Interhospital Conference

(29/07/54)

โรงพยาบาลจุฬาลงกรณ์

History

- เด็กชายไทย อายุ 14 ปี ภูมิลำเนา กทม.
- CC: ตาเหลือง 1 วันก่อนมารพ.
- PI: 1 วันก่อนมารพ. มีไข้สูง น้ำมูก ไอ เจ็บคอ ทานอาหารได้น้อย สังเกตว่ามีตาเหลืองขึ้น ไม่มีอาการปวดท้อง ไม่มีคลื่นไส้ อาเจียน ปัสสาวะปกติ สีเหลือง อุจจาระปกติ ทานยาลดไข้ก่อนมารพ. ปฏิเสธทานยาอื่นๆ มารดาสังเกตว่าเคยมีอาการตาเหลืองมาก่อนหน้านี้เวลาไม่สบาย แต่ไม่ชัดเจน หายไปเองจึงไม่เคยพบแพทย์

Past history

- แข็งแรงดี ไม่มีโรคประจำตัว ไม่มียาที่ทานประจำ
- บุตรคนที่ 1/3 คลอดปกติ หลังคลอดไม่มีอาการตัวเหลืองหรือต้องส่องไฟตอนแรกเกิด
- พัฒนาการปกติ ขณะนี้เรียนชั้น ม. 2 เรียนดี

Family history

- น้องชาย อายุ 11 ปี ไม่มีอาการตัวเหลืองแรกคลอด มารดาสังเกตมีเหลืองเล็กน้อยเวลาไม่สบาย
- น้องสาว อายุ 8 ปี อาการปกติดี
- บิดาและมารดาแข็งแรงดี อาการปกติ ตรวจสุขภาพประจำปีเป็นประจำ ผลเลือดปกติ

Physical examination

- General appearance :A Thai boy looked active

  BW 45 Kg (P 50) Ht 168 cm (P75)
- Vital signs: BT 38.5 °C BP 100/60 mmHg RR 20, PR 80 /min
- HEENT: red conjunctiva, mild icteric sclera, injected pharynx, tonsils not enlarge , TM intact with positive cone of light reflex , cervical lymph node not enlarged.
- Heart : no heave or thrills, regular rhythm, no murmur
- Lung: no crepitation, no wheezing/rhonchi

Physical examination

- **Abdomen: no distension, no hepatosplenomegaly , no mass, active bowel sound**
- **Extremities: no deformities, no rash, no edema, no clubbing fingers**
- **Neuro : E4M6V5, pupil 3 mm RTLBE,EOM full**
  motor grade V all, sensory intact
  clonus negative and BBK : plantar flexion , no abnormal movement

CBC	11/10/53	27/10/53
Hb	15.3	15
Hct	46	45
MCV	88.1	87.6
MCH	29	30
MCHC	32.9	34.3
RDW	13.5	13.4
WBC	6000	5660
N	60	53.7
L	32	38.7
M	5.7	4.8
E	1.8	2.1
B	0.3	0.7
Platelet	186,000	198,000

LFT	11/10/53	27/10/53	Normal
Total protein	6.9	6.7	6.4-8.3 (g/dl)
Albumin	4.6	4.6	3.5-5.2(g/dl)
Globulin	2.3	2.1	
ALP	257	265	200-635 U/L
AST	20	23	<40 (U/L)
ALT	15	18	<37 (U/L)
TB	2.11	0.68	<1.10 (mg/dl)
DB	0.30	0.28	<0.3 (mg/dl)

Chemistry	11/10/53
BUN	15
Cr	0.94
Na	141
K	3.9
Cl	106
CO2	24

U/A	11/10/53
Color	pale yellow
Appearance	Clear
pH	5.0
Specific gravity	1.002
Protein	Negative
Glucose	Negative
bilirubin	Negative
urobilinogen	Negative
RBC	0-1
WBC	0-1
Nitrite	negative

