

# Prolonged Unconjugated Hyperbilirubinemia Associated With Breast Milk and Mutations of the Bilirubin Uridine Diphosphate-Glucuronosyltransferase Gene

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**ABSTRACT.** *Objective.* Breast milk jaundice is a common problem in nursing infants. It has been ascribed to various breast milk substances, but the component or combination of components that is responsible remains unknown. During our study of defects of the bilirubin uridine diphosphate-glucuronosyltransferase gene (*UGT1A1*) in patients with hereditary unconjugated hyperbilirubinemia (Crigler-Najjar syndrome and Gilbert's syndrome) and neonatal hyperbilirubinemia, we encountered a prolonged case associated with breastfeeding; after cessation of breastfeeding, the infant's bilirubin level became normal. Genetic analysis revealed a missense mutation identical to that found in patients with Gilbert's syndrome, which usually causes jaundice after puberty. We analyzed the bilirubin *UGT1A1* of infants with prolonged unconjugated hyperbilirubinemia associated with breast milk to ascertain whether genetic factors are involved.

*Patients and Methods.* We analyzed 17 breastfed Japanese infants with apparent prolonged jaundice (total serum bilirubin concentrations above 171  $\mu\text{mol/L}$  [10 mg/dL]) 3 weeks to 1 month after their birth. Except for jaundice, the infants were healthy and did not show evidence of hemolytic anemia, liver dysfunction, or hypothyroidism. After cessation of breastfeeding, the serum bilirubin concentration began to decrease in all cases. When breastfeeding was resumed, serum bilirubin concentration again became elevated in some infants, but the concentration fell to within normal by 4 months of age. We analyzed the polymerase chain reaction-amplified exon, promoter, and enhancer regions of *UGT1A1* by direct sequencing.

*Results.* Sixteen infants had at least one mutation of the *UGT1A1*. Seven were homozygous for 211G→A (G71R), which is the most common mutation detected in the East Asian population, and the mutant enzyme had one third of the normal activity. G71R is the most common missense mutation we found in our analyses in Japanese patients with Gilbert's syndrome, and it corresponds to a *UGT1A1* polymorphism in the Japanese population (the allele frequency is .16). One was heterozygous for 1456T→G (Y486D) and homozygous for 211G→A. Six were heterozygous for 211G→A. One was heterozygous for both 211G→A and a TATA box muta-

tion (A(TA)7TAA). One had a heterozygous mutation in an enhancer region (C→A at -1353). We did not detect a homozygous A(TA)7TAA mutation, which was the most common cause of Gilbert's syndrome in European population, in this study of Japanese infants with prolonged hyperbilirubinemia triggered by breast milk.

*Conclusions.* The results indicate that defects of *UGT1A1* are an underlying cause of the prolonged unconjugated hyperbilirubinemia associated with breast milk. One or more components in the milk may trigger the jaundice in infants who have such mutations. The mutations we found were identical to those detected in patients with Gilbert's syndrome, a risk factor of neonatal nonphysiologic hyperbilirubinemia and a genetic factor in fasting hyperbilirubinemia. *Pediatrics* 2000;106(5). URL: <http://www.pediatrics.org/cgi/content/full/106/5/e59>; prolonged unconjugated hyperbilirubinemia, breast milk jaundice, bilirubin uridine diphosphate-glucuronosyltransferase gene, *UGT1A1*, infant, Gilbert's syndrome.

ABBREVIATIONS. BMJ, breast milk jaundice; *UGT1A1*, bilirubin uridine diphosphate-glucuronosyltransferase gene.

