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Prevalence of Gilbert Syndrome in Bangladesh

Sanjana Zaman[1,2], Hiroko Fukushima[1], Ryoko Suzuki[1], Mohammad Delwer Hossain Hawlader[2*], Shoji Yoshimatsu[1,3], Yu Kanai[4], Gias U. Ahsan[2], Takashi Fukushima[1]

[1]Department of Child Health, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan
[2]Department of Public Health, North South University, Dhaka, Bangladesh
[3]Department of Pediatrics, University of Tsukuba Hospital, Tsukuba, Japan
[4]Department of Pediatrics, National Hospital Organization Minami Kyoto Hospital, Kyoto, Japan
Email: *mohammad.hawlader@northsouth.edu

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Abstract

Background: Gilbert syndrome (GS) is characterized by an elevated serum bilirubin due to a polymorphism in Uridine Diphosphate Glucuronosyl Transferase (*UGT1A1*) gene. Several studies have found high prevalence of Gilbert Syndrome in some Asian countries but still haven't explored in Bangladesh. Aim of this study was to determine the allele frequencies of two different variants of *UGT1A1* polymorphisms (*UGT1A1 6* and *UGT1A1 28*) among Bangladeshi population. **Materials and method:** Total 150 unrelated volunteer from outpatient unit of the Central Hospital Limited, and Bangabandhu Sheikh Mujib Medical University, Dhaka were enrolled in this study. Peripheral blood was obtained from each subject and DNA extraction was done by Genomic DNA Isolation Kit. Polymorphisms of UGT1A1*6 (c.211G>A) was genotyped using the TaqMan Assay-on-Demand SNP Typing System and UGT1A1*28 (c.-53_-52TA) promoter repeat number polymorphism was determined by PCR method on an ABI PRISM 3130 Genetic Analyzer. **Results:** 57.3% of the study participants were male, mean age of them was 4.05 years. Minor allele frequency (MAF) was 0.442 (44.2%) for *UGT1A1*28* and 0.047 (4.7%) for *UGT1A1*6*. **Conclusion:** This is the first ever study conducted among Bangladeshi population to identify the Gilbert syndrome and found very high prevalence. Drugs those who are conjugated by *UGT1A1* may lead to worse adverse event due to *UGT1A1* polymorphism. Infants having decreased *UGT1A1* enzyme activity develop neonatal jaundice and its further complication like Kernicterus. Higher incidence of Gilbert syndrome among Bangladeshi might be the alert for the clinicians treating neonatal jaundice.

Keywords

Gilbert Syndrome, Uridine Diphosphate Glucuronosyl Transferase

(*UGT1A1*), Hyperbilirubinemia, Bangladesh

1. Introduction

Gilbert syndrome (GS) is defined as a fluctuating or discrete elevation of unconjugated serum bilirubin where hemolysis, liver disease or other causes are excluded. Among the general population, Gilbert syndrome is the main cause of unconjugated hyperbilirubinemia [1]. A. Gilbert [2] described this syndrome as a "imple familial jaundice". Thereafter, Meulengracht described Gilbert syndrome as "icterus intermittens juvenilis" [3], as it is benign and intermittent episodic in character.

In Gilbert syndrome, the mild jaundice occurs as a result of inherited unconjugated hyperbilirubinemia, the most common human metabolic disorders which is caused by polymorphisms in UDP-glucuronosyltransferase 1 (*UGT1A1*). UGT is a member of super family of enzymes which catalyzes the glucuronidation of many substrates (both exo and endogenous) and *UGT1A1* is also the isozyme that is able to conjugate bilirubin, the endogenous yellow pigment which comes from haeme catabolism [4]. Till to date, more than one hundred variants have been found in the *UGT1A1* gene, among them *UGT1A1***28, UGT1A1***6* and *UGT1A1***27* are associated with the phenotype of Gilbert syndrome [3] [4] [5]. Out of those 3 variants, *UGT1A1***28, UGT1A1***6* have been found to be commonly associated in Asian population [6]. The *UGT1* gene expresses 9 functional *UGT1A* proteins, and *UGT1A1* is the major protein that catalyzes the glucuronidation [7]. Variants of the *UGT1A1* gene polymorphism results in the absence or reduction of *UGT1A1* activity which may lead to unconjugated hyperbilirubinemia. The *UGT1A1***28* polymorphism occurs as insertion of a thymine-adenine (TA) dinucleotide in the TATAA box of the promoter region and it results in genotype of A(TA)7TAA and A(TA)8TAA, the mutant variety which is opposite of the A(TA)6TAA the wild variety [8] [9]. *UGT1A1***28* polymorphism is classified depending on the number of TA repeats in 2 alleles: 1) TA6/TA6 (wild type), 2) TA6/TA7 (heterozygous mutant), or 3) TA7/TA7 (homozygous mutant).