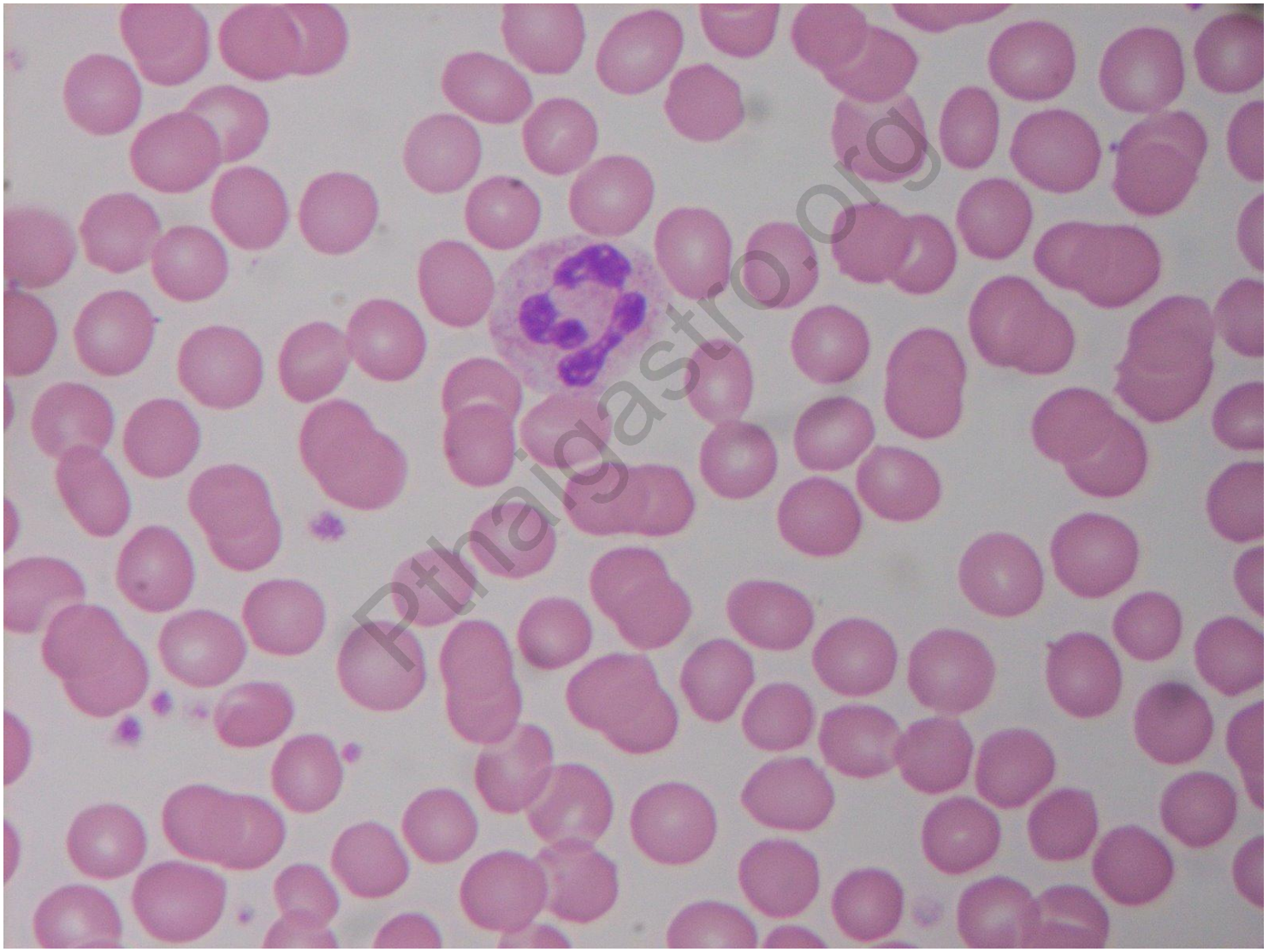
Problem Lists

- Indirect hyperbilirubinemia
- URI
- Family history of jaundice (brother)

Differential diagnosis

- Hemolytic anemia : G-6-PD deficiency , HbH disease, Sickle cell anemia, hereditary spherocytosis
- Drug induced hyperbilirubinemia
- Gilbert syndrome
- Crigler-Najjar syndrome

