Genetic Spectrum of UGT1A1 in Korean Patients with Unconjugated Hyperbilirubinemia

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Dear Editor,

Uridine diphosphate-glucuronosyltransferase 1A (UGT1A1), an enzyme encoded by the UGT1A1 gene on chromosome 2q37, is the major bilirubin-conjugating enzyme [1, 2]. Variants in the promoter and coding regions of UGT1A1 affect the enzyme activity of UGT1A1, leading to unconjugated hyperbilirubinemia disorders, including Gilbert syndrome (GS), Crigler-Najjar syndrome type I (CNI), and Crigler-Najjar syndrome type II (CNII). Variant frequencies show inter-ethnic differences [3, 4]. Reports on the spectrum of variants in Korean patients with hyperbilirubinemia are limited thus far; they are mostly based on a small number of patients evaluating a few mutational hotspots [5, 6]. We retrospectively investigated the spectrum of UGT1A1 variation in a larger study population to examine the allele distribution in Korean patients with unconjugated hyperbilirubinemia.

We collected clinical data of 81 patients with hyperbilirubinemia who underwent UGT1A1 genotyping between April 2013 and March 2019 in Gangnam Severance Hospital, Seoul, Korea. For comparison, we retrieved allele frequencies of 1,722 Korean subjects from the Korean Reference Genome database (KRGDB, http://coda.nih.go.kr/coda/KRGDB/index.jsp), and of 80 Chinese and 71 Japanese healthy subjects from published data [7, 8]. For association analysis of genotypes and total bilirubin (TB) levels, we retrieved allele frequencies and laboratory data from a published study [9]. This study was approved by the Institutional Review Board of Yonsei University Health System, Gangnam Severance Hospital (IRB-2019-0188-001). The need for informed consent of the participants for reviewing medical records was waived on the condition that the research involves no more than minimal risk to the patients and the patient’s privacy was thoroughly protected.

Statistical analyses were conducted using Analyse-it v.5.11 Method Evaluation edition (Analyse-it Software, Ltd., Leeds, UK). Allele frequencies in the control and study groups were compared using Fisher’s exact test. Results were considered significant at P<0.05.

We detected nine variants in this study (Table 1). All variants...
identified in exons were missense variants, and two novel variants (c.864+2T>C and p.Ala61Gly) were detected. The most frequent allele was UGT1A1*28, with a frequency of 43.8% (71/162), followed by the UGT1A1*6 allele, with a frequency of 31.5% (51/162). The frequency of the wild-type allele was 4.9% (8/162) in the 81 hyperbilirubinemia patients. The frequencies of the UGT1A1*28, UGT1A1*6, UGT1A1*27, and UGT1A1*7 alleles were significantly different between patients and the Korean control group.

Table 2 shows the UGT1A1 genotypes detected in 46 patients with available clinical data. Homozygous UGT1A1*7 alleles with homozygous or heterozygous UGT1A1*6 alleles were detected in two CNII patients only, and these patients showed the highest TB levels (79.87 µmol/L and 75.24 µmol/L, respectively). Forty-three GS patients were grouped into 10 different UGT1A1 genotypes. Heterozygous or homozygous UGT1A1*28 (TA6/7, TA7/7)
(58.1%, 50/86) and heterozygous or homozygous UGT1A1*6 (30.2%, 26/86) were frequently identified in GS patients.

In this study, UGT1A1*28 and UGT1A1*6 were the most frequent alleles. While UGT1A1*6 is the most frequent allele in East Asian hyperbilirubinemia patients [3], UGT1A1*28 was the most frequent allele (44.3%, 51/81) in this study. Two CNII patients were homozygous for the UGT1A1*7 allele in combination with the UGT1A1*6 allele. Homozygous genotype of the UGT1A1*7 allele has been previously reported in CNII cases [5-8]. Homozygous UGT1A1*7 allele has a strong association with CNII in the Asian population [6], in line with our results.

Two patients carried novel variants. A 57-year-old female patient had a c.864+2T>C variant combined with a heterozygous UGT1A1*28 allele. c.864+2T>C is a variant at the splice-donor site at the 5’ end of intron 1. An adjacent splice-donor site variant, c.864+1G>C, has been reported in a CN II patient in a homozygous genotype, and this variant is expected to induce splicing at a cryptic site [10]. Therefore, we believe that the c.864+2T>C variant contributed to the medical condition of the patient. A five-year-old male patient had a c.182C>G variant combined with compound heterozygous UGT1A1*6 and UGT1A1*28 alleles. c.182C>G is a missense variant in exon 1. Further evidence based on more patient cases and investigation of the effects of these variants on enzyme activity are needed to assign a pathogenic role to these two novel variants; we interpreted these variants as variant of uncertain significance according to American College of Medical Genetics guidelines [11].

In conclusion, from the spectrum of UGT1A1 variations, UGT1A1*28 and *6 alleles tend to be prevalent in Korean patients with unconjugated hyperbilirubinemia and the UGT1A1*28 allele tends to be more prevalent than in other Asian populations.

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AUTHOR CONTRIBUTIONS

J Kim analyzed the data and wrote the draft; K Lee designed the study and finalized the draft; Y Kim and J Oh reviewed the draft and commented on it. All authors have accepted responsibility for the entire content of the manuscript and approved its submission.

CONFLICTS OF INTEREST

No potential conflicts of interest relevant to this article were reported.

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