

# Effect of a Common Mutation (D442G) of the Cholesteryl Ester Transfer Protein Gene on Lipids and Lipoproteins in Children

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## ABSTRACT

Cholesteryl ester transfer protein (CETP) is thought to regulate plasma HDL. Patients with CETP deficiency caused by mutation of the *CETP* gene [D442G; a missense mutation (Asp442→Gly)] have been reported to show high plasma HDL levels. However, there are no data available on children with D442G. To determine the effects of plasma CETP and *CETP* gene mutation (D442G) on lipids and lipoproteins in children, we screened children by PCR and restriction fragment length polymorphism analysis of the *CETP* gene. Plasma lipids, apolipoproteins, and CETP mass levels were also determined. In the current study, 22 children with D442G were found (21 heterozygotes and a homozygote). A homozygous child showed high plasma HDL level and very low plasma CETP mass. In heterozygous children, plasma concentrations of HDL cholesterol, apo A-I and apo A-II were not increased, whereas plasma CETP mass was significantly decreased. Plasma CETP mass in heterozygous children was correlated with plasma concentrations of total cholesterol,

LDL cholesterol, and apo B. Plasma CETP mass in children without D442G was not correlated with the plasma concentration of any lipid or apolipoprotein. All of these data suggest that the D442G mutation, by itself, might not affect HDL metabolism in children. The CETP mass required for efficient HDL-cholesteryl ester clearance in children may be less than that in older subjects. (*Pediatr Res* 50: 455–459, 2001)

### Abbreviations

**CE**, cholesterol ester  
**CETP**, cholesteryl ester transfer protein  
**HDL-C**, HDL-cholesterol  
**LCAT**, lecithin-cholesterol acyltransferase  
**RFLP**, restriction fragment length polymorphism  
**TC**, total cholesterol  
**TG**, triglyceride

Esterification of cholesterol from peripheral tissues and subsequent transfer of CE from HDL to other lipoproteins are key steps in reverse cholesterol transport, *i.e.* transport from peripheral cells to the liver for excretion (1, 2). In humans, extracellular cholesterol is esterified by the action of LCAT, and the CE generated is transferred to the liver by two known pathways: 1) uptake of HDL particles by the liver (3, 4), and 2) uptake of HDL CE by LDL receptor in the liver via transfer of HDL-CE to VLDL and LDL, in a process mediated by CETP (1, 2, 5). Most LCAT and CETP are associated with HDL particles in human plasma (6, 7). Cholesterol esterification in HDL by LCAT increases the size of HDL particles, and the

transfer of CE from HDL particles reduces the size of HDL. Thus, the size of HDL particles reflects the net rate of CE generation on and CE transfer from HDL particles. Furthermore, we have shown in previous studies that the function of HDL, as well as the particle size, is strongly affected in the presence of LCAT or CETP deficiency (8, 9). These findings, taken together, suggest that LCAT and CETP play a central role in maintaining the antiatherogenic nature of HDL.

To date, several common polymorphisms have been reported in the *CETP* gene (10–12). Most are located within intronic regions and do not appear to affect either the secretion or the function of CETP. Two mutations, an intron 14 splice donor site mutation (Int14A) and a missense mutation within exon 15 (D442G), have been reported in Japanese subjects with high HDL-C levels (>100 mg/dL) (13–15). These mutations affect the structure and function of CETP and are prevalent in Japan but very rare in other countries. Because Int14A and D442G were originally found in subjects with high HDL-C levels, these mutations ought to be responsible for high HDL-C

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levels. However, it is well known that plasma HDL levels are regulated by environmental factors such as alcohol intake and cigarette smoking (16, 17). In addition, there are no data available regarding children with these mutations, who seem to be less affected by environmental factors than subjects reported previously. We have recently screened 500 children for *CETP* gene mutations (Int14A and D442G). No child with Int14A was found in our children screened. Thus, as a first step to clarify the relation between *CETP* gene mutations and HDL, in the present study we characterized children with the D442G gene mutation.

## METHODS

**Subjects.** Outpatients at the Departments of Pediatrics, University of the Ryukyus and Kumamoto University School of Medicine, who had visited the respective university hospitals for a routine check-up were screened for *CETP* gene mutations. Young adults in the present study were students and volunteers from the staff of the Faculty of Medicine, University of the Ryukyus. Venous blood was drawn after an overnight fast. The study protocol had been approved by the ethical committees of the university hospitals, and informed consent was obtained from the parents of all of the children and from the students and volunteers.