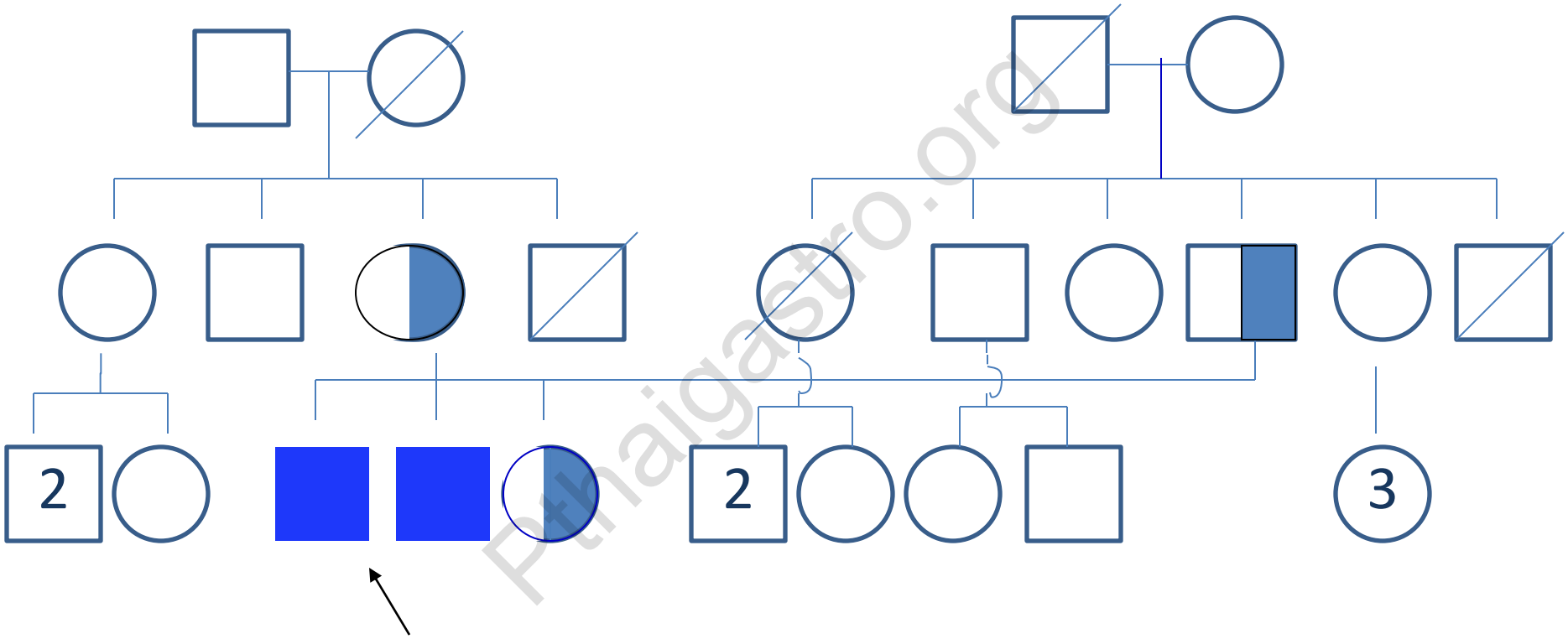
Peripheral blood smear



Other Investigation

Direct coomb's test	negative
Indirect coomb's test	negative
G-6-PD screening	normal
Hemoglobin typing	normal
USG upper abdomen	Liver normal size and shape , no SOL , no bile duct dilatation , GB normal, spleen normal

Pedigree



Hyperbilirubinemia approach

Mixed Unconjugated and Conjugated

Unconjugated (mainly)

