Wilson Disease
α1-Anti Antitrypsin Deficiency
Hereditary Hyperbilirubinemia

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OCTOBER 28, 2014

Wilson Disease

- Wilson Disease: Autosomal Recessive Disorder of copper overload
  - Incidence 1 in 30,000
  - Copper accumulation in the liver, brain, kidney and cornea
  - Related to the gene ATP7B -> mutated ATP7B protein (an ATPase that can't excrete Cu)
  - Symptom onset range 3 to 55 years
  - May present with isolated elevation of LFT's, progressive neurologic/psychiatric disorder or isolated acute hemolysis
  - With fulminant hepatic failure, **acute intravascular hemolysis is usually present**

Wilson Disease: Diagnosis

LIVER FAILURE/CIRRHOSIS/PORTAL HYPERTENSION

Screening for Wilson Disease in Acute Liver Failure: A Comparison of Currently Available Diagnostic Tests

Jessica D. Korman,[1] Irene Volenberg,[2] Jody Balko,[3] Joe Webster,[3] Frank V. Schiodt,[3] Robert H. Squires, Jr,[4] Robert J. Fontana,[5] William M. Lee,[3] Michael L. Schilsky[2] and the Pediatric and Adult Acute Liver Failure Study Groups

Acute liver failure (ALF) due to Wilson disease (WD) is invariably fatal without emergency liver transplantation. Therefore, rapid diagnosis of WD should aid prompt transplant listing. To identify the best method for diagnosis of ALF due to WD (ALF-WD), data and serum were collected from 140 ALF patients (16 with WD), 29 with other chronic liver diseases and 17 with treated chronic WD. Ceruloplasmin (Cp) was measured by both oxidase activity and

J. Korman Hepatology 2008; 48:1167-1174

Table 3. Comparison Screening Tests for Wilson Disease in Acute Liver Failure

Group	Screening Test	Sensitivity %	Specificity %	Likelihood Ratio
Acute:				
	Cp[1] (mg/dL) <20 by oxidase	21	84	1
	Cp (mg/dL) <20 by nephelometry	56	63	2
	Hemoglobin (g/dL) <10	94	74	4
	AP:TB[2] ratio <4	94	96	23
	AP:TB ratio <4 + AST:ALT ratio >2.2	100	100	NA[3]
	Cu[4] (μg/dL) >200	75	96	17
	AST:ALT ratio >2.2	94	86	7
Chronic:				
	Cp (mg/dL) <20 by oxidase	71	97	21
	Cp (mg/dL) <20 by nephelometry	71	79	3

[1]Ceruloplasmin; [2]Alkaline Phosphatase:Total Bilirubin; [3]Not applicable; [4]Serum Copper. In the chronic liver disease group, zero subjects had an AP:TB ratio < 4 three subjects had Hg <10, one had Cu >200, and the AST:ALT ratio was an ineffective marker of WD.

J. Korman Hepatology 2008; 48:1167-1174

Table 2. Serum Tests in Acute Liver Failure: Wilson Disease versus All Other Etiologies

Serum Test	Wilson Disease Median (range) N = 16	All Other Etiologies Median (range) N = 124
ALT (IU/L)	24.5 (7.0–1463.0)	1830.0 (57.0–17670.0)
AST (IU/L)	185.0 (69.0–4481.0)	1337.0 (76.0–28870.0)
Total Bilirubin (mg/dL)	42.1 (7.6–72.4)	7.3 (0.7–49.8)
Alkaline Phosphatase (IU/L)	20.5 (4.0–129.0)	146.5 (56.0–524.0)
Hemoglobin (g/dL)	7.0 (4.7–10.8)	11.6 (4.3–21.0)
Ceruloplasmin-oxidase (mg/dL)	22.7 (7.7–48.4)	30.9 (9.3–108.8)†
Ceruloplasmin-nephelometry (mg/dL)	18.7 (8.4–78.7)	22.9 (1.8–103.0)‡
Copper (μg/dL)	272.0 (105.2–1063.0)	91.5 (32.2–317.8)
Alk Phos:TB ratio	0.5 (0.1–7.8)	20.1 (2.8–194.3)
AST:ALT ratio	7.5 (2.1–18.3)	1.0 (0.1–5.7)

All comparisons have a $P < 0.001$, except for ceruloplasmin by oxidase $P = 0.02$ and ceruloplasmin by nephelometry $P = 0.2$.

J. Korman Hepatology 2008; 48:1167-1174

Wilson Disease: Chronic Diagnosis, Initial Clues

- Hepatic Inflammation, AST:ALT usually >2
- CBC may show anemia, (Coombs-Negative hemolytic anemia)
- Low serum copper concentration
- Low serum uric acid and phosphate (renal tubular dysfunction)

Wilson Disease: Chronic Diagnosis

- Ocular Slit-Lamp Examination
- Ceruloplasmin < 20 mg/dL
  - DDx: Wilson (homozygous vs. heterozygous, other chronic liver disease, intestinal malabsorption, nephrosis, malnutrition, hereditary aceruloplasminemia)
- 24-hour urinary copper excretion (preferably 3 separate), usually 2-3 x Normal, or 100 ug/day
- Hepatic tissue copper concentration > 250 ug/g dry weight of liver is diagnostic of Wilson disease

Aside on Liver Biopsy

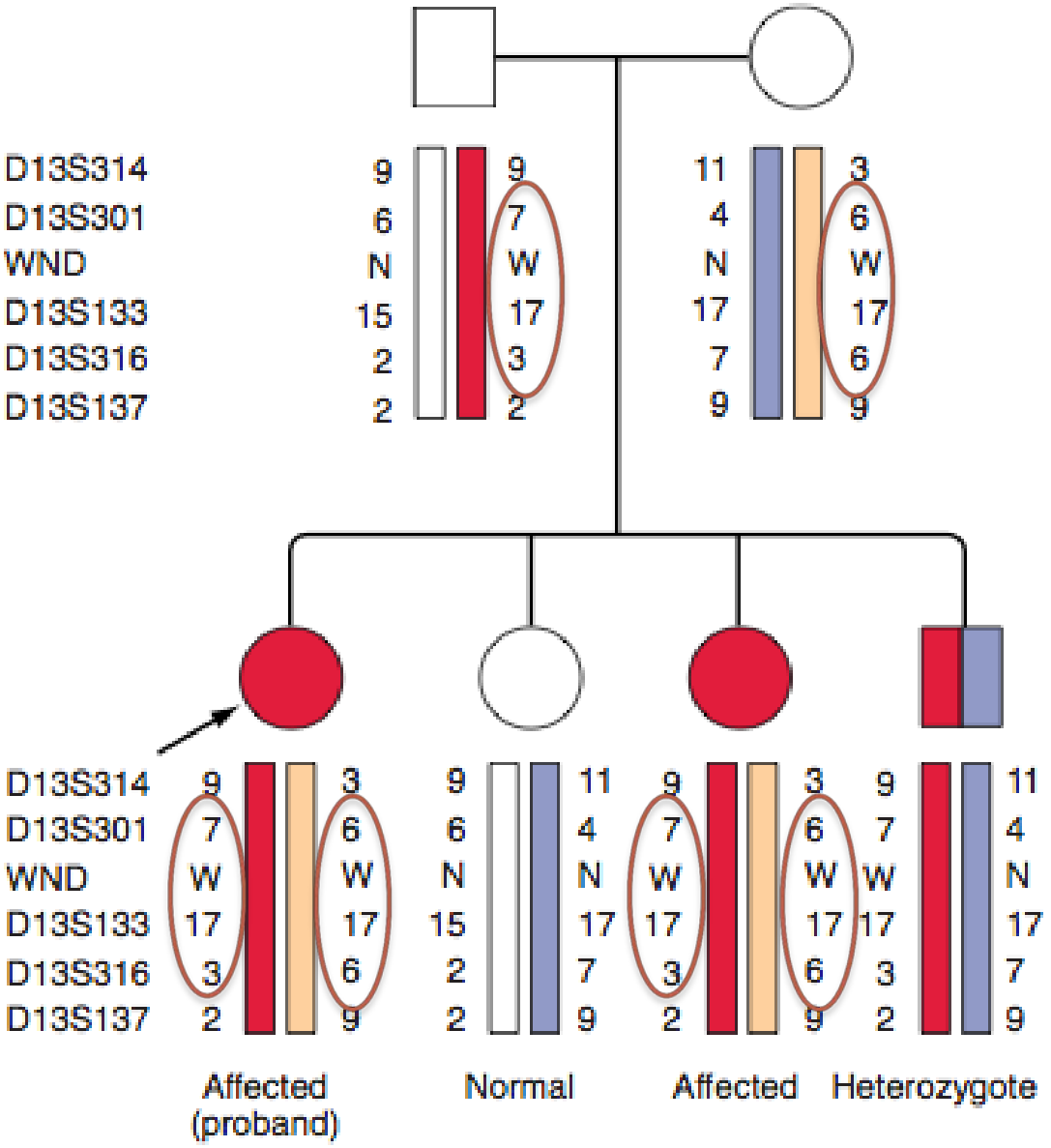
- Require Cu Free Needle (BioPince used at UofL and Jewish Hospital)
- Collect in a plastic container which has been rinsed 3X.
- Quantification of liver Cu is the key. Biopsy can look like anything: NASH, ALD, Sclerosing Cholangitis
- 16 gauge needles are essential (AASLD 2008 Liver Biopsy Position Paper)