Breast milk jaundice (BMJ) was first described in 1963<sup>1,2</sup> and is a problem that pediatricians frequently encounter in nursing infants. BMJ is characterized by prolonged unconjugated hyperbilirubinemia in otherwise healthy infants, is related to ingestion of breast milk, and often results in serum bilirubin levels >171  $\mu\text{mol/L}$  (10 mg/dL), with danger of brain damage in severe cases.<sup>3</sup> The condition has been ascribed to breast milk components such as pregnane-3 $\beta$ ,20 $\alpha$ -diol,<sup>4</sup> nonesterified fatty acids,<sup>5</sup> and glucuronidase,<sup>6</sup> but it is not known exactly which component or combination of components is responsible.<sup>7-9</sup>

During our study of defects of the bilirubin uridine diphosphate-glucuronosyltransferase gene (*UGT1A1*) in patients with hereditary unconjugated hyperbilirubinemia (Crigler-Najjar syndrome and Gilbert's syndrome)<sup>10,11</sup> and neonatal hyperbilirubinemia,<sup>12</sup> we encountered a prolonged case associated with breastfeeding; after cessation of breastfeeding, the infant's bilirubin level became normal. Genetic analysis revealed a missense mutation identical to that found in patients with Gilbert's syndrome, which usually causes jaundice after puberty.<sup>13</sup> Furthermore, Grunebäum et al<sup>14</sup> suggested that there may be a genetic factor in the cause of BMJ. Here, we analyzed *UGT1A1* in Japanese infants with the pro-

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longed unconjugated hyperbilirubinemia associated with breast milk and showed that missense mutations of the gene are an underlying cause of the condition; breast milk may trigger the hyperbilirubinemia in carriers of such mutations.

## METHODS

### Patients

We analyzed 17 Japanese infants who developed prolonged apparent jaundice and had total serum bilirubin concentrations above 171  $\mu\text{mol/L}$  (10 mg/dL) after the third week of life (Table 1). All the infants were nursed with breast milk. Six cases were discovered during the third to fourth week of life when the parents visited our office concerned about the prolonged jaundice (cases 1, 6, 8, 9, 12, and 15). Prolonged jaundice in the other 11 infants was detected at an obligatory health check 1 month after birth (cases 2–5, 7, 10, 11, 13, 14, 16, and 17). Their total and indirect acting bilirubin concentrations ranged from 176 to 543  $\mu\text{mol/L}$  and from 164 to 533  $\mu\text{mol/L}$ , respectively. The direct reacting bilirubin concentrations ranged from 1.8% to 8.7% of the total and the direct Coombs' test was consistently negative. In all the patients, reticulocyte counts were below 20% and thyroid-stimulating hormone concentrations were below 4  $\mu\text{U/mL}$ . Thus, except for jaundice, the infants were healthy and did not show evidence of hemolytic anemia, liver dysfunction, or hypothyroidism. After cessation of breastfeeding, the serum bilirubin concentration began to decrease in all cases. When breastfeeding was resumed, serum bilirubin concentration again became elevated in some infants, but the concentration fell to within normal range (8.55–12.2  $\mu\text{mol/L}$ ), or jaundice disappeared visually for all infants by 4 months of age.

### Sequence Analysis of *UGT1A1*

Genomic DNA was isolated from the leukocytes of patients with the informed consent of the relevant parties. Amplification of exons and of the promoter region of *UGT1A1* by polymerase chain reaction from genomic DNA has been described elsewhere.<sup>12,15</sup> The distal element in the enhancer region of *UGT1A1* was amplified by a primer pair of 5'-CTCTAAGCACATCCCCAAGTA-3' / 5'-TAAGCAAGTTTCCATCCTTCA-3'.<sup>16</sup> The sequences of the amplified DNA fragments were determined directly by use of primers.<sup>15–17</sup>

## RESULTS

Sixteen of the 17 infants had at least 1 *UGT1A1* mutation (Table 2). Fifteen had missense mutations.