Increase bilirubin production

-Hemolysis

- Hematologic dz…

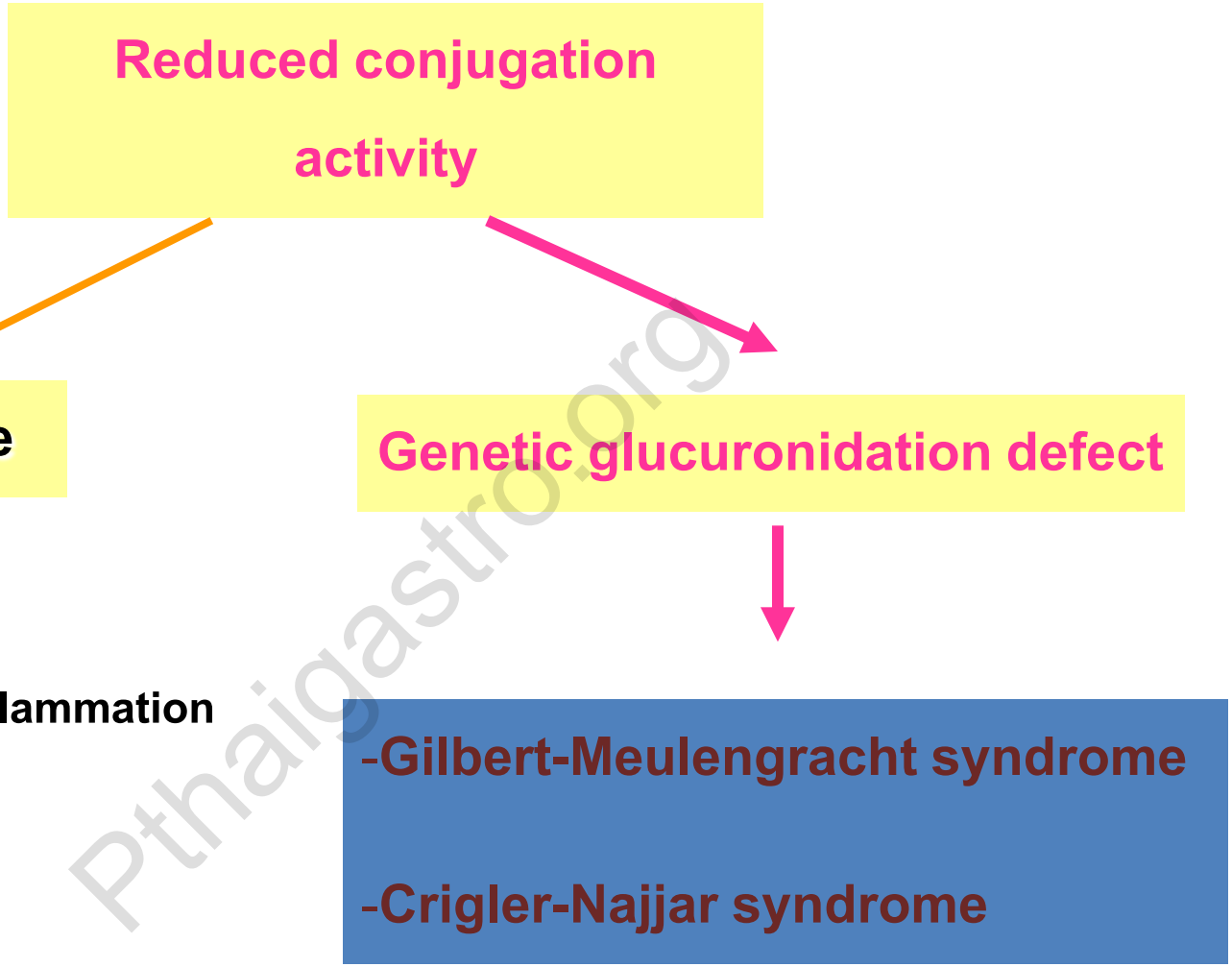
Decrease bilirubin uptake

-Drugs,

-Portosystemic shunt

-Some case Gilbert syndrome..

Reduced conjugation activity



Ref.: Strassburg CP. Hyperbilirubinemia syndrome (Gilbert-Meulengracht, Crigler-Najjar, Dubin-Johnson, and Rotor syndrome).Best Pract Res Clin Gastroenterol. 2010 Oct;24(5):555-71.

Indirect Hyperbilirubinemia

	Bilirubin	AST, ALT	Alb	Glob	PT
hemolysis	5 mg/dl	increase AST	N	N	N
Gilbert's syndrome	5 mg/dl	normal	N	N	N

Gilbert syndrome

- benign, unconjugated hyperbilirubinemia with otherwise normal liver chemistries
- up to 5% of normal population
- polymorphism in TATA box of gene encoding bilirubin UDP-GT