Wilson Disease: Identify Family Members

- More then 500 reported ATP7B gene mutations
- Usually patients are *compound heterozygotes*, carrying two different mutations for the gene

Wilson Disease: Identify Family Members

- Seeking markers of the gene, or *haplotypes*, can reliably indicate the genetic similarity of a sibling to a Wilson Disease patient



Wilson Disease: Chronic Treatment

- Two Phases:
- 1. Removing Copper (chelation)
  - Symptomatic patients or laboratory or histological evidence of aggressive inflammatory injury (2008 Guideline Recommendation, some reports show primary treatment with zinc is adequate)
  - D-Penicillamine, Trientine, Tetrathiomolybdate (experimental)
- 2. Prevent reaccumulation
  - Once stabilization of symptoms or biochemical abnormalities, usually after 2-6 months
  - Zinc

Roberts Hepatology. 2008 Jun;47(6):2089-111

Wilson Disease: Chronic Treatment: Chelation

- Penicillamine 1 to 1.5 g/day PO
  - Give with Pyridoxine 25 mg daily (older Penicillamine formulations interfered with Vit B6 and pyridoxine is still given out of caution)
  - Monitor 24 h urine Cu with goal of 200-500 ug/day as target
  - Monitor CBC, UA and skin examination: Febrile reaction with rash and proteinuria develops in some patients 7-10 days after treatment. Advise changing chelators, but you can restart Penicillamine slowly with glucocorticoids
- Trientine: 2nd line: 1 to 1.2 g/day divided BID-TID.
  - Monitor 24 h urine Cu with goal of 200-500 ug/day as target
  - Monitor CBC, Iron Studies

Roberts Hepatology. 2008 Jun;47(6):2089-111

Wilson Disease: Chronic Treatment: Chelation

- Zinc stimulates *metallothionein* which is an endogenous chelator, inhibits Cu uptake and can create a net negative Cu balance

Long-Term Exclusive Zinc Monotherapy in Symptomatic Wilson Disease: Experience in 17 Patients

Francisca H. H. Linn,[1-3] Roderick H. J. Houwen,[4] Jan van Hattum,[5] Stefan van der Kleij,[4] and Karel J. van Erpecum[6]

Exclusive monotherapy with zinc in symptomatic Wilson disease is controversial. Seventeen symptomatic patients with Wilson disease were treated with zinc only. The mean age at diagnosis and start of treatment was 18 years (range 13-26) with approximately half presenting as adolescents. Presentation was exclusively hepatic, exclusively neurologic, and combined in seven, five, and five patients, respectively. The median follow-up was 14 years (range 2-30). At baseline, two of the 12 patients with hepatic disease exhibited decompensated cirrhosis, five exhibited compensated cirrhosis, and five had less severe disease. Both patients with decompensated cirrhosis improved to a compensated state after initiation of therapy. Two of the five patients with initial compensated cirrhosis progressed to decompensated state, and three remain stable. Three of the five patients with moderate or mild liver disease remain stable and two improved. Apart from decreasing bilirubin levels, no significant changes occurred in the liver biochemistry or function during long-term follow-up. Nine of 10 neurologic patients improved markedly and one deteriorated. Two patients with exclusively neurologic presentation developed liver disease during zinc treatment. Two patients with exclusively hepatic presentation developed mild neurologic symptoms. According to 24-hour urinary copper excretions (213 ± 38 versus 91 ± 23 μg: $P = 0.01$) and serum non–ceruloplasmin-bound copper concentrations (11 ± 2 versus 7 ± 1 μg/dL: $P = 0.1$) at the end of follow-up, the efficacy of decoppering was less in the exclusively hepatic than in the neurologic group. The prescribed zinc dose and 24-hour urinary zinc excretions tended to be less in the exclusively hepatic group. *Conclusion:* The outcome of exclusive zinc therapy is generally good in cases of neurologic disease. A less satisfactory outcome in hepatic disease may relate to less efficient decoppering. (HEPATOLOGY 2009;50:1442-1452.)

HEPATOLOGY
2009;50:1442-1452

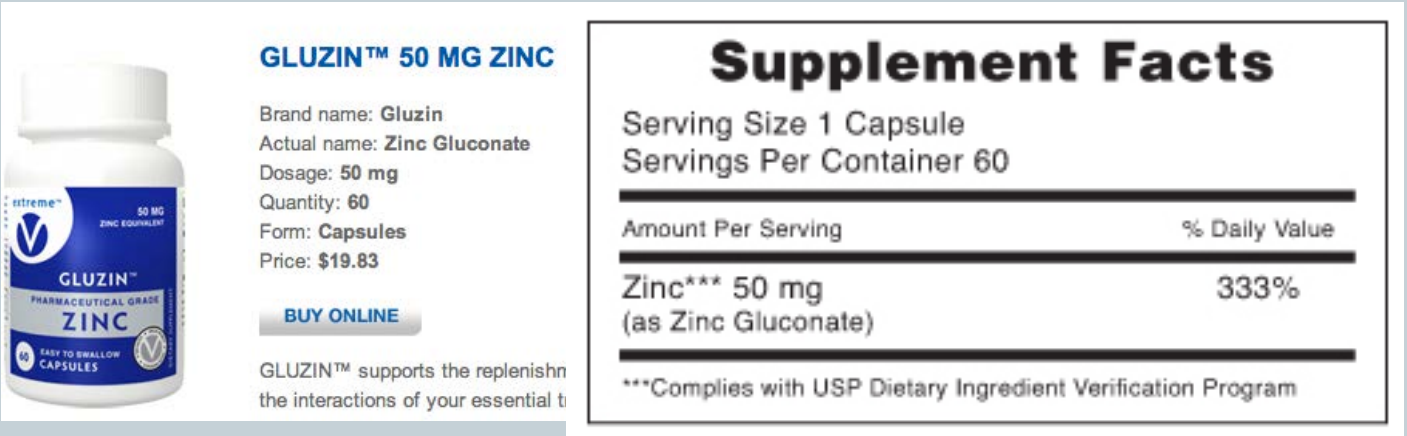
Wilson Disease: Chronic Treatment: Maintenance

- Zinc *50 mg elemental zinc* TID 1 before or after meals
  - Interferes with Cu absorption and increasing excretion of Cu in stool
  - Zinc Sulfate 220 mg 1 tab PO TID (50 mg elemental in 220 mg Zn sulfate)
  - However, Zinc Gluconate and Zinc Acetate doses expressed in mg elemental zinc….

