication bias, showed that the TM6SF2 E167K variant has a significant influence on the levels of circulating TC, LDL-C and TG, but not HDL-C.

In Table 1, we have summarized the studies exploring the association of TM6SF2 E167K variant with plasma lipids traits.

2.2. Variant TM6SF2 and CVD

Elevated plasma levels of TC, LDL-C, and TG and decreased level of HDL-C are important risk factors for cardiovascular diseases [31–34]. The carriers of the TM6SF2 E167K variant were found to