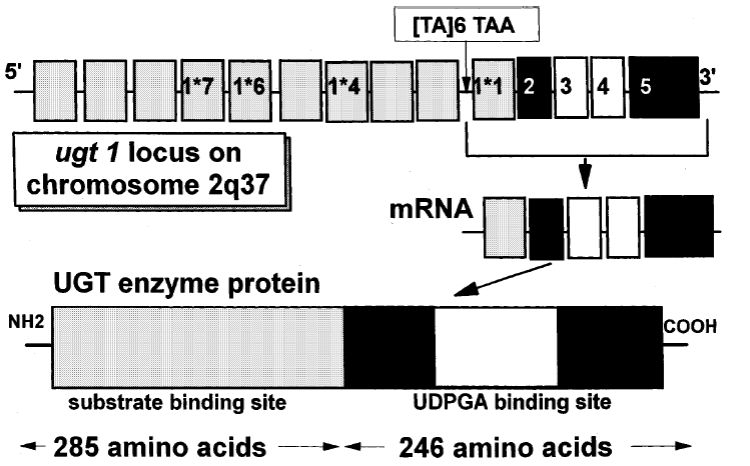
→impair ability to conjugated bilirubin

- prominent in fasting state, systemic illness, some medications

Gilbert syndrome

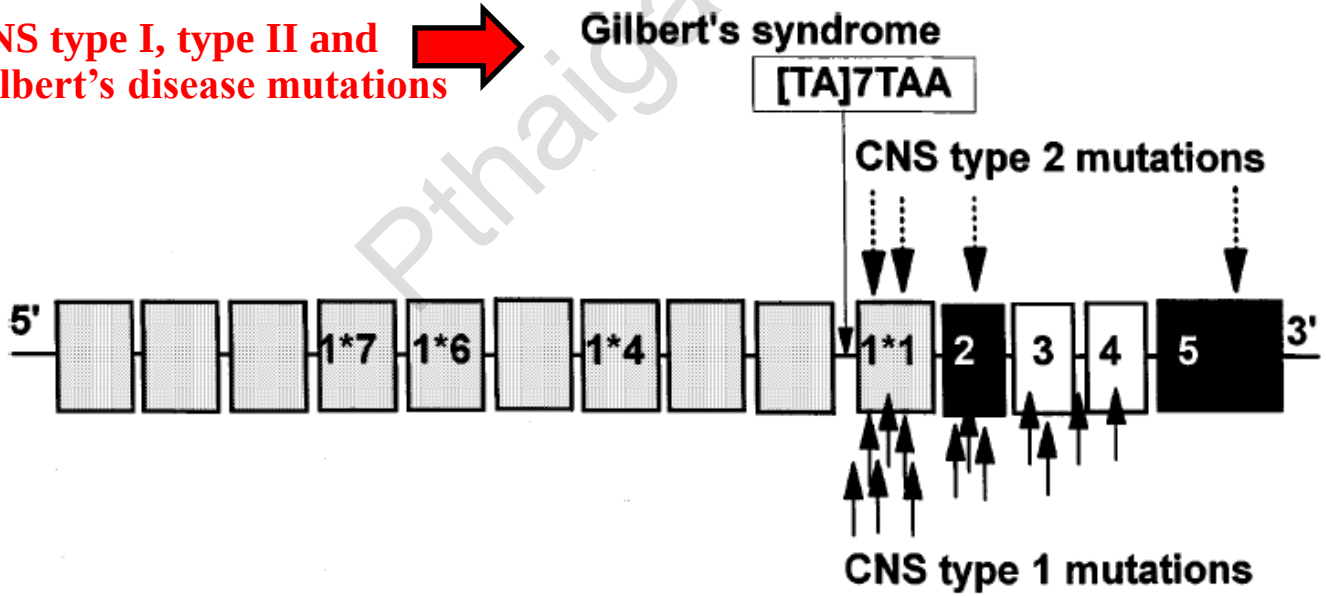
- **Dx :**
  - **asymptomatic, healthy**
  - **mild unconjugated hyperbilirubinemia (<4 mg/dl) with otherwise normal liver chemistries**
  - **exclusion medications and hemolysis**