Zinc Entry at http://www.micromedexsolutions.com.echo.louisville.edu/

Wilson Disease: Chronic Treatment: Maintenance

- Zinc *50 mg elemental zinc* TID 1 before or after meals
- Zinc Gluconate 50 mg TID: (Gluzin or other trade names)



- Zinc Acetate 50 mg TID: (Galzin and other names)

Wilson Disease: Chronic Treatment: Maintenance

- Compliance is the issue: Need to take on empty stomach since food interferes with the effectiveness, but Zinc Sulfate causes gastric irritation and patients want to take it with food
  - Options: Switch to Zn Gluconate, Zn Acetate, or other brand names, or titrate up dose monitoring 24 h urine Cu
  - Goal 24 h urine Cu is <75 ug/day
- Other maintenance therapy:
  - Penicillamine 0.75-1 g/day with goal 24h urine Cu <100 ug/L
  - Trientine 1-1.2 g/day with goal 24h urine Cu <100 ug/L
- Diet: Avoid shellfish, nuts, chocolate, mushrooms, and organ meats

Roberts Hepatology. 2008 Jun;47(6):2089-111

Wilson Disease: Summary

Wilsons Disease manifests as hemolytic anemia.

- Presents Chronic (low cerulopasmin)
- Presents Acute (high ceruloplasmin with Alk Phos/Total Bilirubin ratio < 4)

Diagnosis: Ceruloplasmin/Slit lamp, 24h Urine Cu, Biopsy

Treatment:

- Asymptomatic (screened): Zinc 50 mg elemental TID not during meals
- Chelation in hepatitis can be done with Penicillamine, Trientine and possibly Zinc. Monitor effectiveness with repeated Urine Cu 200-500 ug/day
- Following chelation transition to to Zinc with the goal of 24 h urine Cu < 75 ug/day

Roberts Hepatology. 2008 Jun;47(6):2089-111

Alpha-1-Antitrypsin Deficiency

- One of the most common genetic disease
- α_1-AT normally binds with and promotes degradation of serine proteases, most importantly neutrophil elastase
- Loss of α_1-AT leads to uninhibited elastase activity
- α_1-AT is produced in the hepatocyte endoplasmic reticulum, but structural misfolding and polymerization of the mutant α_1-AT leads to *retention in the hepatocyte*
- Exact mechanism of the liver disease is not known
  - One theory is that the accumulation leads to mitochondrial injury, chronic cell death and regeneration

Alpha-1-Antitrypsin Deficiency: Genetics

- The *normal* allele is PiM. (Pi= Protease Inhibitor)
- Most common variant is PiZ
  - Homozygous Pi ZZ causes the most common classic form of α1AT deficiency
  - Pi ZZ patients have a serum α1 AT activity <15% of normal
  - Risk of liver disease highest in childhood (5-10% of ZZ children)
  - Pi ZZ patients often have LFT's in the normal range
  - Prevalence of cirrhosis for ZZ adults varies, 2-43%
- Less common allele is PiS
  - MS and SS have not been associated with liver disease

Hepatology. 2008 Jan;47(1):127-32.
Clin Gastroenterol Hepatol. 2012 Jun;10(6):575-80.

Alpha-1-Antitrypsin Deficiency: Genetics

- Heterozygous state prevalence ranges 6-12% in the US
  - About 70% are PiMS, 28% are PiMZ, and 1% are PiSZ
- Heterozygous PiMZ are healthy and it does not cause de-novo liver disease, but they overrepresented in adult liver clinics
- In MZ patients with HCV or NAFLD there is an increased severity of liver disease and the need for liver transplantation

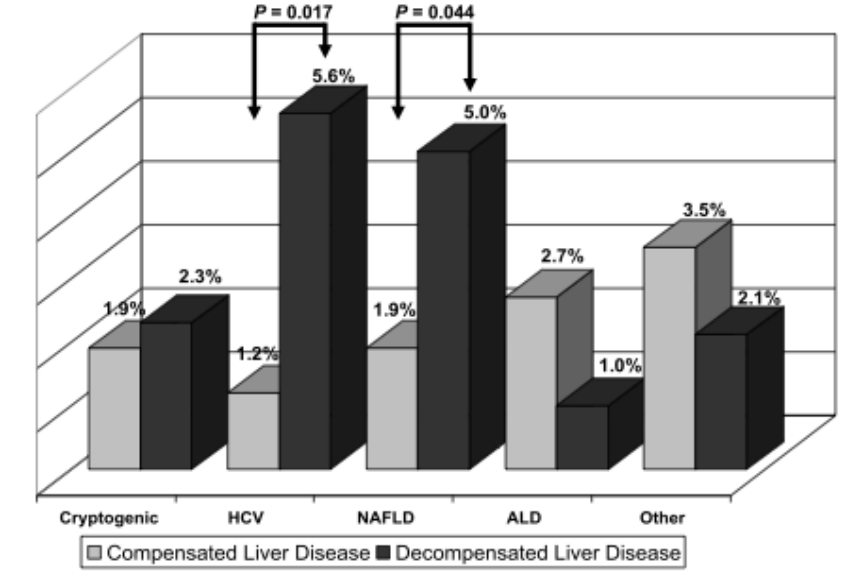


FIG. 2. Prevalence of the PiMZ heterozygous state in patients with chronic liver diseases.

J Pediatr Gastroenterol Nutr, Vol. 43, Suppl. 1, July 2006

Clin Gastroenterol Hepatol. 2012 Jun;10(6):575-80.

J Pediatr Gastroenterol Nutr. 2006 Jul;43 Suppl 1:S30-5.

Testing Options

- Our current practice is to obtain:
  - A1AT Quantification
  - “A1AT Phenotyping” (We think is run by IEF-Isoelectric focusing)
- These tests are available through Quest and LabCorp
- Mayo Clinic has a test (26953) which is called “Alpha-1-Antitrypsin Phenotype” but IEF can’t be ordered separately, instead they are using an algorithm and usually run:
  - A1AT Quantification
  - A1AT Genotyping
  - Reflex to Phenotype by IEF if discordant

Alpha-1-Antitrypsin Deficiency: Diagnosis
Check both the LEVEL and GENOTYPE / PHENOTYPE

- Serum α1-AT concentration is usually 57-80 mg/dL
  - α1-AT level < 11 puts patients at risk for pulmonary emphysema
  - α1-AT is an acute phase reactant, so a ZZ patient can be falsely elevated
- Genotype does allele specific amplification
- Phenotyping uses gel electrophoresis, is labor intensive and somewhat subjective. It can't distinguish between homozygous with limited production from heterozygous with a normal and a non-producing allele.

Am J Gastroenterol. 2008 Aug;103(8):2136-41;
Clin Gastroenterol Hepatol. 2012 Jun;10(6):575-80.

