Associations of cholesteryl ester transfer protein (CETP) gene variants with pituitary adenoma

Agne Sidaraite[a], Rasa Liutkeviciene[b,c], Brigita Glebauskiene[c], Alvita Vilkeviciute[b], Loresa Kriauciuniene[b,c]

Aim. The aim was to evaluate the association of *CETP* (rs5882 and rs708272) single nucleotide polymorphisms with the presence, invasiveness, hormonal activity and recurrence of pituitary adenoma (PA).
Methods. The study group included 142 patients with PA and the control group, 753 healthy subjects. The genotyping of *CETP* (rs5882 and rs708272) was performed using a real-time PCR method.
Results. After statistical analysis we found that *CETP* rs708272 genotype G/A under the over-dominant model was associated with the decreased odds of PA (OR=0.637; 95%CI: 0.443–0.917; *P*=0.015), active PA (OR=0.538; 95%CI: 0.335–0.865; *P* =0.01) and non-recurrent PA (OR=0.602; 95% CI: 0.402 – 0.902; *P* =0.014). When compared to controls, the rs708272 genotype G/A was less frequent in the active PA subgroup (37.5% vs 52.7%, *P* =0.009) and the non-recurrent PA subgroup (40.2% vs 52.7%, *P*=0.013), while the rs5882 genotype A/A was less frequent in the non-recurrent PA subgroup (37.5% vs 46.2%, *P*=0.015).
Conclusion. Our study showed that *CETP* rs708272 genotype G/A may be associated with a decreased risk of PA.

Key words: pituitary adenoma, CETP rs5882, rs708272, gene polymorphism, tumor

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[a]*Lithuanian University of Health Sciences, Medical Academy, Eiveniu 2, Kaunas, Lithuania*
[b]*Neuroscience Institute, Lithuanian University of Health Sciences, Medical Academy, Eiveniu 2, Kaunas, Lithuania*
[c]*Department of Ophthalmology, Lithuanian University of Health Sciences, Medical Academy, Eiveniu 2, Kaunas, Lithuania*
Corresponding author: Agne Sidaraite, e-mail: agne.sidaraite@fc.lsmuni.lt

INTRODUCTION

Pituitary adenomas (PAs) are a group of diverse neoplasms which typically arise from adenohypophysis and rarely metastasize[1]. PA accounts for 12-15% of central nervous system tumors[2]. Women have a two-fold increased risk of developing PA compared to men[3]. PAs are classified according to the type of hormone they produce; if PA does not produce any hormone, it is called inactive PA. Also, PAs can be invasive and noninvasive, recurrent and non-recurrent[4]. Even if PA usually is non-malignant, it tends to recur locally after excision[4-5]. Another problem is the aggressiveness of PA – it does not have a capsule and can grow invasively into surrounding tissues[6]. Not all of these tumors are symptomatic and it is quite hard to diagnose PA while it is in early stages[4,7]. For this reason, scientists are trying to find biomarkers which could help detect PA at early stages[1,7].

There are familial PAs known, which include multiple endocrine neoplasia type 1 and 4 (MEN1 and MEN4, respectively), Carney complex (CNC) and familial isolated PA (FIPA) (ref.[8,9]). However, they make only up to 5% of all cases of PAs. The vast majority of these tumors arise sporadically and their pathogenesis is a common study object[8]. Some studies were carried out in order to find associations between PA and some genes, such as *AIP* (10-11), *MMP-9* polymorphism[12], *MMP-2* polymorphism[13], *FGFR4* polymorphism[14] and others.

The cholesteryl ester transfer protein (CETP) gene is located in the q21 region of chromosome 16. The product of this gene is a protein of 476 amino acids, which forms a glycoprotein[15]. CETP mediates the exchange of lipids between lipoproteins. This process results in the net transfer of cholesteryl esters from high-density lipoproteins (HDL) to lower-density species, which are atherogenic[16-18]. CETP is synthesized and secreted in many tissues and organs including the brain[19]. It is known that high plasma concentrations of CETP are associated with an increased risk of cardiovascular diseases[15-16,20-22]. *CETP* could also be associated with many diseases such as neurodegenerative diseases[23-28], dementia[24-26,28] and cancer[29].