**Analysis of D442G mutation.** *CETP* gene mutations were analyzed by PCR and RFLP analysis. A 3-mL sample of venous blood was collected in an EDTA-containing tube. After separating plasma by centrifugation, genomic DNA was isolated from blood cells using a PUREGENE DNA isolation kit (Gentra, Minneapolis, MN, U.S.A.). Extracted DNA (100 ng) was used as a template. Exon 15 and flanking sequences were amplified using paired synthetic oligodeoxyribonucleotides complementary to the human *CETP* gene (18). The primers used to amplify exon 15 and flanking sequences were as follows: for D442G, 5'-GTGTTTACAGCCCTCATGAAC-3' and 5'-AAGCCAAAGTCCATCTCTGCAG-3'. The reaction was carried out in a final volume of 50  $\mu$ L containing 1.5 mM MgCl<sub>2</sub>, 0.3 mmol of each deoxyribonucleotide triphosphate (Nippon Gene, Wako, Japan), 0.3  $\mu$ mol of each primer, and 2.5 U of *Taq* DNA polymerase (Nippon Gene). DNA was amplified by 35 cycles of 35 s of denaturation at 94°C, 45 s of annealing at 63°C, and 35 s of extension at 72°C. PCR products (287 bp) were digested with *TaqI* restriction enzyme (Nippon Gene) at 72°C for 3–4 h. Digested PCR products were electrophoresed on 8% polyacrylamide gel. *TaqI* RFLPs were detected by ethidium bromide staining. The normal *CETP* gene has two restriction sites for *TaqI*, and one restriction site is lost in the gene with the D442G mutation. As a result, the D442G homozygote, heterozygotes, and subjects without D442G showed two bands (218 bp and 69 bp), four bands (218 bp, 69 bp, 41 bp, and 28 bp), and three bands (218 bp, 41 bp, and 28 bp), respectively.

**Analysis of lipids, apolipoproteins, and CETP mass.** Serum levels of TC, TG, and HDL-C were analyzed using an auto-analyzer and enzymatic methods, or by selective precipitation using sodium phosphotungstate and magnesium chloride (19, 20). LDL-cholesterol was calculated as TC - (HDL-C +

TG/5). Similar to the case of adult, the formula for calculating LDL-C is applicable to children (LDL-C calculated by the formula is closely correlated with LDL-C by direct measurement;  $n = 163$ ,  $r = 0.965$ ,  $p < 0.01$ , Okada T, *et al.*, manuscript in preparation). Apolipoproteins (A-I, A-II, and B) were measured by the turbidity immunoassay method (21). CETP mass was measured by the enzyme immunoassay reported by Kiyohara *et al.* (22).

**Statistical evaluation.** One-way ANOVA, the Mann-Whitney *U* test, and the Pearson correlation coefficient were used to evaluate the data. Differences among groups or correlations with  $p < 0.05$  were considered to be statistically significant.

## RESULTS

Five hundred children were screened for *CETP* gene mutations. We found 30 heterozygotes and a homozygote (5-y-old girl) with the D442G mutation. The incidence of D442G heterozygosity was 6% in children. To further characterize these children, children with and without D442G who were not obese were recalled to the Ryukyu and the Kumamoto University Hospitals; 21 heterozygotes, a homozygote, and 65 children without D442G mutation visited hospitals, and the parents of the remaining refused or ignored our request. None of the children we studied was obese (100% < relative body weight < 120%) or taking alcohol or drugs affecting lipid metabolism. Based on Tanner criteria, stages of sexual maturity rating in our children were mostly 1–2. As shown in Table 1, plasma CETP mass was significantly lower in both boys and girls who were heterozygous for D442G than in their counterparts without D442G ( $p < 0.001$  and  $< 0.05$ ). No significant differences were found in plasma concentrations of lipids and apolipoproteins between heterozygous children and children without D442G. Plasma concentrations of TC, TG, HDL-C, LDL-C, apo A-I, apo A-II, apo B, and CETP mass in the girl who was homozygous for D442G were 251, 54, 110, 130, 224, 36, 85, and 1.3 [mg/dL, except for CETP mass ( $\mu$ g/mL)], respectively.

