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Genetic Polymorphisms of the *Carboxylesterase 1 (CES1)* Gene in a Korean Population

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Human carboxylesterase 1 (CES1) is a serine esterase that hydrolyzes various exogenous compounds. Single nucleotide polymorphisms (SNPs) of *CES1* may lead to inter-individual metabolic variability of its substrates. The allele and haplotype frequencies of known SNPs have been demonstrated to vary among ethnic groups. We analyzed genetic variations of *CES1* in a Korean population. Direct sequencing of all exons and flanking regions of the *CES1* gene was performed on samples obtained from 200 Koreans. We identified 41 SNPs. The most frequent SNPs was -914G>C (frequency: 99.5%), followed by 4256G>A (frequency: 65.8%), -75T>G (frequency: 59.3%). Haplotype analysis using the identified SNPs revealed fifteen haplotypes (≥1% haplotype frequency) in our samples. The most frequent haplotype was Hap1 (frequency: 15.4%). Among the identified 41 SNPs, nine of which are novel variants and 14 SNPs were nonsynonymous variants. Using the functional predictive software PolyPhen-2, the G19V, E221G, and A270S variants were predicted to be most likely damaging to the function and structure of *CES1*. *In-vitro* analyses for two of these variants have been previously performed; however, functional evaluation of E221G (11657A>G, rs200707504) still needs to be conducted. Therefore, further studies are warranted to characterize the functional impact of E221G on CES1 activity.

ORIGINAL ARTICLE

Introduction

Human carboxylesterases (CES) are serine esterases that play an important role in phase I drug metabolism. CES enzymes hydrolyze diverse xenobiotic and endogenous substrates that contain carboxylic acid esters, carbamates, thioesters, and amide compounds.[1-4] Two major subfamilies of identified CES are human carboxylesterase 1 (CES1) and human carboxylesterase 2 (CES2).[2,4] *CES1* gene is located on chromosome 16q13-q22.1 and contains 14 exons.[3,5] To date (29-Apr-2014), a total of 1107 single nucleotide polymorphisms (SNPs) in *CES1* have been documented in the NCBI SNP database (http://www.ncbi.nlm.nih.gov).

CES1 preferentially hydrolyzes a variety of substrates possessing a large acyl group and a small alcohol group, such as methylphenidate, cocaine, heroin, meperidine, demerol, lidocaine, clopidogrel, lovastatin, delapril, temocapril, imidapril, and oseltamivir.[2,6,7] *In-vitro* functional studies have demonstrated that the G143E and the D260fs variants have reduced catalytic function, resulting in the disruption of hydrolytic activity of CES1.[8, 9] In a single-dose pharmacokinetic study, these two *CES1* mutations were identified in one subject who displayed 7-fold higher total methylphenidate (i.e., combined *d*- and *l*-isomers) concentrations compared to that of other subjects (n=19).[2,9] In addition, -75T>G polymorphism was associated with the reduced appetite in attention deficit-hyperactivity disorder (ADHD) youths treated with methylphenidate[10] and the isoniazid-induced hepatotoxicity in latent tuberculosis infection patients.[11] Taken together, these findings suggest that *CES1* gene variants can lead to clinically significant alterations in