The evidence of a possible pathway of tumorigenesis where lipoproteins play a major role is growing. Furberg et al. found that low HDL-C profiles in patients are related to the increased levels of free biologically active estradiol throughout an entire menstrual cycle, especially in women whose body mass index (BMI) is higher. It is known that high levels of estradiol are one of the main risk factors of breast cancer (BC) (ref.[30]). Esau et al. have found a *CETP*-centric cholesterol pathway involved in sensitizing estrogen receptor positive (ER+) BC cells to intrinsic mitochondrial apoptosis. Furthermore, analysis of cell line, tissue and patient data from publicly available databases linked elevated *CETP* expression to cancer, cancer relapse and overall poor survival. The cholesterol pathway constituents, like low-density lipoproteins (LDL) cholesterol,

cholesterol receptors LDLR and SCARB1 and others, have strong correlation with BC progression and clinical outcome[29-35].

We decided to analyze possible associations between *CETP* and PA because of the growing evidence of *CETP* involvement in tumor pathogenesis. To our knowledge, this is the first time when such links between PA and *CETP* are searched.

MATERIALS AND METHODS

Study and control group formation

Permission to undertake the study was obtained from the Ethics Committee for Biomedical Research (No P2-9/2003). The study was carried out in the Department of Ophthalmology and Department of Neurosurgery, Lithuanian University of Health Sciences (LUHS).

Two groups were formed in our study: the pituitary adenoma (PA) group (consisting of 142 patients who were diagnosed with PA) and the control group (consisting of 753 healthy individuals). The inclusion criteria for the PA group were: determined and confirmed PA via magnetic resonance imaging (MRI); good general health condition; consent to participate in the study; age ≥18 years; absence of other brain or any other tumors.

The control group was formed taking into consideration the distribution of age and gender in the PA group. The age median between patients and controls did not differ significantly (P=0.473). Demographic data of the study subjects are presented in Table 1.

General medical examination

Data on hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease and stroke were obtained during an examination by a family doctor and gathered from medical records.

Invasiveness evaluation

PA invasiveness has been described previously[36]. All pituitary adenomas were analyzed based on magnetic resonance imaging (MRI) findings. The preoperative MRI investigations were performed with 1,5 T MRI scanners (Siemens MAGNETOM Avanto, 1,5 T Philips ACHIEVA) using a head coil and a standard pituitary scanning protocol, obtaining T1W sagittal and coronal and T2W/TSE coronal pre-contrast images, and T1W coronal and sagittal gadolinium-enhanced MR images with the intravenous agent gadodiamide (Omniscan, GE Healthcare). The retrospective analysis of MRI data was conducted by an experienced radiologist. The suprasellar extension and sphenoid sinus invasion by PA were classified according to the Hardy classification modified by Wilson[37]. The degree of suprasellar and parasellar extensions was graded as stages A–E. The degree of sellar floor erosion was graded as grades I-IV. Grade III shows localized sellar perforation, and grade IV shows diffuse destruction of sellar floor, which are the signs of invasive PA. The Knosp classification system[38] was used to quantify the invasion of the cavernous sinus. Grade 3 and 4 pituitary tumors were considered to be invasive.

DNA extraction and genotyping

Extraction of DNA and analysis of *CETP* gene polymorphisms (rs5882, rs708272) were carried out in the Laboratory of Ophthalmology, Neuroscience Institute, Lithuanian University of Health Sciences. DNA was extracted from 200 µL venous blood (white blood cells) using the silica-based membrane technology utilizing a genomic DNA extraction kit (GeneJET Genomic DNA Purification Kit, Thermo Scientific), according to the manufacturer's recommendations.