The lab is running LEVEL and GENOTYPE, and if discordant then isoelectric phenotype

- Mayo clinic tested 512 individuals for A1AT Phenotype:
  - A1AT Quantification
  - A1AT Phenotyping (IEF on a gel)
  - A1AT Genotyping by PCR for S and Z alleles:
    - Z/Z Genotype, S/S Genotype
    - Neither Z nor S allele: 2 wild types non-Z/non-S: “probably MM”
    - 1 Z detected: Z/non-Z or Z-heterozygous: “probably MZ”
    - 1 S detected: S/non-S or S-heterozygous: “probably MZ”
  - At end of study Genotypes and Phenotypes reviewed and if discordant then all 3 tests were repeated

Clinical Chemistry 52, No 12, 2006

- 98% Concordence of the Genotype and Phenotype Method with 10 discordent cases.

  - 5/10 were phenotype error due to poor sample quality
  - 2/10 were phenotype error due to error in interpretation
  - 1/10 Presence of a null allele not detected by genotype
  - 1/10 was a patient on A1AT replacement therapy
  - 1/10 undetermined

Clinical Chemistry
52, No 12, 2006

Table 2. Results and interpretations for samples with discordant phenotype and genotype results.

Sample ID	A1AT concentration, g/L	Phenotype Result	Genotype Result	Reason for Discrepancy
121	0.80	M/Z	M/M	Phenotype error due to poor sample quality
234	1.83	M/S	M/M	Phenotype error due to poor sample quality
258	0.98	M/Z	M/M	Phenotype error due to poor sample quality
420	1.39	M/M	M/Z	Phenotype error due to poor sample quality
472	1.12	M/Z	M/M	Phenotype error due to poor sample quality
264	1.31	M/S	S/S	Error in interpretation of initial phenotype IEF gel
327	1.57	M/S	M/M	Error in interpretation of initial phenotype IEF gel and presence of nondeficiency allele not detected by genotype assay
46	0.32	Z/Z	M/Z	Presence of null allele not detected by genotype assay
226	1.45	M/Z	Z/Z	Patient receiving A1AT replacement therapy
361	3.53	M/S	M/M	Undetermined

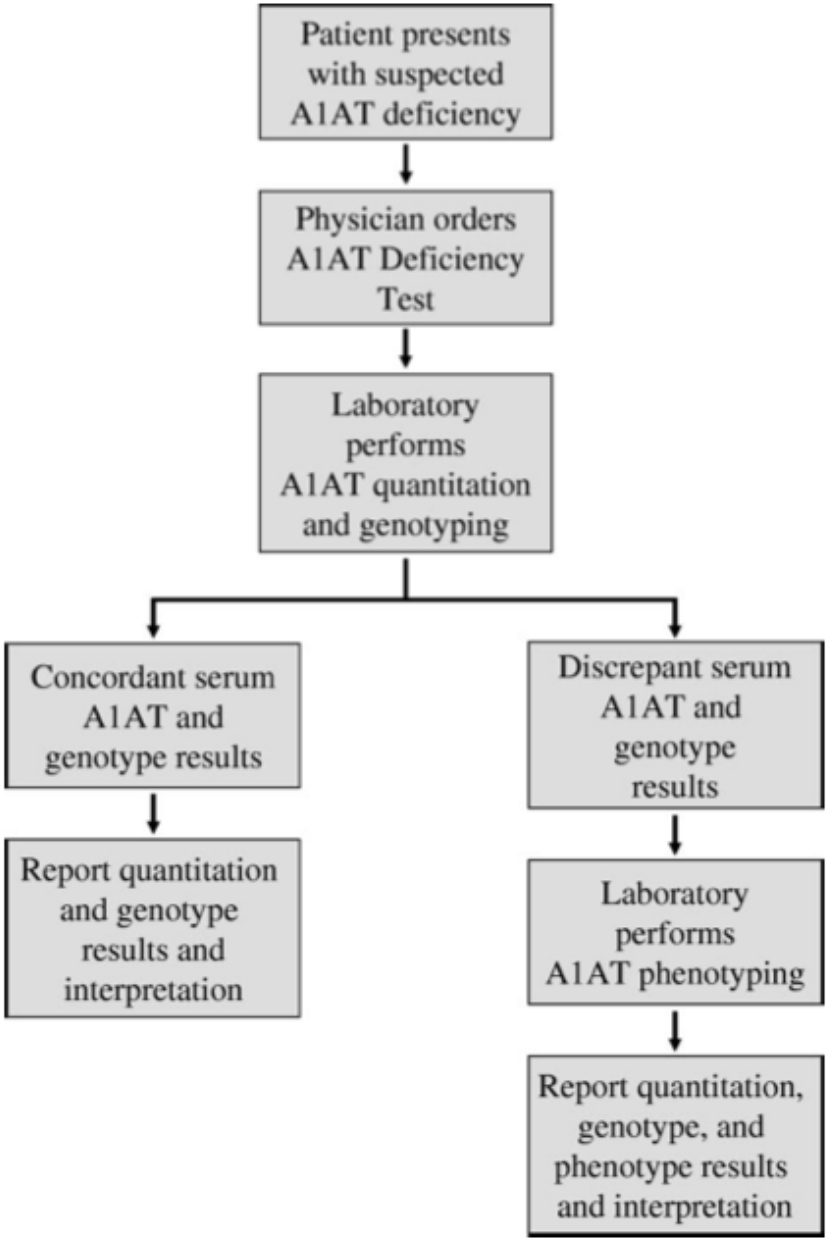
non-Z/non-S genotype, the A1AT concentration should be >1.00 g/L

Z/non-S or S/non-Z heterozygote, a concordant A1AT quantification would be any value >0.70 g/L

S/S genotype would be expected to have an A1AT concentration< 1.00 g/L

Z/Z homozygote should have an A1AT quantification of <0.70 g/L

Results that are not within these ranges for the genotype and quantification, the sample would then reflex to the phenotype assay



Clinical Chemistry 52, No 12, 2006

Alpha-1-Antitrypsin Deficiency: Management

- No current treatment for the liver disease, refer deficient patients to pulmonologist
  - Pulmonary disease (PiZZ, level<11 umol/L, obstruction on spirometry) can be treated with weekly infusion of pooled alpha-1 antiprotease
- Refer siblings of individuals with α1-AT deficiency for genetic counseling
- Smoking cessation, limit alcohol, controlling obesity, HAV and HBV Vaccination
- Assess for liver disease (ultrasound)
  - Cirrhotic patients: Variceal & HCC screening, Vaccinations

Clin Gastroenterol Hepatol. 2012 Jun;10(6):575-80.

Alpha-1-Antitrypsin Deficiency: Future

- Placebo controlled trial for carbamazepine at University of Pittsburgh
  - ZZ or SZ phenotype, serum level < 83 mg/dL
  - "Still Recruiting" Estimated Study Completion Date Jan 2015
- In mice carbamazepine enhanced autophagy and proteasomal disposal of insoluable aggregates of Z α1-AT

N Engl J Med. 2010 Nov 4;363(19):1863-4.

