Turkish Archives of Pediatrics

ORIGINAL ARTICLE
DOI: 10.5152/TurkArchPediatr.2022.21291

Gilbert Syndrome and Genetic Findings in Children: A Tertiary-Center Experience from Turkey

Yeliz Çağan Appak[1], Betül Aksoy[2], Berk Özyılmaz[3], Taha Reşid Özdemir[3], Maşallah Baran[1]

[1]İzmir Katip Çelebi University, Departments of Pediatric Gastroenterology, Hepatology, and Nutrition, İzmir, Turkey
[2]SBU Tepecik Training and Research Hospital, Departments of Pediatric Gastroenterology, Hepatology, and Nutrition, İzmir, Turkey
[3]SBU Tepecik Training and Research Hospital, Genetic Diagnosis Center, İzmir, Turkey

What is already known on this topic?

Gilbert syndrome (GS) is characterized by mildly elevated indirect serum bilirubin levels due to mutation in the promoter of the UGT1A1 gene. Seven or 8 thymine adenine (TA) repeats are responsible for the development of GS. Another molecular genetic etiological cause of GS is sequence variants.

What this study adds on this topic?

This study is important due to the limited Gilbert syndrome (GS) data in children in Turkey. A mild bilirubin elevation can be observed in the cases with 6 TA repetitions that were considered non-risky in terms of GS. We suggested that the variant [c.880_893delinsA (p.Tyr294MetfsTer69)] was causing partial enzyme deficiency leading to the GS phenotype.

ABSTRACT

Objective: Gilbert syndrome (GS) is a disease characterized by mildly elevated indirect serum bilirubin levels due to mutation in the promoter of the *UGT1A1* gene, which causes a decrease in uridine diphosphate glucuronyltransferase enzyme activity. Gilbert syndrome should be considered based on clinical and laboratory findings in differential diagnosis, which can be supported by genetic analysis. This study aimed to evaluate the clinical findings and *UGT1A1* mutations of children with Gilbert syndrome.

Materials and Methods: Patients who were admitted to the pediatric gastroenterology clinic and who were considered to have Gilbert syndrome based on clinical and laboratory findings were included in the study. The *UGT1A1* analysis was performed by Sanger sequence analysis.

Results: A total of 56 children were included in the study. A(TA)7TAA, A(TA)6TAA, and (TA)6/7 allele promoter polymorphism was detected in 75.5%, 22.5%, and 2% of the patients, respectively. Other than these, in 3 patients, 3 different sequence variants associated with GS [c.880_893delinsA (p.Tyr294MetfsTer69) and c.1091C>T(p.Pro365Leu)] were detected.

Conclusion: We detected 7 TA repeats in the majority of our patients. A mild bilirubin elevation was determined in cases with 6 repetitions that were not considered risky for Gilbert syndrome. We concluded that the c.880_893delinsA (p.Tyr294MetfsTer69) variant, previously shown to be associated with Crigler–Najjar syndrome type I, may also be associated with partial enzyme deficiency leading to the Gilbert syndrome phenotype.

Keywords: Gilbert syndrome, UDP glucuronyl transferase, polymorphism, hyperbilirubinemia

INTRODUCTION

Gilbert syndrome (GS), which causes mild indirect hyperbilirubinemia without hemolysis or a liver disease, is an autosomal recessive genetic disease. The frequency of GS is reported to be 3%–13%.[1] Hunger, insomnia, infection, and stress can trigger attacks of jaundice in GS.[2] When jaundice is noticed or indirect bilirubin is detected in tests, it may cause anxiety in parents and children. Many unnecessary tests can be performed on patients to detect liver disease.

Gilbert syndrome is caused by mutation in the promoter region of *UGT1A1* gene (2q37), which causes a decrease in uridine diphosphate glucuronyltransferase (UGT) enzyme activity. In GS and Crigler–Najjar syndrome, more than 130 *UGT1A1* variants have been reported.[3] The number of thymine adenine (TA) repeats determines the activity of the *UGT1A1* enzyme. When the TA repeat is high, the enzyme activity is less. UGT1A1*28, UGT1A1*37, and UGT1A1*36 variants have 7 TA repeats, 8 TA repeats, and 5 TA repeats, respectively (Table 1). Common polymorphic mutations in GS include a TA insertion mutation in the TATA box (A(TA)7TAA) (UGT1A1*28) and

Corresponding author:
Yeliz Cagan Appak
✉yelizcagan@yahoo.com
Received: October 4, 2021
Accepted: December 9, 2021

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Cite this article as: Çağan Appak Y, Aksoy B, Özyılmaz B, Reşid Özdemir T, Baran M. Gilbert syndrome and genetic findings in children: A tertiary-center experience from Turkey. *Turk Arch Pediatr.* 2022;57(3):295-299.