The genotyping of *CETP* polymorphisms (rs5882 and rs708272) was carried out using the real-time PCR. All single-nucleotide polymorphisms (SNPs) were determined using TaqMan® Genotyping assays (Thermo

Table 1. Demographic data for control and PA groups.

Characteristic	Group		*P*
	Pituitary adenoma n = 142	Control n = 753	
Age, median, (Interquartile Range)	53.5 (22)	53 (0)	0.473*
Men, n (%)	55 (38.7)	274 (36.4)	0.330
Women, n (%)	87 (61.3)	479 (63.6)	
Invasiveness			
Yes	84 (59.15)	–	–
No	58 (40.85)		
Activity			
Yes	80 (56.34)	–	–
No	62 (43.66)		
Recurrence			
Yes	30 (21.13)	–	–
No	112 (78.87)		

*Mann – Whitney test

Scientific). Genotyping was performed using a Rotor-Gene Q real-time PCR quantification system (Qiagen, USA). Appropriate real-time PCR mixtures of CETP (rs5882, rs708272) were prepared for determining SNPs.

A PCR reaction mixture (9 μL) was poured into each of 72 wells of the rotor disc, and then 1 μL of matrix DNA of the samples (~10 ng) and 1 μL of negative control (−K) were added.

The Allelic Discrimination program was used during the real-time PCR. Then, the assay was continued following the manual provided by the manufacturer (www.qiagen.com, Allelic Discrimination). After that the Allelic Discrimination program was completed and the genotyping results were received. The program determined individual genotypes according to the fluorescence intensity rate of different detectors (VIC and FAM).

Statistical analysis

Statistical analysis was performed using the SPSS/W 20.0 software (Statistical Package for the Social Sciences for Windows, Inc., Chicago, Illinois, USA). Data are expressed as absolute numbers with percentages. Frequencies of genotypes are expressed in percentages.

Hardy-Weinberg analysis was performed to compare the observed and expected frequencies of *CETP* SNPs (rs5882, rs708272) using the χ^2 test in all groups. The distribution of *CETP* SNPs (rs5882, rs708272) in the PA and control groups was compared using the χ^2 test or the Fisher exact test. Binomial logistic regression analysis was performed to estimate the impact of genotypes on PA development. Odds ratios and 95% confidence intervals are presented. The selection of the best genetic model was based on the Akaike Information Criterion (AIC); therefore, the best genetic models were those with the lowest AIC values.

For multiple comparisons of the *CETP* SNPs studied, we used a significance value corrected by the Bonferroni approach. This adjustment was done for *CETP* SNPs (rs5882, rs708272) resulting in a 'corrected' significance threshold of $\alpha = 0.025$ (0.05/2) for genetic data.

Differences were considered statistically significant when $P<0.05$.

RESULTS

When we compared frequencies of genotypes and alleles in the PA and control groups, we found that the rs5882 G/A genotype was less frequent in the PA group than the control group (38% vs 46.2%, $P=0.033$) while the rs708272 G/G genotype was more frequent in the PA group than the control group (38.7% vs 29.8%, $P=0.034$). The rs708272 genotype G/A was less frequent in the PA group than the control group (41.5% vs 52.7%, $P=0.015$) and only this result remained significant after the Bonferroni correction (Table 1 in the supplementary material).

We performed binomial logistic regression analysis of patients with PA and control group subjects. Only over-dominant variables were statistically significant in the rs5882 polymorphism (OR=0.677; 95%CI: 0.473–0.971; $P=0.034$) but this result did not survive Bonferroni correction (Table 2). When we analyzed the rs708272 polymorphism, we found that co-dominant (G/A OR=0.605; 95%CI: 0.405–0.905; and A/A OR=0.864; 95% CI: 0.522-1.429; $P=0.043$), dominant (OR=0.670; 95%CI: 0.462–0.972; $P=0.035$) and over-dominant (OR=0.637; 95%CI: 0.443–0.917; $P=0.015$) variables were statistically significant but only the latter result remained significant after the Bonferroni correction (Table 2).