Alpha-1-Antitrypsin Deficiency: Summary

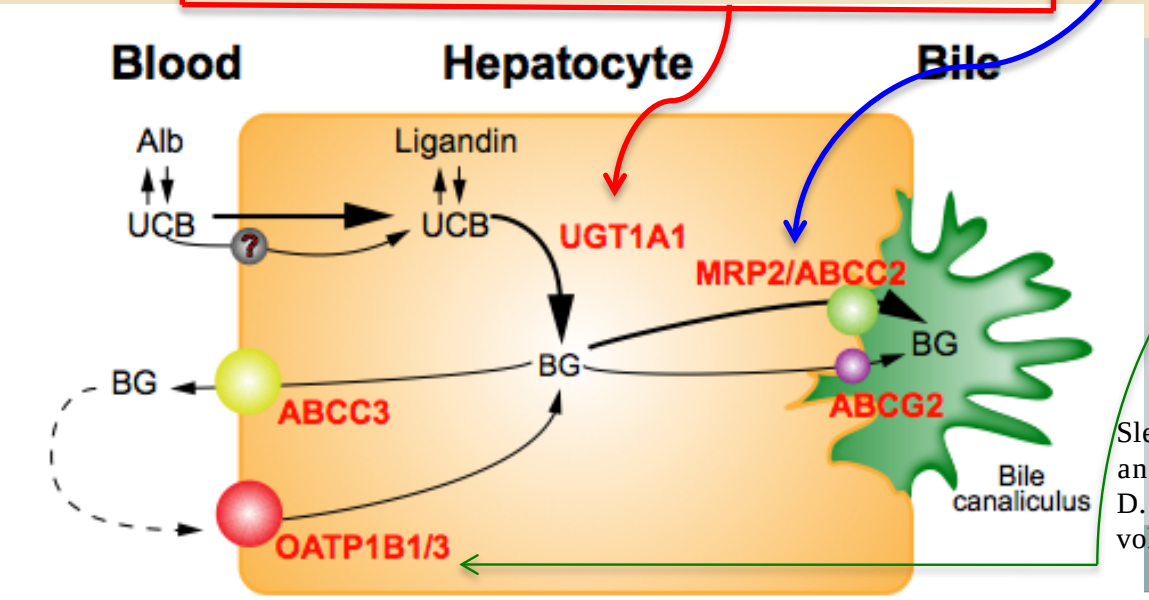
- α1-AT as the sole cause of liver disease is usually the PiZZ phenotype
- Testing is usually Level + Genotype -/+ Phenotype; when in doubt order “Phenotype” but realize the test may be done using PCR for common genotypes
- Heterozygous PiMZ can contribute to decompensation of HCV and NAFLD
- Routine cirrhotic care
- Possibly carbamazepine in the future

Hereditary Hyperbilirubinemia

- Ask about family history of jaundice or liver disease

Table 20-2 Hereditary Disorders of Bilirubin Metabolism and Transport

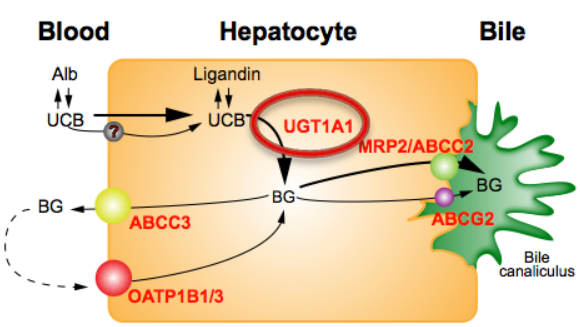
	Syndrome				
PARAMETER	**GILBERT'S**	**CRIGLER-NAJJAR TYPE I**	**CRIGLER-NAJJAR TYPE II**	**DUBIN-JOHNSON**	**ROTOR'S**
Incidence	6%-12%	Very rare	Uncommon	Uncommon	Rare
Gene affected	*UGT1A1*	*UGT1A1*	*UGT1A1*	*MRP2*	Unknown
Metabolic defect	↓Bilirubin conjugation	No bilirubin conjugation	↓↓Bilirubin conjugation	Impaired canalicular export of conjugated bilirubin	Impaired canalicular export of conjugated bilirubin

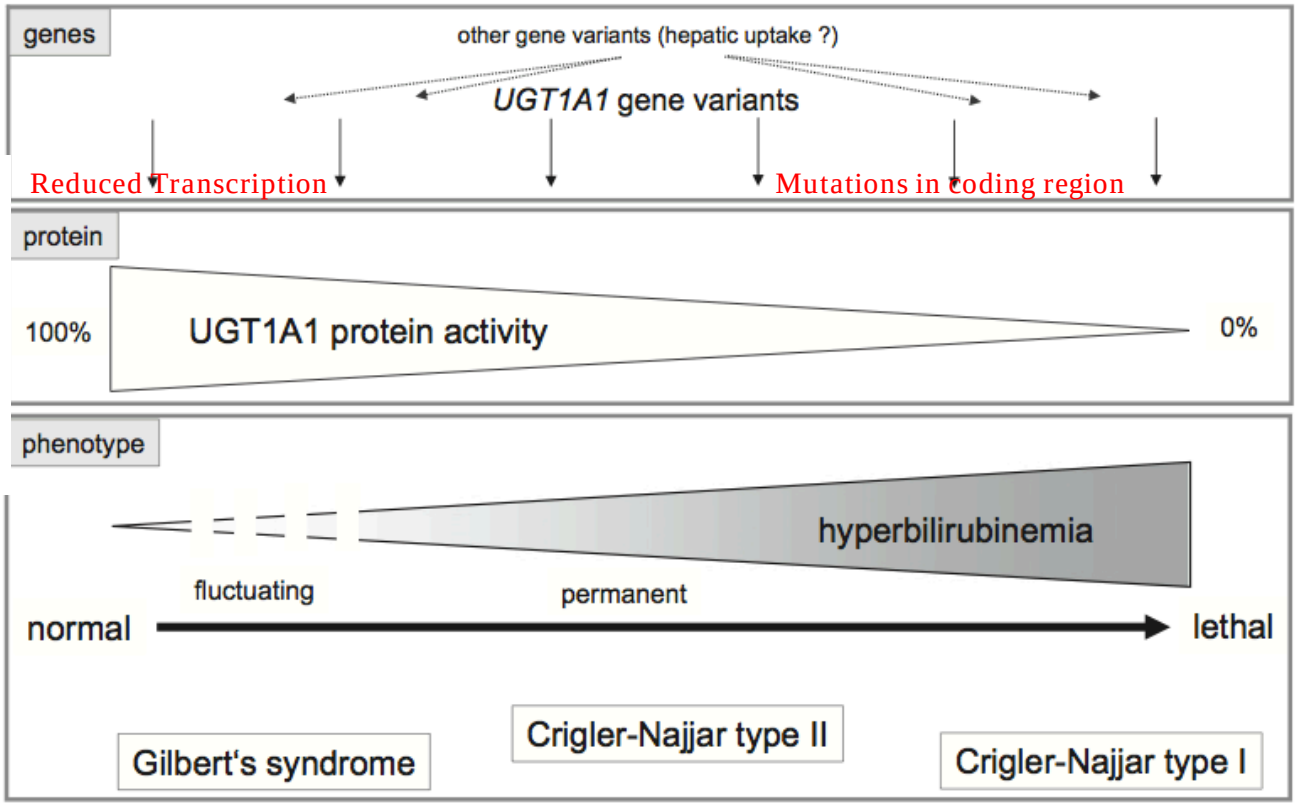


Sleisenger and Fordtran's gastrointestinal and liver disease, Chapter 20, 2010
D. Dhumeaux, Journal of Hepatology 2013 vol. 58 388–390

Unconjugated Hyperbilirubinemia

- Gilbert's, Crigler-Najjar Type I and Type II
- Bilirubin UDP-glucuronyl transferase (B-UGT) Reduced Activity