Table 1. Primers sequences used for the human *CES1* gene analysis

Primer name	Region	First Long PCR Primer sequence (5'-3')	Product size (bp)	PCR condition (°C)
CES1 ZtF CES1 ZtR	Promoter-Exon6	TGTCAGAGGCTGCAGCCAGACC GGTTGTTCCACTTACCAGCCATTAGG	16,532	68
CES1 Zt2F CES1 Zt2R	Exon7-Exon14	CTTGTGTCTCTCTGGGTCTGCCTAATG TTGCAAGGCACATGGTTCCCTC	25,188	68
Primer name	Region	Nested PCR primer sequence (5'-3')	Product size (bp)	PCR condition (°C)
CES1PF CES1PR	Promoter	TGCTCTTTGTGTACAAGCTTTTGTG CGATCTTAAATTTCATCGAGTCCC	755	64
CESE1F CESE1R	Exon1	TCTGACACCGATGGTGTGTGAC CCAAGTCCAAGTCCTAATATGGAA	819	65
CESE2F CESE2R	Exon2	ACTCACTTAGAAAGCGGCAAACT CACAGCAGGTGCTCAATAAACATG	486	64
CESE3F CESE3R	Exon3	CTGGGAGTTCCAAAGGCTCTGGA CCTTGACCAGGGGGTCCCACAA	425	65
CESE4F CESE4R	Exon4	GGTGATGGGAGTGTCCTCCC AAAGTGCAGTGAGGAGAGTCCG	501	64
CESE5F CESE5R	Exon5	TTAAGGGTTCACTGAGAACCCCT AGGGCCAGTCCTGAATTCAGGTA	374	64
CESE6F CESE6R	Exon6	GAGCTGTAGGAAGACTTCCACCTC GTGTCCAGCCGGAGACGTACCA	313	64
CESE7F CESE7R	Exon7	GGGCTTGGGATAGAATGCCACT TCTGGGACCAAGTTTACAGGGT	239	64
CESE8F CESE8R	Exon8	TGATGCGGGAAGAACCTGACA CAGAAACAAACACGCAGGAGTTA	259	64
CESE9F CESE9R	Exon9	AGTCATGGAGACCTACCCCCCTA AGCTGCCCAGGACTCAGAGTGCA	411	64
CESE10F CESE11R	Exon10-11	TCATGCCCTTAAAAGCCCCCATA TGGGGTTTGTGTCCCTCCCG	659	64
CESE12F CESE12R	Exon12	ATGCAGCCCGGAGCGCATCA CAAGACTGGAACCCAAGTCTCTAAC	337	64
CESE13F CESE14R	Exon13-14	AGACTCGCATGTGATGTTGACG ACCGTTCTGTCTCTGAGGACAAAGT	886	64

CES1: carboxylesterase 1

pharmacokinetic profiles and drug response of CES1 substrates.[2,8]

Although their functional consequences remain uncertain, several *CES1* variants have been reported in NCBI SNP database. The *CES1* allele and estimated haplotype frequencies showed significant differences between African and European populations.[5] However, the exploration of *CES1* polymorphisms and their allele and haplotype frequencies in a Korean population have not been performed. We obtained 200 samples from healthy Korean subjects and sequenced the *CES1* gene to characterize the polymorphisms that are present in a Korean population. Ideally, this may lead to optimized personalized pharmacotherapy in Koreans, particularly for frequently used prescription drugs that are CES1 substrates.

Methods

Whole blood samples from a total of 200 healthy male Korean subjects were used in this study. Samples were stored in the DNA Repository of the Seoul National University Hospital (SNUH). All of the subjects provided written informed consent before participating in the study. This study was approved by the Institutional Review Board of SNUH. Personal information was blinded, and the samples were delivered to the Pharmacogenomics Research Center of Inje University, where DNA extraction, purification and sequencing were performed. Genomic DNA was isolated from whole blood cells from the study sub-

Table 2. Summary of SNPs and their frequencies in the *CES1* gene in a Korean population