Table 1. Definitions of Most Often *UGT1A1* Allele and TA Repeats in Gilbert syndrome

***UGT1A1* alleles**	**(TA)nTAA promoter repeats**
UGT1A1*36	A(TA)5TAA
UGT1A1*1	A(TA)6TAA
UGT1A1*28	A(TA)7TAA
UGT1A1*37	A(TA)8TAA

c0.211G>A (p.G71R) in exon 1 (UGT1A1*6).[4,5] A(TA)7TAA is also shown as c.-53TA.[6,7] (TA)6 repeats in the *UGT1A1* gene promoter are considered a non-risky GS allele. Wild-type *UGT1A1* contains 6 TA repeats (A(TA)6TAA) in its promoter region.[8] (TA)7 and (TA)8 repeats are held responsible for the development of GS. UGT1A1*6 also contributes to the elevation of serum bilirubin but does not cause GS. The heterozygous state of UGT1A1*28 (TA)7 causes the enzyme's activity to decrease by 25%, and its homozygous state causes decreased activity by 70%.[8] This situation leads to GS, a mild form of intermittent unconjugated hyperbilirubinemia that lacks hemolysis or hepatocellular injury.[9]

This study was planned due to the limited GS data in children in Turkey. Therefore, we aimed to evaluate the clinical, demographic, and genetic mutations of Turkish children with GS.

MATERIALS AND METHODS

Study Population

Patients who were admitted to the Pediatric Gastroenterology Clinic between September 2017 and December 2020 and who were considered to have GS based on clinical and laboratory findings were retrospectively included in the study. Gilbert syndrome was diagnosed when the patients have isolated unconjugated hyperbilirubinemia, normal liver enzymes, and no additional symptoms or signs which suggest hepatobiliary and hemolytic disease. These clinical and laboratory findings were considered sufficient for the diagnosis of GS. Genetic analysis was applied as a further investigation only when there was doubt about the diagnosis and when the diagnosis was desired to be supported and showed by genetic analysis.

The demographic data, laboratory findings, clinical findings at application, and factors triggering jaundice of these patients were obtained from medical records. It was shown that the patients did not have liver and hemolytic diseases that can cause elevated levels of indirect bilirubin. Patients who were not considered to have GS based on the results of a *UGT1A1* gene analysis were excluded from the study.

Genetic Analysis

The *UGT1A1* gene analysis was performed by Sanger sequencing. Genomic DNA was isolated from peripheral blood leukocytes according to the manufacturer's protocols. For the Sanger sequencing of the *UGT1A1* gene, polymerase chain reaction (primers used for PCR are presented in Table 2), purification (ExoSAP-IT®, Affymetrix, Santa Clara, CA), and cycle sequencing PCR (BigDye® Terminator v3.1, Applied Biosystems, Foster City, CA) reactions were carried out. Products were purified (ZR DNA Sequencing Clean-up Kit TM, Zymo Research) and run by capillary electrophoresis (3500 Genetic Analyzer, Thermo Scientific). The DNA sequences obtained were analyzed in the

Table 2. Primers Used for the Sanger Sequencing of *UGT1A1* Gene

UGT1A1: ex1-1F	TCTCTGAAAGTGAACTCCCTGC
UGT1A1: ex1-1R	GGCACTGGGTAGCCTCAAAT
UGT1A1: ex1-2F	AGGACTCTGCTATGCTTTTGTCT
UGT1A1: ex1-2R	GCTCAGCATATATCTGGGGCT
UGT1A1: ex2-F	CAGGAACCCTTCCTCCTTTAGA
UGT1A1: ex2-R	AAGTGGCAGGGAAAAGCCAA
UGT1A1: ex3-F	CGGAAGTTGCCAGTCCTCAG
UGT1A1: ex3-R	GTGTTACTCACATGCCCTTGC
UGT1A1: ex4-F	TGGCCAACATATCCTACATTGC
UGT1A1:ex4-R	ATCATGAATGCCATGACCAAAGT
UGT1A1: ex5-F	TCTTCTTAAGCAGCCATGAGCA
UGT1A1: ex5-R	ATCAAAGACACCAGAGGGGG

Sequencing Analysis Program and compared with the reference sequences. The insertion status of TA sequence in the TATAA box of the promoter region and rare sequence variants were reported. The genetic and clinical findings of the patients were evaluated by a comparison. An ethics committee approval was obtained from the ethical committee of the SBU Tepecik Training and Research Hospital (2020/13-13).