Human *ugt1A1* gene



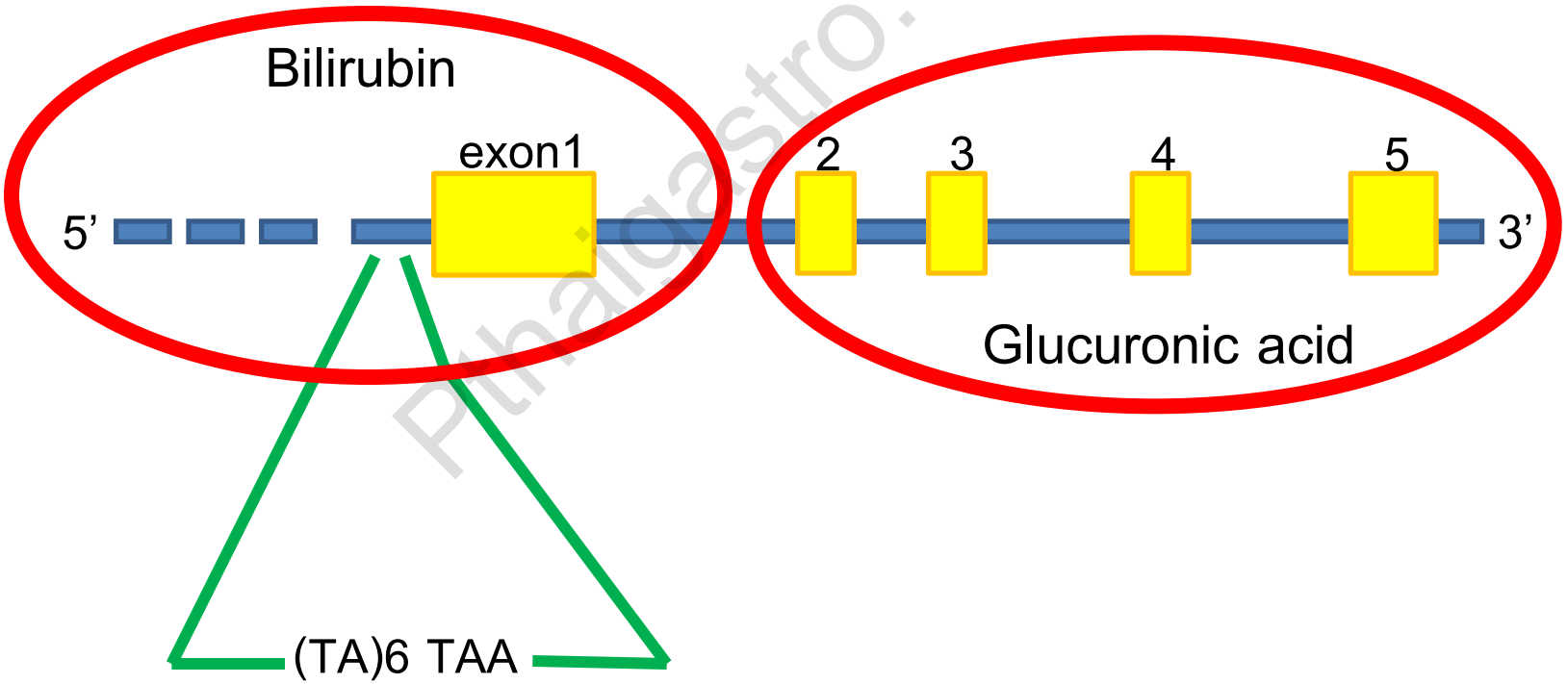
Promoter region: a sequence with 6 TA repeats.
B-UGT is encoded by exons 1*1, and exons 2-5
Crigler-Najjar syndrome (CNS) type I, II and Gilbert's syndrome results from mutation of *ugt1* gene