**Relationships between plasma CETP mass and other lipoprotein variables.** Because no sex-related differences were found in the levels of plasma lipids, apolipoproteins, and CETP mass in the children we studied, we combined the data for boys and girls in the following analysis. As shown in Table 2, a significant relation was found between CETP mass and TC ( $r = 0.628$ ,  $p < 0.001$ ), CETP mass and LDL-C ( $r = 0.683$ ,  $p < 0.001$ ), and CETP mass and apo B ( $r = 0.584$ ,  $p < 0.001$ ). Among children without D442G, no significant correlations were observed between CETP mass and either lipid or apolipoprotein variables (Table 2). To evaluate the effect of aging, we then studied the relationship between CETP mass and lipid and lipoprotein variables in young adults without D442G. As shown in Table 3, plasma concentrations of HDL-C, apo A-I, and CETP mass were significantly higher in women than those in men ( $p < 0.05$  or  $< 0.01$  or  $< 0.001$ ). No significant relationship was observed between CETP mass and either lipid or apolipoprotein variables except for HDL-C in women (Table 4).

**Table 1.** Plasma lipids, apolipoproteins, and CETP concentrations in children with (D442G+) and without heterozygote D442G (D442G-)

Variable	Boys		Girls	
	D442G- (n = 32)	D442G+ (n = 10)	D442G- (n = 33)	D442G+ (n = 11)
Age (y)	10 ± 1	9 ± 1	10 ± 1	9 ± 1
TC (mM)	4.39 ± 0.10	4.45 ± 0.39	4.50 ± 0.10	4.65 ± 0.31
TG (mM)	0.98 ± 0.11	0.83 ± 0.15	0.83 ± 0.07	1.01 ± 0.18
HDL-C (mM)	1.61 ± 0.05	1.66 ± 0.10	1.71 ± 0.05	1.55 ± 0.10
LDL-C (mM)	2.33 ± 0.10	2.43 ± 0.39	2.43 ± 0.10	2.61 ± 0.28
Apo B (g/L)	0.77 ± 0.04	0.76 ± 0.12	0.77 ± 0.03	0.83 ± 0.07
Apo A-I (g/L)	1.48 ± 0.04	1.55 ± 0.08	1.54 ± 0.03	1.47 ± 0.07
Apo A-II (g/L)	0.33 ± 0.01	0.33 ± 0.02	0.32 ± 0.01	0.31 ± 0.02
CETP (mg/L)	2.7 ± 0.1	1.9 ± 0.2†	2.6 ± 0.1	2.0 ± 0.1*

Values are expressed as mean ± SEM.

\*  $p < 0.05$ .

†  $p < 0.001$ .

**Table 2.** Pearson correlation coefficients for CETP versus other lipoprotein variables in children with (D442G+) and without heterozygote D442G (D442G-)

CETP versus	D442G+ (n = 21)	D442G- (n = 65)
TC	0.628*	0.159
Log TG	0.119	-0.204
HDL-C	-0.209	-0.033
LDL-C	0.683*	0.243
Apo B	0.584*	0.175
Apo A-I	-0.242	0.039
Apo A-II	-0.393	-0.204

\*  $p < 0.001$ .

**Table 4.** Pearson correlation coefficients for CETP versus other lipoprotein variables in young adults without heterozygote D442G (D442G-)

CETP versus	D442G- Male (n = 61)	D442G- Female (n = 42)
TC	0.124	-0.026
Log TG	-0.025	-0.027
HDL-C	-0.022	-0.343*
LDL-C	0.180	0.145
Apo B	0.123	0.208
Apo A-I	-0.064	-0.234
Apo A-II	-0.021	-0.173

\*  $p < 0.05$ .

**Table 3.** Plasma lipids, apolipoproteins, and CETP concentrations in young adults without heterozygote D442G (D442G-)

	D442G- Male	D442G- Female
Subject (n)	61	42
Age (y)	24 ± 1	24 ± 1
TC (mM)	4.47 ± 0.10	4.65 ± 0.13
TG (mM)	1.15 ± 0.10	0.90 ± 0.07
HDL-C (mM)	1.66 ± 0.05	1.92 ± 0.05‡
LDL-C (mM)	2.20 ± 0.08	2.40 ± 0.10
Apo B (g/L)	0.72 ± 0.03	0.68 ± 0.03
Apo A-I (g/L)	1.45 ± 0.03	1.57 ± 0.04†
Apo A-II (g/L)	0.31 ± 0.01	0.29 ± 0.01
CETP (mg/L)	2.5 ± 0.1	2.9 ± 0.1*

Values are expressed as mean ± SEM.

\*  $p < 0.05$ .

†  $p < 0.01$ .

‡  $p < 0.001$ .

## DISCUSSION

In the present study, we found that 1) plasma concentrations of HDL-C, apo A-I, and apo A-II were not increased in children who were heterozygous for D442G, 2) plasma CETP mass is significantly decreased in children who are heterozygous for D442G, 3) plasma CETP mass in children who are heterozygous for D442G is correlated with plasma concentrations of TC, LDL-C, and apo B, and 4) plasma CETP mass in children and young adults without D442G is not correlated with the plasma concentration of any lipid or apolipoprotein except for HDL-C in young adult women.