We compared frequencies of genotypes and alleles in the invasive and noninvasive PA subgroups and did not find any significant results. We also compared each subgroup by invasiveness with the control group and we found that the rs5882 genotype A/A was less frequent in the noninvasive PA subgroup than in controls (32.8% vs 46.2%, $P=0.047$), while the rs708272 genotype G/A was less frequent in the invasive PA subgroup than in the control group (40.5 % vs 52.7%, $P=0.043$). The rs708272 genotype G/G was more frequent in the invasive PA subgroup than in control subjects (40.5% vs 29.8%, $P=0.033$). Unfortunately, all these results did not survive after the Bonferroni correction (Table 2 in the supplementary material).

After binomial logistic regression analysis of patients with invasive and noninvasive PA and control group sub-

Table 2. Binomial logistic regression analysis of patients with PA and control group subjects.

Genotype, allele			OR (95 % CI)	*P*	AIC
rs5882	Co-dominant	G/A	1.439 (0.745 – 2.781)	0.105	782.497
		A/A	0.970 (0.495 – 1.902)		
	Dominant	G/A + A/A	0.834 (0.441 – 1.579)	0.578	784.697
	Recessive	A/A	1.400 (0.969 – 2.023)	0.073	781.747
	Over-dominant	G/A	0.677 (0.473 – 0.971)	0.034	780.505
	Additive		0.856 (0.652 – 1.123)	0.262	783.770
rs708272	Co-dominant	G/A	0.605 (0.405 – 0.905)	0.043	780.703
		A/A	0.864 (0.522 – 1.429)		
	Dominant	G/A + A/A	0.670 (0.462 – 0.972)	0.035	780.659
	Recessive	A/A	1.156 (0.734 – 1.820)	0.533	784.636
	Over-dominant	G/A	0.637 (0.443 – 0.917)	**0.015**	779.031
	Additive		0.865 (0.665 – 1.125)	0.280	783.845

Values in bold indicate significance after the Bonferroni correction ($P<0.05/2$).

jects, we found that only in the invasive PA subgroup the rs708272 polymorphism dominant (OR=0.623; 95%CI: 0.392–0.989; *P*=0.045) and over-dominant (OR=0.610; 95%CI: 0.385–0.965; *P*=0.034) variables were statistically significant. Also, these results did not remain significant after the Bonferroni correction (Table 3 in the supplementary material).

After comparison of frequencies of genotypes and alleles in the active and inactive PA subgroups, we did not find any significant results; then compared each subgroup's frequencies with the control group. This analysis showed that the rs5882 genotype G/A was more frequent in the inactive PA subgroup than in the control group (58.1% vs 43.8%, *P*=0.030), while the rs5882 genotype A/A was less frequent in the inactive PA subgroup (32.2% vs 46.2%, *P*=0.034). We also found that the rs708272 genotype G/G was more frequent in the active PA subgroup than in controls (41.3% vs 29.8%, *P*=0.034), while the rs708272 genotype G/A was less frequent in the active PA subgroup (37.5% vs 52.7%, *P*=0.009). Only the last result remained significant after the Bonferroni correction (Table 4 in the supplementary material).

After binomial logistic regression analysis of the patients with active and inactive PA group and the control group, we found that in the inactive PA group only the rs5882 polymorphism's variables were statistically significant: recessive (OR=0.554; 95%CI: 0.319–0.962; *P*=0.036) and over-dominant (OR=1.775; 95%CI: 1.050–2.999; *P*=0.032) (Table 3). Unfortunately, these results were not significant after the Bonferroni correction (Table 3). We found that in the active PA subgroup the rs708272 co-dominant (G/A: OR=0.513; 95%CI: 0.305–0.864; and A/A: OR=0.874; 95% CI:0.469-1.631; *P*=0.034), dominant (OR=0.603; 95%CI: 0.376–0.967; *P*=0.036) and over-dominant (OR=0.538; 95%CI: 0.335–0.865; *P*=010) variables were statistically significant but only the last result survived the Bonferroni correction (Table 3).