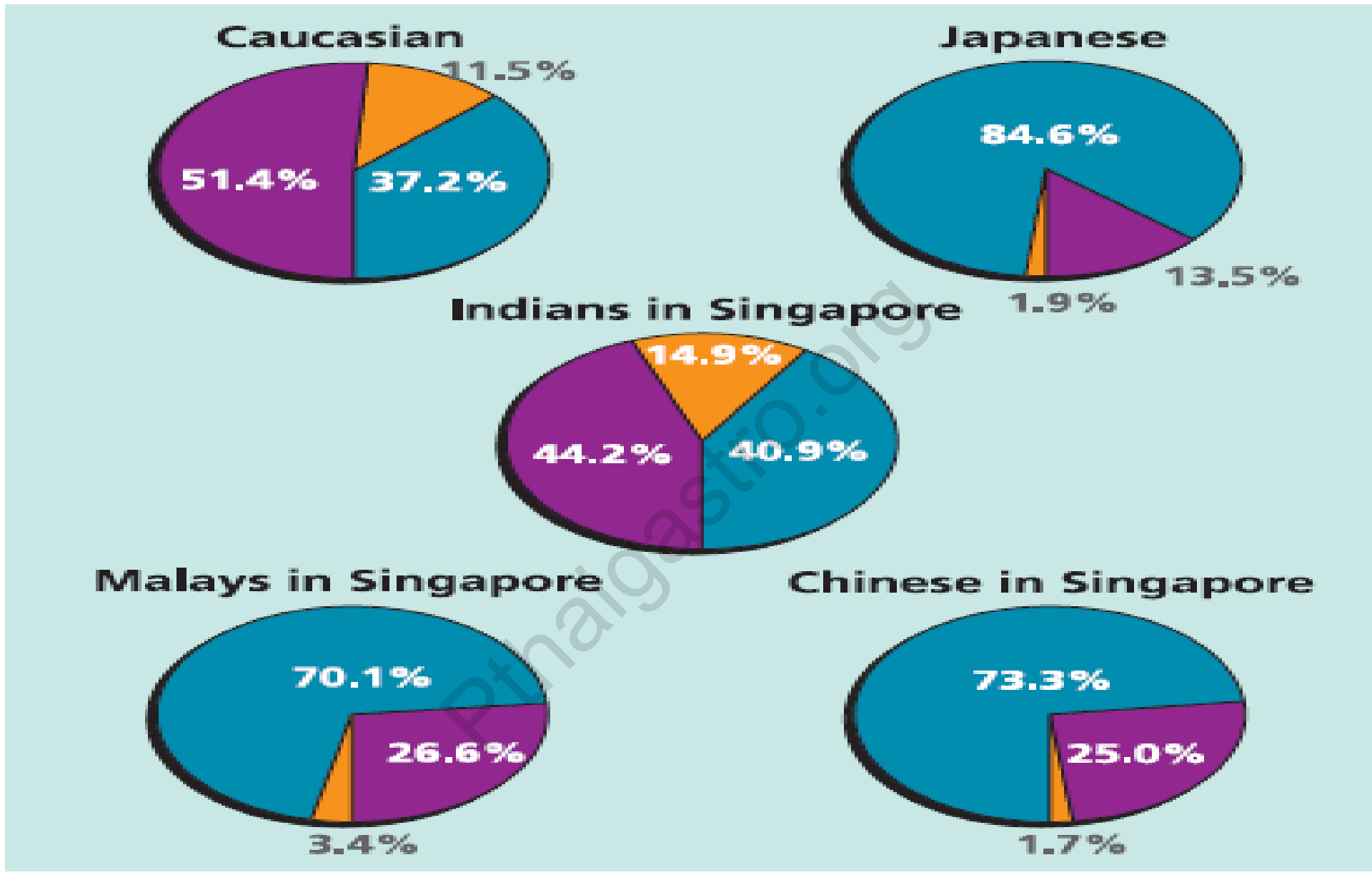
CNS type I, type II and Gilbert's disease mutations



Uridine Glucuronosyltransferase (UGT1A1)