The TA6/TA7 or TA7/TA7 mutants are associated with decreased enzyme activity and, which may account for increased irinotecan related toxicity [10]. *UGT1A1 28* has been reported to cause approximately 70 per cent reduction of *UGT1A* enzyme activity [10] *UGT1A1 28* has severe toxicities with irinotecan which is an anti-cancer drug compared to wild type *UGT1A1 1* or heterozygous *UGT1A1 28*.

There is ethnic variability in *UGT1A1***28* polymorphism. The prevalence of homozygous TA7/TA7 was significantly higher among African (12% - 27%) and in Caucasian (5% - 15%) but it is lower (1.2% - 5%) in South-east Asian (1.2% - 5%) and Pacific region [11] [12] [13] [14]. The *UGT1A1* gene TA7 variant is as-

sociated with increased bilirubin levels in normal individual [4], or glucose-6-phosphate dehydrogenase (G6PD) deficiency [15], or in β-thalassemia minor (heterozygous) [16], and it is also associated with neonatal jaundice in G6PD deficiency [17] and hereditary spherocytosis [18]. Genotyping of polymorphisms in *UGT1A1* gene is an important step to determine the etiology of free hyperbilirubinemia. Till now, distribution of Gilbert Syndrome (GS) from Bangladesh has not been reported. Therefore, we aimed to determine the genetic profile (prevalence of polymorphisms of *UGT1A1*) which causes the Gilbert syndrome among Bangladeshi population.

2. Materials and Methods

A total of 150 apparently healthy Bangladeshi children presented with minor diseases such as colds, diarrhea, or other minor illnesses were enrolled over a one-year period between January 2013 and December 2013 from the outpatient department of Bangabandhu Sheikh Mujib Medical University (BSMMU) and Central Hospital Limited, Dhaka, Bangladesh. We explained the objectives of the study to the legal guardians. After obtaining written informed consent from all participants, venous blood sample was obtained in Ethylene diamine tetra acetic acid (EDTA) tubes from each subject. After collection, blood sample were shifted to the University of Tsukuba, Japan and then genetic analysis was performed in the genetic lab of the University of Tsukuba. This study was approved by the ethical review committees of BSMMU, Central Hospital Limited, and the University of Tsukuba Hospital.

3. DNA Extraction and Genotyping

DNA was extracted using Genomic DNA Isolation Kit (QiAamp DNA Blood Mini Kit, Qiagen, Vealo, Netherlands) from 0.5 to 2 ml peripheral blood following the manufacturer's instructions. Polymorphisms of UGT1A1*6 (c.211G > A) was genotyped using the TaqMan Assay-on-Demand SNP Typing System (Applied Bio Systems, Foster City, CA, USA) following the manufacturer's instructions. PCR was performed on a 384-well format with 5 ng of DNA each, and automatic allele calling was performed using ABI PRISM 7900HT data collection and analysis software, version 2.2.2 (Applied Biosystems). UGT1A1*28 (c.-53_-52TA) promoter repeat number polymorphism was determined by PCR method on an ABI PRISM 3130 Genetic Analyzer (Applied Biosystems). Descriptive statistics were performed by using SPSS statistics version 21.0 (IBM Corporation, NY, USA) and data were expressed as number, percentage, mean and standard deviation.

4. Results

Table 1 shows that among the 150 study children, 86 (57.3%) were male and rest of them were female. Age of the study participants was 4.03 ± 2.05 (mean ± SD) years. Weight and height of the study participants was 15.86 ± 5.88 kg (mean ±

SD) and 101.80 ± 16.50 cm (mean ± SD) respectively. Mid upper arm circumference (MUAC) of the study participants was 15.35 ± 2.62 (mean ± SD). Out of 150 blood sample, all samples were successfully genotyped for *UGT1A1*6* and 149 were genotyped for *UGT1A1*28*. Table 2 shows that minor allele frequency of UGT1A1*28 are: wild/wild is 31.33% (47), wild/mutant is 48% (72), mutant/mutant 20% (30) and this table also shows that majority of minor allele frequency of UGT1A1*6 is wild/wild (94.66%), few of them is wild/mutant (4.66%) and only 1 is mutant/mutant. Overall minor allele frequency (MAF) were 0.442(44.2%) for *UGT1A1*28* and 0.047(4.7%) for *UGT1A1*6*. Table 3 shows the comparison of allele frequencies of *UGT1A1*28* & *UGT1A1*6* in different ethnicity and found *UGT1A1*28* is very high among Bangladeshi population in compare to other ethnicity but low in UGT1A1**6* in compare to other Asian population.

Table 1. Characteristics of the study participants.

Characteristics	mean ± SD
Age (year)	4.03 ± 2.05
Weight (kg)	15.86 ± 5.88
Height (cm)	101.80 ± 16.50
Sex	n (%)
Male	86 (57.33%)
Female	64 (42.66%)

Table 2. Frequency of minor allele.