We compared frequencies of genotypes and alleles between recurrent and non-recurrent PA subgroups and did not find any significant results. We also compared these frequencies between each subgroup by recurrence and the control group and found that the rs5882 genotype A/A was less frequent in the non-recurrent PA subgroup than in controls (37.5% vs 46.2%, *P*=0.015) and this result remained significant after the Bonferroni correction. The rs708272 genotype G/G was more frequent in the non-recurrent PA subgroup than in the control group (40.2% vs 29.8%, *P*=0.026), while the genotype G/A was less frequent in the non-recurrent PA subgroup than in controls (40.2% vs 52.7%, *P*=0.013). The last result remained significant after the Bonferroni correction (Table 5 in the supplementary material).

After the binomial logistic regression analysis of patients with recurrent and non-recurrent PA and the control group, we found that only in the non-recurrent PA subgroup and in the rs708272 polymorphism there were significant variables: co-dominant (G/A: OR=0.564; 95%CI: 0.362–0.880; and A/A: OR=0.830; 95% CI: 0.477-1.443; *P*=0.038), dominant (OR=0.630; 95%CI: 0.419–0.949; *P*=0.027) and over-dominant (OR=0.602; 95% CI: 0.402 – 0.902; *P*=0.014) (Table 4). Only the last result survived the Bonferroni correction (Table 4).

DISCUSSION

To our knowledge, it is the first time that an association between *CETP* and PA has been searched.

Cholesterol and lipoproteins are two of the most important substances in human body. They are essential for brain maturation and white matter development, and decreased cholesterol early in life may limit both the number and efficacy of synapses. Even though CNS cholesterol concentration does not depend on serum cholesterol levels[39], the changes in serum have been associated with variations in the healthy brain's white matter structure[40]. Also,

Table 3. Binomial logistic regression analysis of patients with active and inactive PAs and control group subjects.

		Genotype, allele		OR (95 % CI)	*P*	AIC
rs5882	Inactive	Recessive	A/A	0.554 (0.319 – 0.962)	0.036	435.961
		Over-dominant	G/A	1.775 (1.050 – 2.999)	0.032	435.922
rs708272	Active	Co-dominant	G/A	0.513 (0.305 – 0.864)	0.034	524.002
			A/A	0.874 (0.469 – 1.631)		
		Dominant	G/A + A/A	0.603 (0.376 – 0.967)	0.036	524.655
		Over-dominant	G/A	0.538 (0.335 – 0.865)	**0.010**	522.182

Values in bold indicate significance after the Bonferroni correction (*P*<0.05/2).

Table 4. Binomial logistic regression analysis of patients with recurrent and non-recurrent PAs and the control group.

	Genotype, allele			OR (95 % CI)	*P*	AIC
rs708272	Non-recu-rrent	Co-dominant	G/A	0.564 (0.362 – 0.880)	0.038	664.126
			A/A	0.830 (0.477 – 1.443)		
		Dominant	G/A + A/A	0.630 (0.419 – 0.949)	0.027	663.970
		Over-dominant	G/A	0.602 (0.402 – 0.902)	**0.014**	662.570

Values in bold indicate significance after the Bonferroni correction (*P*<0.05/2).