Statistical Analysis

Statistical analysis was performed with the International Business Machines the Statistical Package for Social Sciences version 23.0 software (IBM Corp.; Armonk, NY, USA). While categorical data were expressed as number and percentage (%), continuous data were expressed as mean ± standard deviation. The Shapiro–Wilk's test was performed to examine the normality of parameters. Non-parametric and parametric continuous variables were assessed using Mann–Whitney *U* test and independent samples *t*-test, respectively. Fisher's exact test was applied to compare the differences between 2 groups for categorical variables. A *P*-value of less than 0.05 was considered statistically significant.

RESULTS

This study included 56 children who were considered to have GS based on clinical characteristics and laboratory findings. The majority of the patients were diagnosed in the adolescent age group (mean age 13.9 ± 4.0) with overall male preponderance (male : female, 2.7 : 1). Two (6%) patients had a family history of GS. Twelve (21.4%) patients with GS had a history of parental consanguinity. The most common symptoms were jaundice (64.5%), asthenia (16%), and prolonged jaundice (3.5%), and in 16% of patients, hyperbilirubinemia was detected on routine pediatric examination. The trigger factors for hyperbilirubinemia were prolonged fasting (5.4%), infections (5.4%), and sleeplessness (1.8%). In 87.5 of patients, the trigger factors were unclear.

The mean serum total, direct bilirubin level, and indirect bilirubin level was 2.5 ± 1.1 mg/dL, 0.4 ± 0.1 mg/dL, and 2.0 ± 1.1 mg/dL, respectively. The aspartate aminotransferase and alanine aminotransferase levels of all patients were in the normal range. In 64.3% of patients, the serological assays for hepatitis A, B, and C virus were assessed; all of these were negative. In patients evaluated by different physicians,

etiological examinations for chronic liver diseases were evaluated in 42.9% of patients. Chronic liver disease was not detected in any patient. Ultrasonography of abdomen was performed in 71.4% of patients, and hepatosteatosis was detected in 7.1% of patients.

It was observed that 49 of the 56 patients (87.5%) included in the study could be screened for *UGT1A1* mutations. In mutation screening of *UGT1A1*, A(TA)6TAA and A(TA)7TAA, allele promoter polymorphism was detected in 11 (22.5%) patients and 37 (75.5%) patients, respectively. One case (2%) with (TA)6/7 was detected in the *UGT1A1* promoter region. This patient, who was 16 years old, had no complaints and hyperbilirubinemia. The control examinations revealed a total serum bilirubin of 2.3 mg/dL and an indirect bilirubin of 1.65 mg/dL. A comparison of 2 polymorphism groups ((TA)7/7 and (TA)6/6) with regard to the demographic, clinical characteristics, and laboratory findings is shown in Table 3.

In 3 patients (0.05%), 2 different sequence variants [c.880_893delinsA (p.Tyr294MetfsTer69) and c.1091C>T(p.Pro365Leu)] were detected in the heterozygous state. Two of these patients exhibited (TA)6/6 promoter region polymorphism, whereas 1 patient exhibited (TA)6/7 promoter region polymorphism.

