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Letter to editor

γGT and *PCSK9* variants in subjects with hyper-LDL-cholesterolemia

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To the Editor,

Proprotein convertase subtilisin/kexin type-9 (PCSK9) elevates circulating low-density lipoprotein (LDL)-cholesterol (LDL-C) with the PCSK9-induced LDL-receptor (LDLR) degradation (1). This is a cardiovascular disease (CVD) risk factor (1). Gain-of-function (GOF) variants of *PCSK9* gene enhance the CVD risk (1,2). Oxidative stress (OS) is also involved in the CVD development in relation to the LDL and PCSK9 function (3). Gamma-glutamyl transpeptidase (γGT) is a pro-oxidant and CVD risk marker (4). γGT is expressed on cell membranes and released into the blood in response to OS (4). As both γGT and PCSK9 exist in the hepatocytes and blood (1, 4), there may be an association between γGT and *PCSK9* variants for CVD. We examined the γGT activity by a GOF variant, p.E32K, in subjects with hyper-LDL-cholesterolemia, an at-risk state of CVD.

We examined 114 CVD-free subjects with hyper-LDL-cholesterolemia (> 5.17 mmol/L, an at-risk level of CVD) (5). This study was approved by the Institutional Ethics Committee (19-023). All subjects provided written informed consent. Excluded were subjects with severe liver and/or gallbladder disorders. Besides self-reported lifestyles, serum lipids and γGT were enzymatically measured. The p.E32K variant was detected by real-time polymerase chain reaction system (Thermo Fisher Scientific, Waltham, MA, USA). The between-group difference was analyzed by Student's *t*-test and Chi-square/Fisher's exact test. A regression analysis adjusted with all measured variables was performed to compare γGT values between the groups. The γGT values were log-transformed in analyzing because of the skewed distribution. The R package (version 3.3.0) were used for all statistics and significance was set at $P < 0.05$.

A heterozygous p.E32K variant was seen in 12 subjects (Table 1). The variant frequency followed Hardy-Weinberg equilibrium. The γGT activity of subjects with p.E32K was significantly lower than that of subjects without the variant ($P = 0.02$). The difference in γGT activity between the groups remained significant after a multivariate-adjusted analysis ($P = 0.03$).

The inverse association, low γGT activity in the GOF variant of *PCSK9*, p.E32K, might be unexpected as both γGT and PCSK9 have a positive CVD risk (2,4), but their association may suggest the presence of γGT-*PCSK9* linkage via an OS pathway. The possible explanations for the finding are raised: generally, excessive LDL uptake in the liver produces LDL-induced OS and/or PCSK9 itself limits accumulation of OS-inducers (e.g., fatty acids) in hepatocytes (5). Then, lowering LDL uptake under the LDLR degradation promoted by GOF variants of *PCSK9* and/or suppressing OS-inducers by PCSK9 functionalized by GOF variants may reduce OS in the liver, resulting in less releasing γGT into the blood.

There is an epidemiological observation that the GOF variants including p.E32K show a relatively low CVD risk compared with other genes (i.e., *LDLR* and *APOB*) causing hyper-LDL-cholesterolemia (2,6). This unsettled observation may be partly explained by the GOF variants' OS reduction as expressed in low γGT activity.

Table 1. Characteristics of the subjects by a *PSCK9* gene variant, p.E32K.

Variables	p.E32K (-), n = 104	p.E32K (+), n = 12	*P* value	*P* value (adjusted)
Age, years	59 ± 11	55 ± 14	0.29	0.79
Male, n (%)	35 (34)	3 (25)	0.75	0.57
Alcohol habit, n (%)	39 (38)	5 (42)	0.76	0.51
Smoking habit, n (%)	35 (34)	3 (25)	0.75	0.66
Statin use, n (%)	20 (19)	1 (8)	0.69	0.65
Body mass index, kg/m^2	24.3 ± 3.9	24.4 ± 3.5	0.88	0.37
Triglycerides, mmol/L	1.47 (1.07-2.02)	1.31 (1.06-1.45)	0.06	0.97
HDL-C, mmol/L	1.44 ± 0.01	1.68 ± 0.41	0.08	0.05
LDL-C, mmol/L	5.67 ± 0.53	5.55 ± 0.53	0.46	0.50
γGT, IU/L	30 (18-49)	21 (16-28)	0.02*	0.03*

Mean ± standard deviation; median (interquartile range); PCSK9, proprotein circulating convertase subtilisin/kexin type 9; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; γGT, gamma-glutamyl transferase. * significance level, $P < 0.05$.

Collectively, we acknowledge study limitations (i.e., a small sample-size, use of single variant, non-measurement of additional OS markers), which should be addressed. On the other hand, elucidating low γGT activity associated with the GOF variant of *PCSK9*, p.E32K, may help understand the CVD development by *PCSK9* variants.

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