***UGT1A1*28* (genotyped 149)** n(%)	
Wild/wild	47 (31.33)
Wild/mutant	72 (48.00)
Mutant/mutant	30 (20.00)
Not genotyped	1 (00.66)
UGT1A1*6 (genotyped = 150)	
Wild/wild	142 (94.66)
Wild/mutant	7 (4.66)
Mutant/mutant	1 (0.66)

Table 3. Comparison of Allele frequencies of *UGT1A1*28* & *UGT1A1*6* in other ethnicity.

Ethnicity	*UGT1A1*28*	*UGT1A1*6*
Caucasian	0.312	0.029
Japanese	0.104	0.196
Chinese	0.186	0.186
Indian	0.280	0.160
Bangladeshi	0.442	0.047

*UGT1A1*28 & *6 in other ethnicity; *Li Minmin *et al.* 2014, Agrawal SK *et al.* 2009; MAF data of Caucasian was collected from NCBI dbSNP database.

5. Discussion

This is the first ever study where we evaluated the frequency of the main genetic determinant of Gilbert Syndrome (*UGT1A1*28* and *UGT1A1*6*) among Bangladeshi population. Our result confirms that *UGT1A1*28* polymorphism is a highly frequent condition among Bangladeshi population. Previously it was believed that, this is not a disease of Bangladeshi population, that's why there was no interest to conduct research on Gilbert syndrome among Bangladeshi population. We believe this finding will completely change the perception level of clinician as well as researcher in Bangladesh. Now a day it is evident that there is an inter-individual and interethnic variation in glucuronidation [19]. There is a wide range of diversification among UGT family. This is best explained by the *UGT1A1* gene, which is responsible for over 50 genetic lesions [20]. It has been reported that, among Caucasian the frequency of the *UGT1A1*28* variant allele is 30% - 45%. Among African and Indian populations, the distribution is twice that of the 10% - 20% reported in East Asian populations [21] [22] [23] [24] [25]. In Uzbekistan, the incidence of *UGT1A1*28* homozygotes was 9.3%, which was higher than that in the Japanese population was studied previously [26]. Other published reports shown that, *UGT1A1*28* homozygotes is high in distribution in Europe (5% - 14.8%), Africa (5.9% - 17.9%), and India (12.8% - 19.3 %); and less frequent in Japan and East Asia and (0% - 5.9 %) [27]-[36].

Individuals with Gilbert syndrome have reduced UGT activity due to *UGT1A1*gene polymorphism. This reduced UGT activity causes jaundice under the conditions such as illness, physical exertion or fasting. Study among Malaysian population concluded that Gilbert syndrome is associated with a homozygous (TA7) in Malaysian population. They found the levels of serum bilirubin in GS patients from 20 μM to 90 μM [37]. Due to decreased *UGT1A1* enzyme activity, neonates with this syndrome have higher risk to develop neonatal jaundice results in further complications like Kernicterus and irreversible brain damage. In a recent study, higher polymorphism of the *UGT1A1*gene was found to be significantly associated with hyperbilirubinemia among North Indian neonates [38]. Another study concludes that, *UGT1A1*polymorphism is a risk factor for severe neonatal unconjugated hyperbilirubinemia among Malaysian population [39]. Moreover, *UGT1A1*28* allele is associated with reduced levels of enzyme. Therefore modification of dosage of irinotecan should be done on the basis of patients' *UGT1A1* genotyping. Thereby, adverse effects of this drug can be avoided to some extent. The FDA in USA approved an amendment of the label for Camptosar (irinotecan hydrochloride) which is invariably used as chemotherapeutic agent for the treatment of colon cancer, which includes the warning to reduce the starting dose of irinotecan for *UGT1A1*28* homozygous patients. For East Asian individuals, requires both *UGT1A1*6* and *UGT1A1*28* genotyping, since there is no linkage disequilibrium between the two polymorphisms [40].

6. Conclusion

Our study found the evidence of very high prevalence of *UGT1A1* polymorphism among Bangladeshi population. This newly discovered result might be the alert for the clinicians treating neonatal jaundice at children hospital in Bangladesh. It is well known that most of the children with Kernicterus have no underlying etiological identity to explain the hyperbilirubinemia. In fact, preventing a case of Kernicterus might be one of the most valuable strategies in all healthcare settings, resulting in a healthy baby rather than a child with a life-time of debilitating neurodevelopment handicaps. *UGT1A1* polymorphism also has an implication in case of treatment of cancer. We recommend genotyping of *UGT1A1* prior to management of neonatal jaundice as well as before treating by irinotecan chemotherapy as patients with *UGT1A1* polymorphism having more adverse effects of this chemotherapeutic agent. Furthermore, study regarding the correlation between prevalence of polymorphism and hyperbilirubinemia is an urgent need.

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