C.P. Strassburg, Best Practice & Research Clinical Gastroenterology 24 (2010) 555–571

Unconjugated: Gilbert's Syndrome

PARAMETER	GILBERT'S
Incidence	6%-12%
Gene affected	*UGT1A1*
Metabolic defect	↓Bilirubin conjugation
Plasma bilirubin (mg/dL)	≤3 in absence of fasting or hemolysis, almost all unconjugated
Liver histology	Usually normal, occasional ↑lipofuscin
Other distinguishing features	↓Bilirubin concentration with phenobarbital
Prognosis	Normal
Treatment	None

- Episodic mild jaundice after fasting, infections, dehydration, surgery, physical exertion and lack of sleep.
- Drugs that inhibit glucuronyltransferase activity: gemfibrozil, simvastatin, protease inhibitors atazanavir, indiavir
- Usually autosomal recessive

Claridge BMJ 2011;342:d2293

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Other distinguishing features	↓Bilirubin concentration with phenobarbital
Prognosis	Normal
Treatment	None

- Ask: Abdominal pain, pruritus, pale stools, dark urine (should be negative).
- Exam: Check for hepatosplenomegaly and liver disease
- Labs: Direct/Indirect Bilirubin, hemolysis workup. UA should have no bilirubinuria

Claridge BMJ 2011;342:d2293

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Prognosis	Normal
Treatment	None

- Diagnosis:
  - Conjugated Bili within normal range or <20% of Total Bilirubin
  - Normal aminotransferases and albumin
  - No signs of liver disease
  - Negative hemolysis screen
- No need for imaging, or genetic testing
- Tx: Reassurance, recommend the patient inform future health professionals. No dietary or alcohol restrictions

Claridge BMJ 2011;342:d2293

Unconjugated: Gilbert's Syndrome

- Predominant abnormality is impaired bilirubin conjugation
- Other contributing phenotypic expression include decreased bilirubin uptake

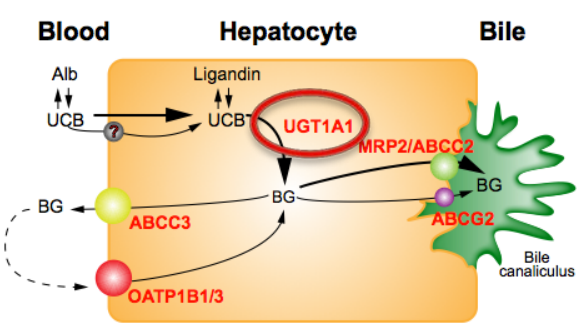
Additional abnormalities in Gilbert-Meulengracht syndrome patients.

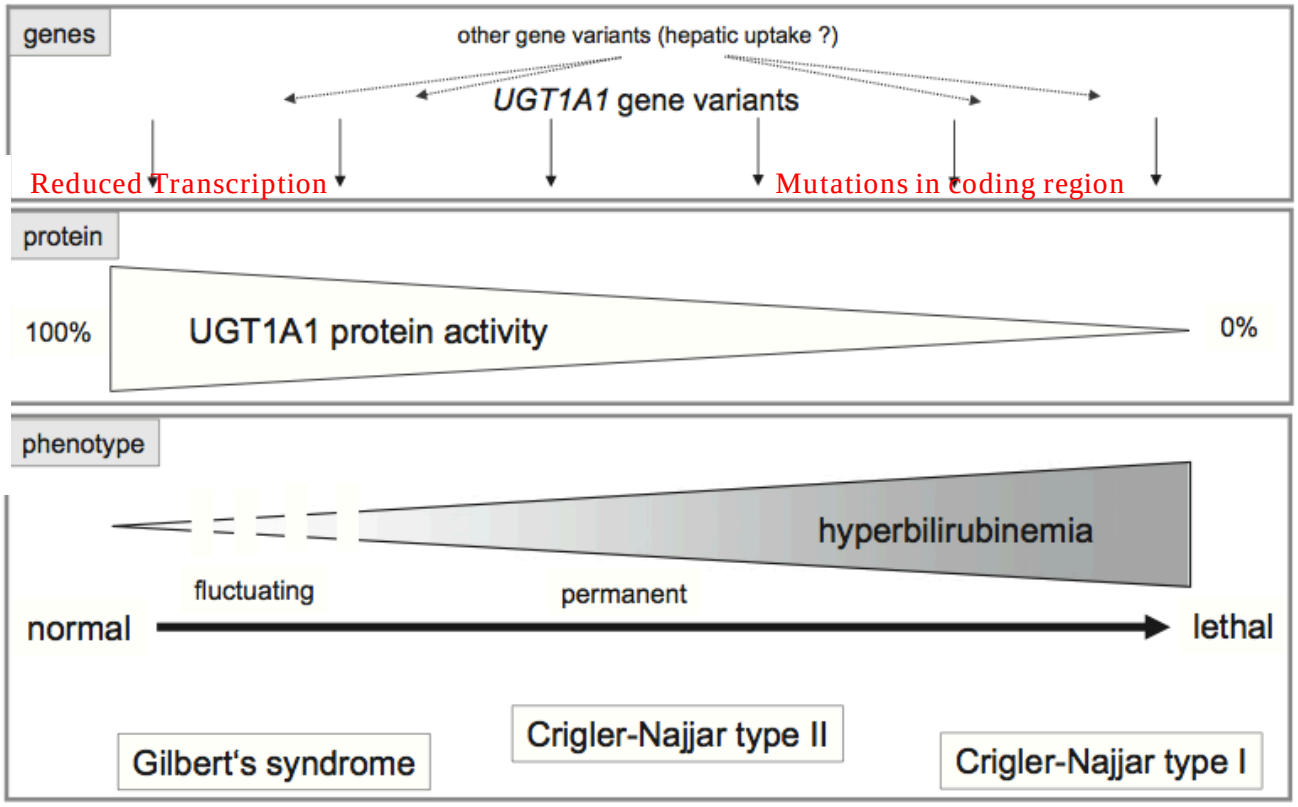
Abnormality	Potential mechanism
Reduced indocyanine green clearance	Altered transport
Reduced bromosulphthaleine clearance	Altered transport
Impaired hepatic bilirubin uptake	Altered transport, SCLO1B1?
Impaired tolbutamide clearance	Altered hepatic uptake?
	Genome wide association of hyperbilirubinemia with UGT1A1 and SCLO1B1

C.P. Strassburg, Best Practice & Research Clinical Gastroenterology 24 (2010) 555–571

Unconjugated Hyperbilirubinemia

- Gilbert's, Crigler-Najjar Type I and Type II
- Bilirubin UDP-glucuronyl transferase (B-UGT) Reduced Activity





C.P. Strassburg, Best Practice & Research Clinical Gastroenterology 24 (2010) 555–571