Seven were homozygous for the identical transition mutation at nucleotide number 211 in exon 1; the substitution of adenine for guanine changed the codon from GGA to AGA, causing arginine to replace glycine at position 71 of the corresponding protein (G71R). One infant homozygous for G71R was heterozygous for a transversion mutation at nucleotide number 1456 in exon 5; the substitution of guanine for thymine changed the codon from TAC to GAC, causing aspartic acid to replace tyrosine at position 486 of the corresponding protein (Y486D). Six infants were heterozygous for G71R. One was heterozygous for G71R and a TATA box mutation (A(TA)<sup>7</sup>TAA). None of the infants was homozygous for the latter mutation (Table 2), although a homozygous mutation in the TATA box has been reported and has been shown to cause Gilbert's syndrome.<sup>18</sup> No additional mutations were detected in exons 2 through 4. Case 5 was heterozygous for a mutation in the enhancer region: the distal element<sup>16</sup> at -1353 from the initiation codon as +1 changed from C to A (C→A at -1353). The remaining case (case 14) had no mutation in either the promoter or the coding regions of *UGT1A1*. A review of the medical records showed that, in addition to BMJ, all patients except for 1 (case 16) had nonphysiologic neonatal hyperbilirubinemia during the first postpartum week and had received phototherapy.

## DISCUSSION

Fifteen of the 17 cases of the prolonged unconjugated hyperbilirubinemia associated with breast milk had missense mutations of the bilirubin *UGT1A1* gene (Table 2). Missense mutations identical to those found in the infants with the hyperbilirubinemia were also detected in our previous studies for Gilbert's syndrome and Crigler-Najjar syndrome type II.<sup>10,11,19</sup> G71R is the most common missense mutation we found in our analyses,<sup>10</sup> and it corresponds to a *UGT1A1* polymorphism in the Jap-

**TABLE 1.** Characteristics and Blood Examination of Infants With BMJ

Case	Sex	Birth Weight (Grams)	At Visit or an Obligatory Health Check (From Three Weeks to One Month Old)				At Four Months Old
			Bilirubin* ( $\mu\text{mol/L}$ )	Hb (Grams/dL)	GOT (IU/L)	GPT (IU/L)	
1	Female	3276	478 (465)	13.3	10	48	12.2
2	Male	3098	352 (336)	13.8	34	18	10.2
3	Male	2660	343 (333)	10.2	22	2	ND
4	Female	3110	270 (259)	10.5	49	23	10.2
5	Male	3066	176 (160)	12.5	21	10	ND
6	Female	2162	383 (372)	11.5	31	14	8.5
7	Female	1895	321 (300)	11.5	30	10	11.9
8	Male	2726	543 (533)	12.4	32	25	8.5
9	Female	2808	330 (318)	11.7	25	27	ND
10	Male	2240	176 (164)	13.2	28	8	ND
11	Female	3250	314 (297)	12.0	31	16	10.2
12	Male	3272	487 (422)	12.0	25	30	12.4
13	Female	2896	226 (214)	15.9	54	18	ND
14	Male	3242	218 (209)	12.6	45	25	9.2
15	Male	3090	223 (206)	13.6	27	15	ND
16	Male	3150	237 (234)	14.5	28	16	13.3
17	Male	3624	306 (295)	10.5	23	18	11.1

Hb indicates hemoglobin; GOT, glutamine oxaloacetate transaminase; GPT, glutamine pyruvate transaminase; ND, not determined. When serum bilirubin concentration was ND, disappearance of jaundice was determined visually.

\* Value in parentheses is concentration of indirect acting bilirubin.

**TABLE 2.** *UGT1A1* Mutations in Infants With BMJ

Case No.	211G→A G71R	1456T→G Y486D	A(TA)7TAA	Other Mutation
1	Homo	N	N	
2	Hetero	N	N	
3	Hetero	N	N	
4	Homo	N	N	
5	N	N	N	Distal element*
6	Hetero	N	N	
7	Homo	N	N	
8	Homo	Hetero	N	
9	Homo	N	N	
10	Hetero	N	Hetero	
11	Homo	N	N	
12	Homo	N	N	
13	Hetero	N	N	
14	N	N	N	
15	Hetero	N	N	
16	Hetero	N	N	
17	Homo	N	N	

Homo indicates homozygous mutation; hetero, heterozygous mutation; N, no mutation.