DISCUSSION

Seven TA repeats responsible for the development of GS were detected in the majority of the patients (75.5%) in our study. Mildly elevated bilirubin levels were detected in the cases with 6 repetitions, which was considered non-risky in terms of GS. In a study from Serbia, GS non-risk *UGT1A1* (TA)n promoter genotypes TA 6/6 and TA 6/7 were detected in 3.9% of patients and 15.8% of patients, respectively.[9] In our study, (TA) 6/7 heterozygous mutation was detected in the *UGT1A1* promoter region of 1 patient (2%), and (TA)6/6 mutation was detected in 22.5%. The patient, who had (TA)6/7 mutation with mild hyperbilirubiemia, had no complaints. A study from Iran presented 2 rare mutations (TA6/8 and TA6/5) detected in 2 children with normal bilirubin levels.[10] UGT1A1*6 was reported to cause GS in the homozygous state in Japanese, Chinese, and Korean populations.[11,12] Homozygosity for the mildly pathogenic variant UGT1A1*6 (rs4148323, c.211G>A, and p.Gly71Arg) is also a common cause of GS in East Asians. The UGT1A1*28 variant was found to be higher in Malays and Indians with an allele frequency of 25% and 28%, respectively.[13] In Caucasian and African populations, almost all GS individuals are homozygotes for UGT1A1*28.[4,14]

Another molecular genetic etiological cause of GS other than promoter region polymorphisms is sequence variants. In 3 patients, 2 different sequence variants [c.880_893delinsA (p.Tyr294MetfsTer69) and c.1091C>T(p.Pro365Leu)] were detected. The c.1091C>T(p.Pro365Leu) variant was detected in 2 of our patients in a heterozygous state. This variant was reported as "Likely Pathogenic" in the ClinVar database (rs34946978) and was previously associated with a significant reduction in *UGT1A1* enzyme activity and GS phenotype.[15] The c.880_893delinsA (p.Tyr294MetfsTer69) variant was detected in 1 patient in a heterozygous state. This variant was reported as "Pathogenic" in the ClinVar database (rs587776761). This variant was previously associated with Crigler–Najjar syndrome type 1; however, since Crigler–Najjar syndrome is an autosomal recessive disorder and was detected in a heterozygous state, we suggested that the variant was causing partial enzyme deficiency leading to the GS phenotype.[16] Because the patient's clinical and laboratory findings were detected to be compatible with GS.

To determine the cause of idiopathic hyperbilirubinemia in newborns from Turkey, a study assessed the *UGT1A1* promoter polymorphism. In this study, in the idiopathic hyperbilirubinemia group, higher peak bilirubin levels, higher heterozygous and variant homozygous genotypes, and higher (TA)7 allele frequencies were observed. Similar to our study, (TA)5 and (TA)8 polymorphisms were not detected.[17] The frequency of (TA)7/7 genotype was detected as 5.8% in this study, but it has

Table 3. Comparison of Demographic, Clinical Characteristics and Laboratory Findings of (TA)7/7 and (TA)6/6 Polymorphism Groups

	Total (n = 56)	A(TA)6TAA (n = 11) (22.5%)	A(TA)7TAA (n = 37) (75.5%)	*P*
Demography	13.9 ± 4.0	11.9 ± 4.4	14.0 ± 4.0	.036[a]
Age (mean ± SD) (years)	41 (73.2)	10 (90.9)	25 (67.6)	.246[b]
Sex (male), n (%)				
Family history, n (%)	2 (3.6)	-	2 (5.4)	
Parental Consanguinity, n (%)	12 (21.4)	1 (9.1)	9 (24.3)	
Symptoms at presentation, n(%)	36 (64.5)	8 (72.7)	22 (59.5)	.367 [b]
Jaundice	9 (16)	1 (9.1)	7 (18.9)	
Asthenia	9 (16)	2 (18.2)	6 (16.2)	
Incidental	2 (3.5)	-	2 (5.4)	
Prolonged jaundice				
Laboratory profile (mean ± SD)	13.9 ± 1.5	12.8 ± 1.5	13.8 ± 1.3	.038[c]
Hemoglobin (g/dL)	24.2 ± 11.6	29.7 ±2 0.1	23.7 ± 9.2	.350[a]
AST (IU/L)	17.8 ± 13.5	16.5 ± 8.5	19.4 ± 15.6	.969[a]
ALT (IU/L)	2.5 ± 1.1	2.3 ± 0.9	2.6 ± 1.3	.376[a]
Total bilirubin (mg/dL)	0.4 ± 0.1	0.4 ± 0.2	0.4 ± 0.1	1.000[a]
Direct bilirubin (mg/dL)	2.0 ± 1.1	1.9 ± 0.9	2.1 ± 1.2	.434[a]
Indirect bilirubin (mg/dL)				

AST, aspartate aminotransferase; ALT, alanine aminotransferase.
[a]Mann–Whitney *U* test; [b]Fisher's exact test; [c]independent samples *t*-test.