Unconjugated: Crigler-Najjar Syndrome

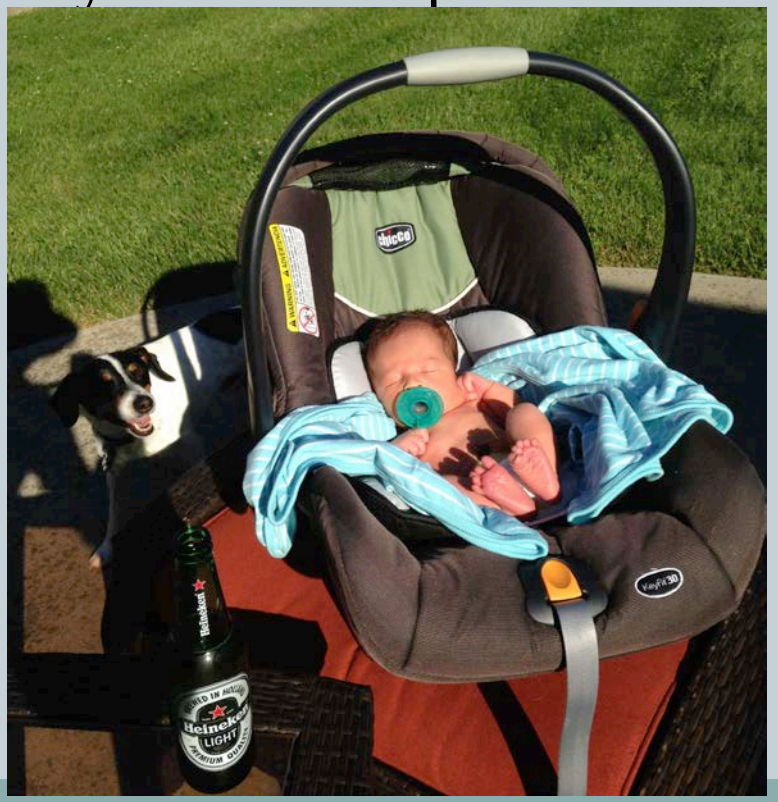
PARAMETER	CRIGLER-NAJJAR TYPE I	CRIGLER-NAJJAR TYPE II
Incidence	Very rare	Uncommon
Gene affected	*UGT1A1*	*UGT1A1*
Metabolic defect	No bilirubin conjugation	↓↓Bilirubin conjugation
Plasma bilirubin (mg/dL)	Usually >20 (range, 17-50), all unconjugated	Usually <20 (range, 6-45), almost all unconjugated
Liver histology	Normal	Normal
Other distinguishing features	No response to phenobarbital	↓Bilirubin concentration with phenobarbital
Prognosis	Death in infancy if untreated	Usually normal
Treatment	Phototherapy as a bridge to liver transplantation	Phenobarbital for ↑↑bilirubin concentration

- Type I:
  - Autosomal Recessive
  - Absent B-UGT activity
  - Neonatal death from kernicterus
  - Phototherapy bridge to liver transplantation
- Type II:
  - Asymptomatic in neonatal period, diagnosed in early childhood
  - Total Bili 6-45 with fall to 2-5 mg/dL with phenobarbital (increases expression of UGT1A1 and thus B-UGT activity)
  - Normal life expectancy
  - May use phenobarbital at 5 mg/kg/day

El-Shabrawi Paediatr Drugs. 2011 Dec 1;13(6):371-83

Unconjugated: Physiologic Jaundice of the Newborn

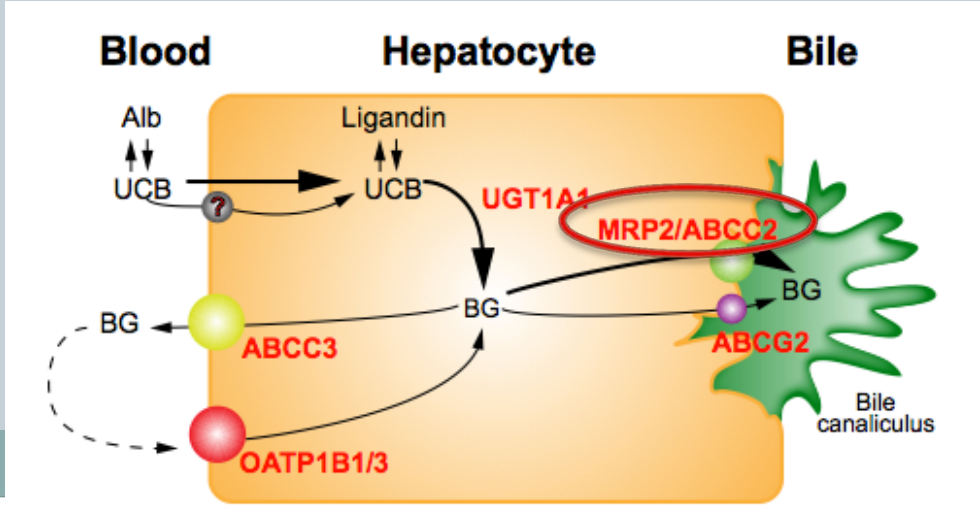
- Delayed developmental expression of UDP-glucuronyl transferase
- Brief course of phototherapy may be used to prevent kernicterus



Conjugated: Dubin-Johnson Syndrome

PARAMETER	DUBIN-JOHNSON
Incidence	Uncommon
Gene affected	*MRP2*
Metabolic defect	Impaired canalicular export of conjugated bilirubin
Plasma bilirubin (mg/dL)	Usually <7, about half conjugated
Liver histology	Coarse pigment in centrilobular hepatocytes
Other distinguishing features	↑Bilirubin concentration with estrogens; ↑↑urinary coproporphyrin I/III ratio; slow BSP elimination kinetics with secondary rise
Prognosis	Normal
Treatment	Avoid estrogens

- Selective decrease in bilirubin secretion into the bile canalicus
- Absence of organic anion transporter MRP2/ABCC2 (synonymous names)
  - MRP2=Multidrug resistance-associated protein 2
  - ABCC2=ATP-binding cassette sub-family C member 2



Conjugated: Dubin-Johnson Syndrome

PARAMETER	DUBIN-JOHNSON
Incidence	Uncommon
Gene affected	*MRP2*
Metabolic defect	Impaired canalicular export of conjugated bilirubin
Plasma bilirubin (mg/dL)	Usually <7, about half conjugated
Liver histology	Coarse pigment in centrilobular hepatocytes
Other distinguishing features	↑Bilirubin concentration with estrogens; ↑↑urinary coproporphyrin I/III ratio; slow BSP elimination kinetics with secondary rise
Prognosis	Normal
Treatment	Avoid estrogens

- Rare, autosomal recessive, more frequent in Sephardic Jews
- Normal aminotransferases except Fluctuating Total Bili and no hemolysis
- Bilirubin is 50% Conjugated, 50% Unconjugated
- Worsened by oral contraceptives, pregancy and concurrent illness
- Diagnosis: Wait for it… coming slides.
- Histology: Dark lysosomal melanin-like pigment deposits, but liver biposy and genetic testing is not necessary

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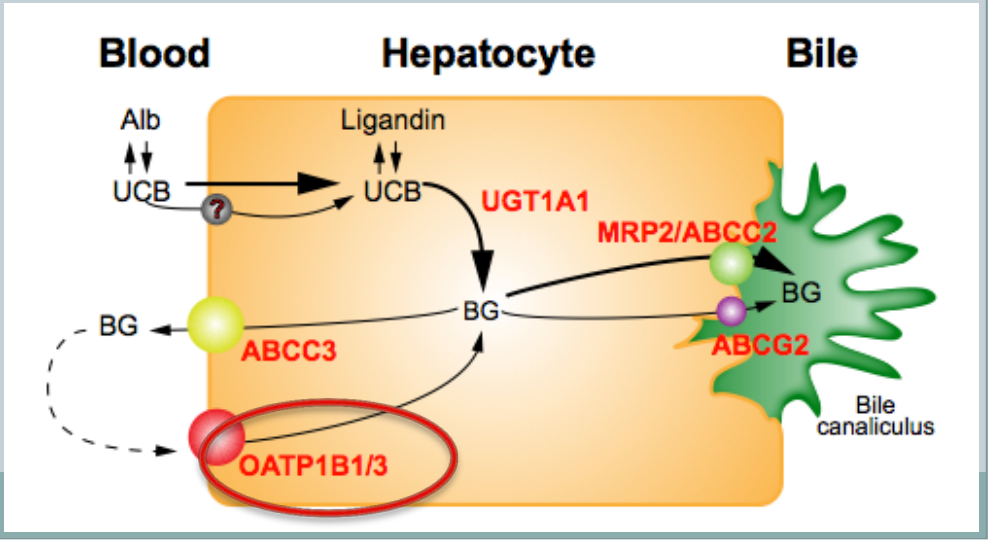
Conjugated: Rotor's Syndrome