CES1 : Reference sequence NG_012057.1					
SNP (NT change)	Location	CDS change *	Amino Acid substitution	rs ID †	Allelic frequency (%)
-1114G>A	5'UTR	-	-	rs34428341	10.3
-914G>C	5'UTR	-	-	rs28759040	99.5
-757delC	5'UTR	-	-	rs57810510	35.3
-722G>A‡	5'UTR	-	-	-	0.3
-610G>A‡	5'UTR	-	-	-	0.3
-322T>G‡	5'UTR	-	-	-	0.3
-161A>G‡	Exon01 (5'UTR)	-	-	-	0.3
-75T>G	Exon01 (5'UTR)	-	-	rs3815583	59.3
-46A>G	Exon01 (5'UTR)	-	-	rs12149373	25.3
-39A>G	Exon01 (5'UTR)	-	-	rs12149371	25.3
-30G>A	Exon01 (5'UTR)	-	-	rs144950224	1.0
-21G>C	Exon01 (5'UTR)	-	-	rs12149322	25.3
-20A>G	Exon01 (5'UTR)	-	-	rs12149370	25.3
-2C>G	Exon01 (5'UTR)	-	-	rs12149368	24.8
11G>C	Exon01	11G>C	R4P	rs111604615	24.8
15C>T‡	Exon01	15C>T	A5A	-	24.8
16T>C	Exon01	16T>C	F6L	rs201577108	24.8
19A>G	Exon01	19A>G	I7V	rs114788146	24.8
34T>G	Exon01	34T>G	S12A	rs12149366	24.8
68A>G	Intron01	-	-	rs12149359	24.8
73insT	Intron01	-	-	rs56278207	36.0
4067A>C	Intron01	-	-	rs3826189	1.5
4085G>T	Exon02	56G>T	G19V	rs3826190	1.5
4256G>A	Exon02	227G>A	S76N	rs2307240	3.3
4363C>T	Intron02	-	-	rs3848300	65.8
6635A>G	Intron02	-	-	rs143802684	0.5
11607C>A	Exon05	612C>A	D204E	rs2307227	0.3
11657A>G	Exon05	662A>G	E221G	rs200707504	2.0
11720C>G	Intron05	-	-	rs2307234	0.3
12630C>T	Exon06	747C>T	G249G	rs202228585	0.5
13423G>T	Exon07	808G>T	A270S	rs115629050	0.8
13447A>G	Exon07	832A>G	T278A	rs200489319	0.3
16094A>G‡	Exon08	907A>G	K303E	-	0.3
19917G>A	Intron08	-	-	rs3859093	41.3
19923T>C	Intron08	-	-	rs3859092	41.3
22041T>G	Intron09	-	-	rs2302722	41.5
22280C>T‡	Intron10	-	-	-	0.3
22351C>T	Intron10	-	-	rs146930283	17.3
22359C>A	Intron10	-	-	rs147989545	42.0
22445A>T‡	Exon11	1224A>T	T408T	-	0.3
26503C>A‡	Intron11	-	-	-	0.3

SNPs: single nucleotide polymorphisms, CES1: carboxylesterase. 1. *CDS: coding DNA sequence. †rs ID: reference SNP ID, ‡Novel variant allele detected in this study.

Table 3. Summary of haplotypes and their frequencies in the CES1 gene in a Korean population