D442G mutation is prevalent in the Japanese population, but rare in other ethnic groups. In the present study, the rate of D442G mutation was 6%. This value is similar to those in other reports from Japan (15). The site of the D442G mutation is close to the active site of CETP, and the cellular expression of mutant cDNA leads not only to a reduction in CETP secretion but also to a decrease in the specific activity, compared with the wild type (14). In addition, the coexpression of wild-type and mutant cDNAs reduces wild-type secretion and activity, which suggests that the D442G mutation has a dominant role during cellular expression (14). These data in *in vitro* experiments are apparently consistent with the clinical finding that D442G heterozygotes and homozygotes have similar plasma concentrations of HDL-C whereas D442G heterozygotes have higher plasma HDL-C concentrations than Int14A heterozygotes (their plasma CETP concentration is half of normal and the specific activity of CETP is normal) (14, 15). From these results, it seems reasonable to consider that diminished CETP mass and activity caused by D442G mutation could be responsible for the increased HDL-C in subjects with D442G mutation. However, children who are heterozygous for D442G show normal HDL-C concentrations despite a decreased plasma concentration of CETP (Table 1), although a child who is homozygous for D442G has a very high plasma HDL-C concentration (110 mg/dL). Furthermore, the plasma concentration of CETP in D442G heterozygotes does not correlate with plasma HDL-C, apo A-I, and apo A-II levels (Table 2). In the preliminary study, similar results were obtained in het-

erozygous young adults with D442G ( $n = 8$ ). Most previous clinical studies on D442G mutation were conducted in older subjects with a mean age of more than 50 y (14, 15, 23). As mentioned previously, plasma HDL levels are regulated by many environmental factors as well as genetic factors. Alcohol intake, cigarette smoking, physical activity, and obesity have all been reported to affect plasma HDL levels (16, 17). Environmental factors could modify the effect of D442G mutation on HDL metabolism. Children seem to be less affected by environmental factors. As an obvious example, none of the children we studied was obese or taking alcohol or smoked. Thus, differences in environmental factors may explain our present data. Hegele *et al.* (24–26) had reported the associations of genomic variations in apo C-III, apo E, angiotensinogen, intestinal fatty acid binding protein, and paraoxonase genes with variations in plasma lipoproteins in children. Different from our study, the associations were stronger in children than in adults. However, similar to our speculation, they concluded relative absence of age-dependent environmental factors could be responsible for the stronger associations. Further studies are needed to clarify the mechanism that underlies the effect of environmental factors on lipoprotein-genotype associations.

It has been reported that HDL-CE is transported to the liver by two pathways: a direct uptake pathway, mediated by hepatic scavenger receptor B-I (in humans, CLA-1, CD36, and lysosomal integral membrane protein II analog-1 receptor) (3, 4, 27, 28), and an indirect pathway, involving the exchange of HDL-CE for TG in TG-rich lipoproteins by CETP (1, 2, 5). It is well known that CETP is a key protein in the indirect pathway. Recently, Collet *et al.* (29) reported that remodeling of HDL by CETP and hepatic lipase leads to the enhanced uptake of HDL-CE by cellular scavenger receptor B-I. This suggests that both direct and indirect pathways are affected in subjects with D442G mutation. If both pathways do not operate efficiently, plasma HDL ought to increase, as found in older subjects with D442G mutation. However, plasma HDL is not increased in children who are heterozygous for D442G, although plasma CETP mass is decreased. Plasma CETP mass in children who are heterozygous for D442G is correlated with plasma concentrations of TC, LDL-C, and apo B. From the lack of an association between plasma concentrations of CETP and either lipid or apolipoprotein levels in children without D442G and young male adults, and an inverse association between plasma concentrations of CETP and HDL-C in young female adults, the relative importance of the direct uptake and indirect pathways might be different under different *in vivo* conditions. Judging from higher plasma CETP mass, more CETP mass may be required for efficient reverse cholesterol transport in young female adults. Further studies addressing the role of sexual hormones and plasma lipases on HDL metabolism are needed.

In conclusion, the plasma CETP mass required for efficient reverse cholesterol transport in children must be less than that in older people. When we consider the results in children who are heterozygous for D442G, less than half of the plasma CETP might be required for efficient HDL-CE clearance in

children. However, a deficiency in CETP mass for efficient reverse cholesterol transport increases the plasma HDL concentration, even in children, as found in a child who was homozygous for D442G.

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