\* Distal element<sup>16</sup>: a heterozygous mutation on the distal element of *UGT1A1*

anese population (the allele frequency is .16).<sup>12</sup> G71R may be the most common *UGT1A1* mutation in Asians.<sup>20</sup> Recently we revealed the mutation to be a genetic basis of fasting hyperbilirubinemia.<sup>21</sup>

In our in vitro expression study the G71R form of the enzyme had 32% and 60% of normal activity in the homozygous and heterozygous states, respectively.<sup>22</sup> Our recent study of neonatal hyperbilirubinemia showed that heterozygous G71R was a risk factor for elevated serum bilirubin levels in the early neonatal period.<sup>12</sup> Indeed, as noted earlier, 16 of the 17 infants in this study had nonphysiologic neonatal hyperbilirubinemia during the first postpartum week.

No specific component or combination of components in breast milk has been demonstrated to be the cause of BMJ, although extensive investigations have been conducted since BMJ was first described. In contrast, bilirubin *UGT1A1* activity in early infancy is <1% of the adult activity, which is reached by 3 months of age.<sup>23</sup> BMJ is usually observed before 3 months of age and then disappears even if breastfeeding is continued, implying a close relationship between BMJ and enzyme activity. Those facts and our present results suggest that the *UGT1A1* mutations detected in this study may be an underlying cause of BMJ and that breast milk component(s) may trigger BMJ in neonates who have those mutations.

We found a mutation of the distal element in the enhancer region (Table 2, case 5) that had been reported previously.<sup>16</sup> Although our in vitro expression study demonstrated that the C→A mutation at -1353 of the element decreased transcriptional activity of *UGT1A1* to ~85% of normal,<sup>16</sup> it is uncertain whether the mutation would cause the elevation of serum bilirubin level in this case.

Recently, a homozygous 2-basepair insertion mutation in the TATA box (A(AT)7TAA) has been reported to be a contributory factor for prolonged neonatal jaundice.<sup>24</sup> We did not detect that mutation, however, in this study of Japanese infants with prolonged hyperbilirubinemia triggered by breast milk. The G71R polymorphism has only been observed in

East Asians,<sup>12,20</sup> and our latest study revealed that G71R but not A(TA)7TAA is a risk factor for non-physiologic neonatal hyperbilirubinemia.<sup>12</sup> Furthermore, the frequency of the A(TA)7TAA allele is considerably lower in the Japanese population (.107–.15)<sup>12,16</sup> than in the European population (.4).<sup>25</sup> Thus, we might not detect homozygous A(TA)7TAA in Japanese infants with BMJ.

Mild BMJ is not a clinically significant problem, and we did not analyze infants with mild jaundice in this study. The analysis of more severe BMJ, however, revealed that 8 of 17 neonates (47%) were homozygous and 7 (41%) were heterozygous for missense mutations of *UGT1A1*. In our previous study of Japanese cases with Gilbert's syndrome, most (93%) of the patients with missense mutations were heterozygotes.<sup>10</sup> Furthermore, there is a G71R *UGT1A1* polymorphism among Japanese.<sup>12</sup> These facts suggest that mild BMJ may also be associated with the missense mutation of *UGT1A1* and may be an infantile phenotype of Gilbert's syndrome. Analysis of *UGT1A1* in infants with moderate to severe prolonged unconjugated hyperbilirubinemia associated with ingestion of breast milk would help differentiate this condition from Crigler-Najjar syndrome.

## CONCLUSION

We suggest that an underlying cause of prolonged unconjugated hyperbilirubinemia associated with breast milk is mutations in *UGT1A1* and that the hyperbilirubinemia may be an infantile and inducible phenotype of Gilbert's syndrome. We are following the serum bilirubin concentrations of these cases to further elucidate the relationship between BMJ and Gilbert's syndrome.

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