Haplo-type	26503C>A	22445A>T	22359C>A	22351C>T	22280C>T	22041T>G	19923T>C	19917G>A	16094A>G	13447A>G	13423G>T	12630C>T	11720C>G	11657A>G	11607C>A	6635A>G	4363C>T	4256G>A	4085G>T	4067A>C	73insT	68A>G	34T>G	19A>G	16T>C	15C>T	11G>C	-2C>G	-20A>G	-21G>C	-30G>A	-39A>G	-46A>G	-75T>G	-161A>G	-322T>G	-610G>A	-722G>A	-757delC	-914G>C	-1114G>A	Frequency (%)
Hap1	C	A	C	C	C	T	T	G	A	A	G	C	C	A	C	A	C	G	G	A	-	A	T	A	T	C	G	C	A	G	G	A	A	T	A	T	G	G	C	C	G	15.4
Hap2	C	A	C	C	C	T	T	G	A	A	G	C	C	A	C	A	T	G	G	A	T	G	G	G	C	T	C	G	G	C	G	G	G	G	A	T	G	G	C	C	G	12.5
Hap3	C	A	A	C	C	G	C	A	A	A	G	C	C	A	C	A	T	G	G	A	-	A	T	A	T	C	G	C	A	G	G	A	A	G	A	T	G	G	-	C	G	12.3
Hap 4	C	A	C	C	C	T	T	G	A	A	G	C	C	A	C	A	C	G	G	A	-	A	T	A	T	C	G	C	A	G	G	A	A	G	A	T	G	G	-	C	G	7.7
Hap 5	C	A	A	T	C	G	C	A	A	A	G	C	C	A	C	A	T	G	G	A	-	A	T	A	T	C	G	C	A	G	G	A	A	G	A	T	G	G	-	C	G	5.7
Hap 6	C	A	A	T	C	G	C	A	A	A	G	C	C	A	C	A	T	G	G	A	T	G	G	G	C	T	C	G	G	C	G	G	G	G	A	T	G	G	C	C	G	5.2
Hap 7	C	A	C	C	C	T	T	G	A	A	G	C	C	A	C	A	C	G	G	A	T	A	T	A	T	C	G	C	A	G	G	A	A	T	A	T	G	G	C	C	A	5.1
Hap 8	C	A	C	C	C	T	T	G	A	A	G	C	C	A	C	A	T	G	G	A	-	A	T	A	T	C	G	C	A	G	G	A	A	G	A	T	G	G	-	C	G	4.3
Hap 9	C	A	A	C	C	G	C	A	A	A	G	C	C	A	C	A	T	G	G	A	-	A	T	A	T	C	G	C	A	G	G	A	A	T	A	T	G	G	C	C	G	4.2
Hap 10	C	A	A	T	C	G	C	A	A	A	G	C	C	A	C	A	T	G	G	A	-	A	T	A	T	C	G	C	A	G	G	A	A	T	A	T	G	G	C	C	G	3.0
Hap 11	C	A	C	C	C	T	T	G	A	A	G	C	C	A	C	A	T	G	G	A	-	A	T	A	T	C	G	C	A	G	G	A	A	T	A	T	G	G	C	C	G	2.4
Hap 12	C	A	C	C	C	T	T	G	A	A	G	C	C	A	C	A	C	G	G	A	T	G	G	G	C	T	C	G	G	C	G	G	G	G	A	T	G	G	C	C	G	2.4
Hap 13	C	A	A	C	C	G	C	A	A	A	G	C	C	A	C	A	T	G	G	A	T	G	G	G	C	T	C	G	G	C	G	G	G	G	A	T	G	G	C	C	G	1.9
Hap 14	C	A	A	C	C	G	C	A	A	A	G	C	C	G	C	A	T	G	G	A	-	A	T	A	T	C	G	C	A	G	G	A	A	G	A	T	G	G	-	C	G	1.9
Hap 15	C	A	A	T	C	G	C	A	A	A	G	C	C	A	C	A	T	G	G	A	T	A	T	A	T	C	G	C	A	G	G	A	A	T	A	T	G	G	C	C	A	1.6

The data ≥ 1% in haplotype frequency presented.

jects using the Qiagen DNA Blood Mini Kit (Qiagen, Hilden, Germany). To differentiate from a *CES1* pseudogene, we first performed long polymerase chain reaction (PCR) using primers to specifically amplify *CES1* (Table 1). To specifically amplify *CES1*, we conducted long PCR in separate regions, Promoter-Exon6 and Exon7-Exon14, before performing nested PCR in each exon. The initial long PCR was performed in a total reaction volume of 50 μL in the presence of 250 ng of genomic DNA, Z-taq buffer, 3.0 mM $MgCl_2$, 0.2 M primers, and 1 μM dNTP using Z-taq (Takara Shuzo, Tokyo, Japan). The PCR conditions for this initial amplification were 30 cycles at 94°C for 1 min, 98°C for 5 sec, and 68°C for 3 min 20 sec. Nested PCR was conducted in total volume of 30 μL with 20 ng of the initial PCR product, D-taq buffer, 0.5 M primers, and 250 mM dNTP using D-taq (Sun Genetics, Daejeon, Korea). The nested PCR conditions were as follows: initial denaturation at 94°C for 1 min, followed by 35 cycles of 98°C for 20 sec, 64–65°C for 30 sec, 72°C for 30 sec–1 min, and a final elongation step at 72°C for 5 min. All primer sequences and the annealing temperatures are listed in detail in Table 1. After DNA purification, PCR products were directly sequenced using ABI PRISM 3130 DNA Analyzer (Applied Biosystems, Foster City, CA). Haplotype frequencies were estimated using Haploview ver. 4.2 software (http://www.broad.mit.edu/mpg/haploview/). *In-silico* analyses were conducted to predict the possible impact of amino acid substitutions on the structure and function of the CES1 protein using PolyPhen-2 software version 2.2.2 (http://genetics.bwh.harvard.edu/pph2). [12,13] Because a CES1 protein identifier was unavailable, we used the p23141 protein identifier as the reference, which is considered to be the most similar to the CES1 protein identifier. However, when compared to the CES1 reference protein identifier, the p23141 had an amino acid deletion of alanine at position 18. Therefore, when conducting amino acid substitution analysis using PolyPhen-2 software, we removed position 18 from the results position value. The analysis results are represented as 4 categories: probably damaging, possibly damaging, benign, and unknown.