- Chromosome 2q37





UGT1A1 haplotype mutation among Asians in Singapore. ; Zhou YY

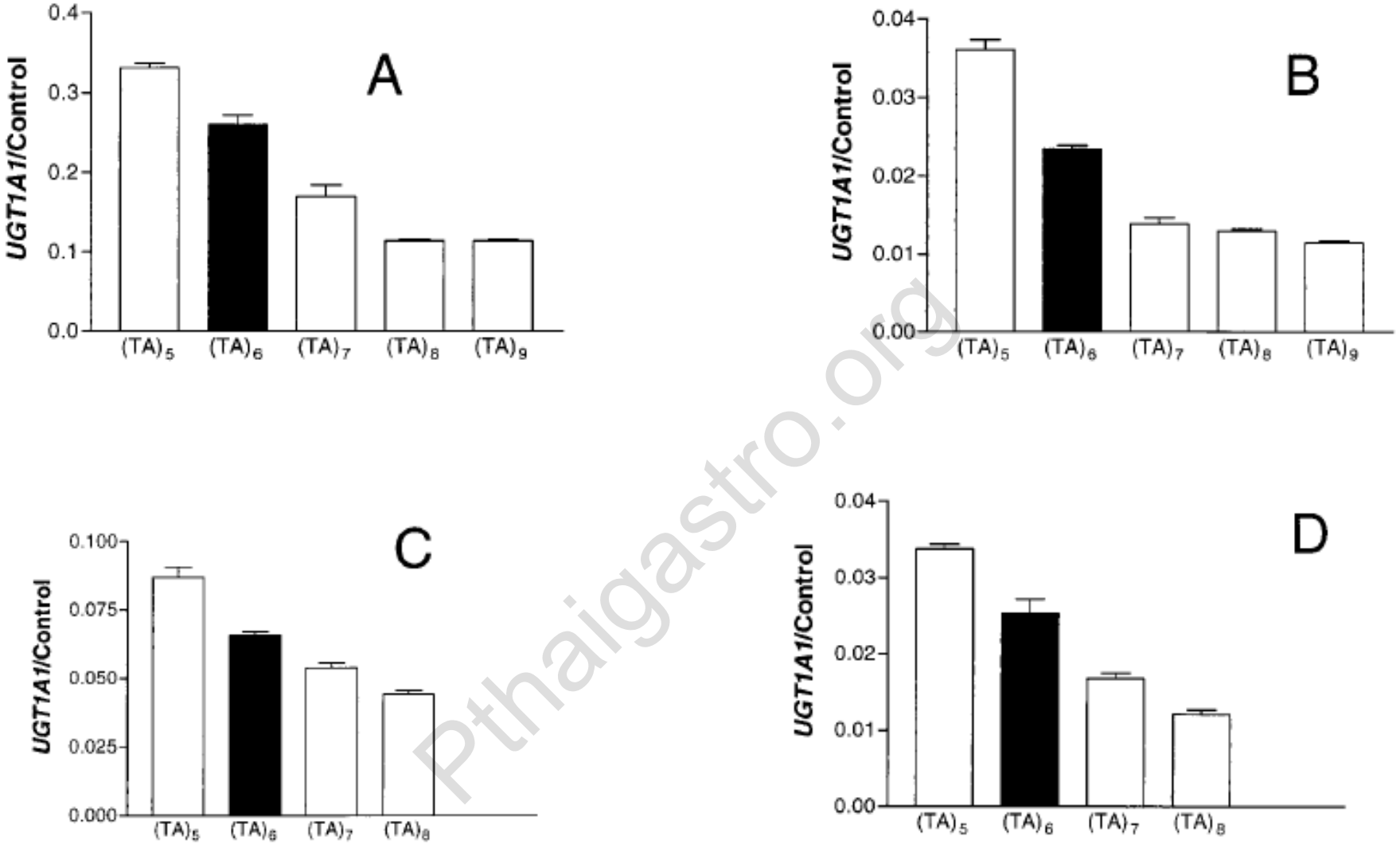


FIG. 2. The effectiveness of the *UGT1A1* promoters containing the variable (ta) repeats using a luciferase reporter. Promoter activity was analyzed in two human hepatoma cell lines: HepG2 (*A* and *C*) and HuH7 (*B* and *D*). The shorter promoter constructs (*C* and *D*) were 229 bp for the $(ta)_6$, and the longer constructs (*A* and *B*) were an additional 32 bp in length. Promoter activity with a firefly luciferase reporter gene was compared with an internal control of Renilla luciferase with an simian virus 40 promoter. Mean values of three to six replicate wells and their standard errors are shown. The short *UGT1A1* constructs in HepG2 cells (*C*) were assayed 24 hr after transfections instead of 48 hr because the cells had reached confluency. The "wild type" $(ta)_6$ is shown as a solid bar; the variants are shown as open bars. Note that the $(ta)_9$ promoter was made by mutagenesis. All other promoters are naturally occurring.

Table 2. *UGT1A1* promoter genotypes in three different ethnic groups

Genotype	European	Asian	African
6/6	24	33	26
6/7	39	13	37
7/7	8	1	19
7/8	0	0	6
8/8	0	0	2
6/8	0	0	4
7/5	0	0	5
6/5	0	0	2
Total	71	47	101

Table 3. *UGT1A1* promoter gene frequencies (number of chromosomes) in three different ethnic groups

Allele	European	Asian	African
5	0 (0)	0 (0)	0.035 (7)
6	0.613 (87)	0.840 (79)	0.470 (95)
7	0.387 (55)	0.160 (15)	0.426 (86)
8	0 (0)	0 (0)	0.069 (14)

	Mutation types	Clinical data (serum bilirubin values: mg%)	Bilirubin-UDP-Glucuronosyltransferase
Crigler-Najjar type I deficiency	exons 1*1, 2,3,3/4 intron-exon boundary and exon 4	>20	Complete
Crigler-Najjar type II deficiency	Promoter ± exons 1*1, 2,5	6-20	Moderate
Gilbert's disease	promoter (7 TA repeats)	1-6	Mild deficiency