previously been reported as 0.6%, 8.5%, and 10% in other studies with neonates with jaundice from different regions of Turkey.[17-20] Apart from these studies, no study evaluating the genetic findings of GS in Turkish older children has been reported. Regarding *UGT1A1* mutations, case reports and case series with Crigler–Najjar syndrome are primarily reported from Turkey.[21,22]

A patient presenting with jaundice can be a cause of concern for physicians. When bilirubin elevation is detected, it may cause cases to be examined for liver disease and hematological diseases. Because of high indirect bilirubin levels, many unnecessary tests may be performed for the diagnosis. Additionally, children are referred to gastroenterology outpatient clinics for further examination. In patients with isolated indirect hyperbilirubinemia, GS should be considered in differential diagnosis. Determination of clinical and laboratory findings compatible with GS is considered sufficient for the diagnosis.[1] As a result, diagnosis of GS can be made without the need for many unnecessary tests.[23] The fact that these unnecessary tests were performed in some patients in our study has been a point where we criticize ourselves. It is seen that abdominal ultrasonography and etiological examinations for chronic liver diseases were applied to some of the patients unnecessarily. Hepatosteatosis has been detected in some of the GS patients who underwent abdominal ultrasonography in our study. There is no relationship between GS and hepatosteatosis. Therefore, further examination for hepatosteatosis has been planned in these patients. Genetic analysis could also be used to support the diagnosis in suspicious cases. The reason for the high number of genetic analysis of the patients in our study is that it was desired to show genetic data as well as suspicious cases.

Rare de novo variants have been reported in GS and are more common in boys than girls. Serum indirect bilirubin is usually <3 mg/dL in GS. Rarely, indirect bilirubin can be seen between 3 mg/dL and 6 mg/dL.[1] In our study, the mean indirect bilirubin level was 2.0 $\pm$ 1.1 mg/dL. Gilbert syndrome is rarely clinically manifested before puberty. Males are more often diagnosed with GS than females, 2 to 7 times more frequently, because there is a larger bilirubin load per kilogram body weight in males, and androgen steroid hormone suppresses hepatic bilirubin clearance.[24,25] In our study, 73.2% of the patients were male, and their mean age was 13.9 $\pm$ 4.0 years, which is consistent with the literature.

Fluctuating mild hyperbilirubinemia is seen, but cases are generally asymptomatic. In our study, in 16% of the patients, who had no complaints, hyperbilirubinemia was detected on routine pediatric examination. When jaundice or indirect bilirubin elevation is detected in tests, it can be concerning to families and children. Clinicians should explain to parents and children that GS is a benign condition and inform them about the triggering factors (such as hunger, sleeplessness, infection, and stress).[26] In our patients, the main trigger factors for hyperbilirubinemia were prolonged fasting, infections, and sleeplessness. In particular, patients should be made aware of the potential for temporary attacks of jaundice, which does not harm the patient. It should be explained to the patient and family that GS does not require any treatment.

The present study has limitations common to retrospective studies. Prospective studies with larger numbers of patients are needed to provide additional evidence on the clinical and genetic profiles of GS in Turkish children.

CONCLUSION

Gilbert syndrome should be considered in differential diagnosis based on history and clinical findings in patients who present with jaundice and have indirect hyperbilirubinemia, even if there is no consanguinity and family history. Clinicians should explain to patients that jaundice attacks in GS, which can be concerning for families, are not harmful and to recommend ways that patients can avoid triggers. There are many *UGT1A1* mutations and variants; their frequency varies in each population, and clinical findings may differ according to the genetic characteristics of GS.

Ethics Committee Approval: This study was approved by Ethics committee of SBU Tepecik Training and Research Hospital (Approval No: 2020/13-13).

Informed Consent: Verbal and Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – Y.C.A.; Design – Y.C.A., B.A., M.B.; Supervision – Y.C.A., M.B.; Materials – Y.C.A., B.A., B.Ö., T.R.Ö.; Data collection and/or Processing – Y.C.A., B.A., B.Ö., T.R.Ö., M.B.; Analysis and/or Interpretation – Y.C.A., B.A., B.Ö., M.B., T.R.Ö.; Literature Search – Y.C.A., B.Ö., B.A., T.R.Ö; Writing Manuscript – Y.C.A., B.A., B.Ö., M.B.; Critical Review – Y.C.A, B.Ö., M.B.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

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