Results

The distribution of alleles is presented in Table 2. The -914G>C, -4256G>A, and -75G>C variants were frequently reported with allele frequency of 99.5%, 65.8%, and 59.3%, respectively. A total of 15 common haplotypes (≥1% haplotype frequency) were identified. The most frequent haplotype was Hap1 (frequency: 15.4%), followed by Hap2 (frequency: 12.5%) and Hap 3 (frequency: 12.3%) (Table 3).

A total of 41 SNPs were identified in this study. Nine novel SNPs were identified in the study population, -722G>A, -610G>A, -332T>G, -161A>G, 15C>T, 16094A>G, 22280C>T, 22445A>T, and 26503C>A. Among the total SNPs identified, 14 SNPs were located in coding regions, and all of these SNPs were nonsynonymous variants (Table 2).

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Discussion

Because *CES1* is considered to be the most important hydrolytic enzyme, variations in the *CES1* gene can influence substrate pharmacokinetic and/or pharmacodynamic properties and may lead to increases in adverse effects, toxicity, sensitivity, or resistance.[14,15] Studies examining the potential therapeutic implications of *CES1* gene variants have been extensively investigated and reported in biomedical literature.[2,15]

In this study, we evaluated the frequencies of the *CES1* genetic variations and their allele and haplotype frequencies in Koreans. The SNP -914G>C showed the highest rate of *CES1* gene polymorphism. The next frequently reported SNPs were 4256G>A and -75T>G. Regarding *CES1* haplotype frequency, Hap1 exhibited the highest frequency in our samples.

CES1 gene allele and haplotype frequencies have distinct ethnic differences.[2,5,8,14,16] The minor allele frequency (MAF) of G143E was estimated to be 3.7%, 4.3%, 2.0%, and 0% in European-American, African-American, Hispanic, and Asian populations, respectively.[2,8,16] In addition, the allele frequency of the -816A>C polymorphism was 30.9%, 23.8%, and 24.8% in Chinese Yao population, Chinese Han population, and Japanese, respectively.[14,17] As expected, the G143E polymorphism, which has been reported to be 0% in Asian populations[2,8,16] and the D260fs polymorphism, which has been observed to be a rare variant in all ethnic groups[15] were not found in this study. On the other hand, the -816A>C variants, which has been reported more than 20% in Asian, were not observed in this study. To our best knowledge, this is the first study to explore *CES1* polymorphisms and their allele and haplotype frequencies in a Korean population.

Among the 14 nonsynonymous SNPs identified, three three variants were expected to alter human protein structure and function. G19V, E221G, and A270S were classified as most likely damaging (score: 0.992), possibly damaging (score: 0.937), and possibly damaging (score: 0.761), respectively. In our *in-silico* prediction analysis using PolyPhen-2 software, G19V and A270S were denoted as G18V and A269S, respectively, after inserting p23141 protein sequence. In previously performed in-vitro functional studies, the *CES1* variants G18V and A269S did not produce significant effects on CES1 mediated metabolism of substrates including clopidogrel and methylphenidate.[15] However, the effect of E221G (11657A>G, rs200707504; 2% frequency in Koreans) on *CES1* enzymatic activity has not been characterized to date. Therefore, additional studies, including *in-vitro* functional analysis and clinical studies in humans, are needed to elucidate the role of the E221G variant in phase I drug biotransformation. These studies regarding *CES1* genetic variants will have the potential to provide clinically relevant information about the optimal use of *CES1* drug substrates by predicting pharmacokinetic profiles and drug responses.

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Conflict of Interest

None of the authors have any conflicts of interest to disclose.

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