cholesterol is used in the essential synthesis of various hormones (estrogen, progesterone and testosterone) for maintaining internal homeostasis[41]. Abnormal cholesterol and lipoprotein levels result in dyslipidemia, which is one of the characteristics of obesity. It includes high levels of triglycerides in very-low-density lipoproteins (VLDL) and low levels of HDL-C (ref.[42-44]). The low levels of HDL-C were linked with various types of cancer due to prolonged inflammation which is caused by cytokines, adipokines and hormones[44-48]. Moreover, some authors have found more evidence of the possible pathway of tumorigenesis where lipoproteins play a major role. Furberg et al. have found that low HDL-C profiles in patients are related to the increased levels of free biologically active estradiol throughout the entire duration of a menstrual cycle, especially in women whose body mass index (BMI) was higher. It is known that high levels of estradiol are one of the main risk factors for breast cancer[30]. Li and others have tried to determine if raft levels in human cancer cells differ from normal human cells. They found that breast cancer and the prostate cancer cell lines had more lipid rafts and were more sensitive to cholesterol depletion-induced cell death than normal cells[49].

Having in mind relations between cancer and lower levels of HDL-C, some studies were performed to find any connection between brain tumors and a higher body mass index[50-54]. Sergentanis et al. have carried out a meta-analysis which showed increased risk of meningioma for obese men and women, while presence of gliomas was associated with a higher BMI for women only[54]. Wiedmann *et al.* have conducted a large population-based prospective cohort study in which they have found that presence of PA was associated with both overweight (HR 1.39; 95% CI 1.21–1.61) and obesity (HR 1.43; 95% CI 1.09–1.88) in men and women, with no significant difference between these two groups[55].

Some studies were carried out in order to find out if *CETP* could be associated with Alzheimer's disease (AD) knowing that cholesterol dysregulation is linked with this neurodegenerative disease[23-28]. The meta-analysis done by Chen *et al.* has shown that *CETP* rs5882 polymorphism could be associated with higher susceptibility to AD (especially in Caucasians) but polymorphism rs708272 does not play an important role in the pathogenesis of this neurodegenerative disease[27].

Association between *CETP* and dyslipidemia is known and studied[15-16,20-22]. Kuivenhoven et al. have proved that *CETP* rs708272 polymorphism's B1 allele was linked with higher CETP and lower HDL-C levels[16]. Ridker et al. have carried out a prospective cohort and have found that only single nucleotide polymorphisms near or in the *CETP* gene were associated with both HDL-C and risk of incident myocardial infarction and the latter risk remained after adjustment for HDL-C (ref.[22]). Mirmiran et al. have found that B2 allele carriers had a greater risk of cardiovascular diseases among alcohol drinkers and patients with diabetes[15].

Only one study has tried to determine if *CETP* polymorphisms could be associated with cancer. Baez and others have searched for genetic variants which could be linked to gallbladder cancer (GBC) and gallbladder stones[56] because there are proofs that they are one of the risk factors of this type of cancer[57]. They found that *CETP* polymorphism rs798272 may be related to gallbladder cancer: the frequency of T/T genotype was higher in gallbladder cancer patients than in gallbladder stone patients (OR = 5.04, *P*=0.012), but when they compared each of these two groups with controls, no significant difference was found. It is hard to make any statements from this study about a possible *CETP* role in tumorigenesis – it is likely that gallstones play more important role in GBC pathogenesis[56].

The strength of our study was a thorough examination of the control group – only healthy individuals with no record of present or past hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, malignant tumors and stroke were included in the control group. Also, the PA group was formed very carefully: invasiveness was evaluated by universally acknowledged classification systems. Our control group was quite large, so the analysis and gathered results were more reliable. The weakness of this study - the cholesterol level and body mass index were not evaluated.

Our study showed that the *CETP* rs708272 genotype G/A may be associated with a decreased risk of PA and its active and non-recurrent types, while the rs5882 genotype A/A may be linked to a decreased risk of non-recurrent PA. All in all, we can conclude that further research of the mechanisms of PA pathogenesis and of genes involved in this process is needed.

Author contributions: RL, BG, AV, LK: study design; RL, AS, BG, AV, LK performed the research; RL, AV, AS, BG: data analysis and manuscript writing.

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Supplemental Material:

The online version of this article (doi: 10.5507/bp.2019.016) offers supplemental material.