PARAMETER	ROTOR'S
Incidence	Rare
Gene affected	Unknown
Metabolic defect	Impaired canalicular export of conjugated bilirubin
Plasma bilirubin (mg/dL)	Usually <7, about half conjugated
Liver histology	Normal
Other distinguishing features	Mild ↑urinary coproporphyrin I/III ratio; very slow BSP* elimination kinetics without secondary rise
Prognosis	Normal
Treatment	None available

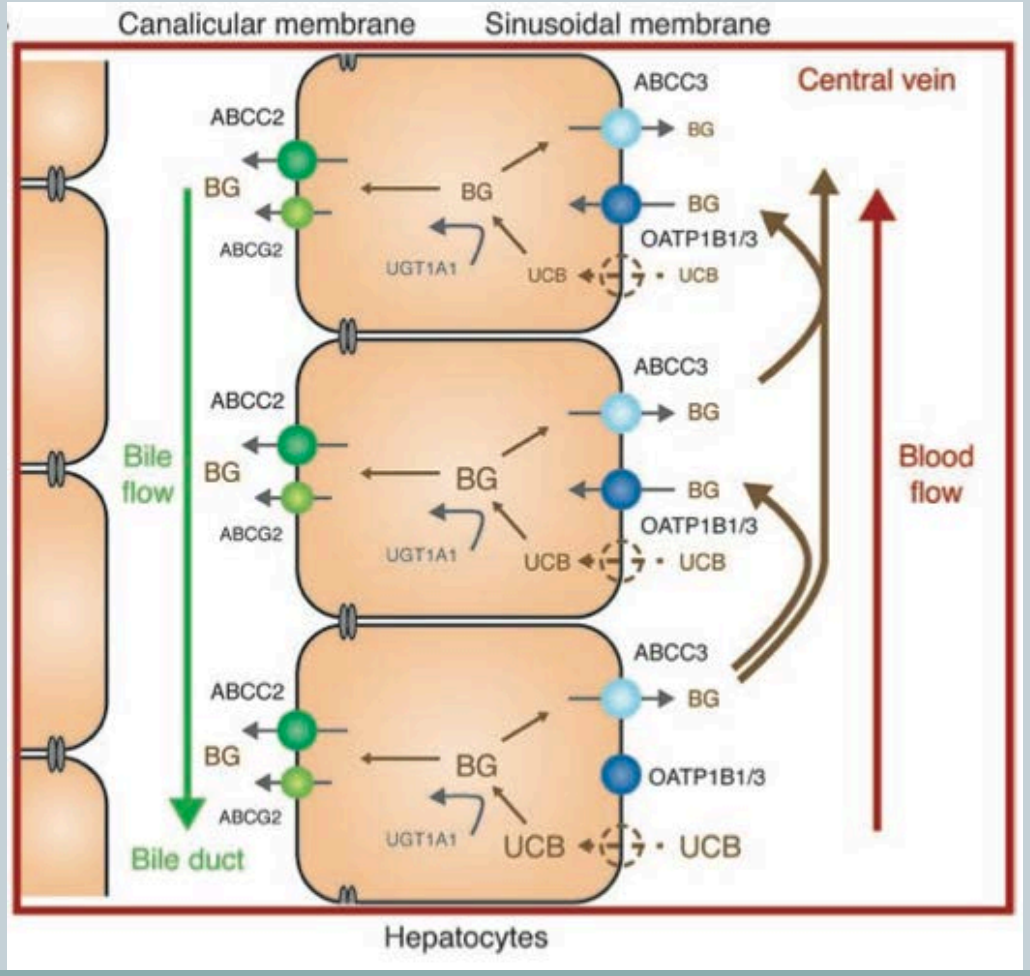
- Autosomal recessive disease with defects organic anion transporting polypeptides OATP1B1 and OATP1B3 which normally re-uptake conjugated bilirubin into the hepatocyte



Conjugated: Rotor's Syndrome

PARAMETER	ROTOR'S
Incidence	Rare
Gene affected	Unknown
Metabolic defect	Impaired canalicular export of conjugated bilirubin
Plasma bilirubin (mg/dL)	Usually <7, about half conjugated
Liver histology	Normal
Other distinguishing features	Mild ↑urinary coproporphyrin I/III ratio; very slow BSP* elimination kinetics without secondary rise
Prognosis	Normal
Treatment	None available

- Hepatocyte Hopping Cycle



van de Steeg J Clin Invest. 2012 Feb 1; 122(2)519028

Conjugated: Rotor's Syndrome

PARAMETER	ROTOR'S
Incidence	Rare
Gene affected	Unknown
Metabolic defect	Impaired canalicular export of conjugated bilirubin
Plasma bilirubin (mg/dL)	Usually <7, about half conjugated
Liver histology	Normal
Other distinguishing features	Mild ↑urinary coproporphyrin I/III ratio; very slow BSP* elimination kinetics without secondary rise
Prognosis	Normal
Treatment	None available

- Normal aminotransferases except Fluctuating Total Bili and no hemolysis
- Diagnosis:
  - Wait for it… coming slides….
  - *In the past, BSP clearence test (No longer done)
- Normal Prognosis, benign disease
- Steroid hormones and pregnancy can accentuate Rotor's Syndrome

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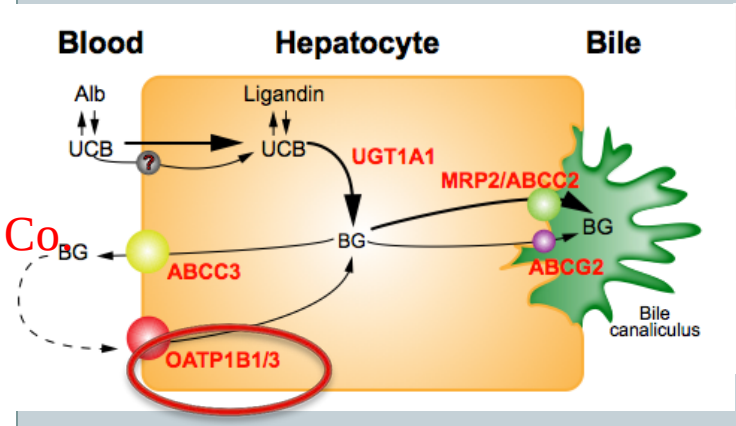
Conjugated Hyperbilirubinemia Diagnosis: Measuring Corproporphyin Isomers (Co. I and III)

- Dubin-Johnson's: Co. III is retained in the liver, resulting in a higher ratio of Co. I is in the urine, but the total level is normal
- Rotor's: Postulated that Co. I and III and also substrates for the defected OATP1B1/3, there is decreased Re-Uptake, raising the total levels in the urine



Test	Normal	Dubin-Johnson's	Rotor's
Urine Coproporphyrin (Co) Level	Normal Level	Normal Level	Elevated 2-5 Fold
Co. I / Total	20-45%	80% of total	65% of total

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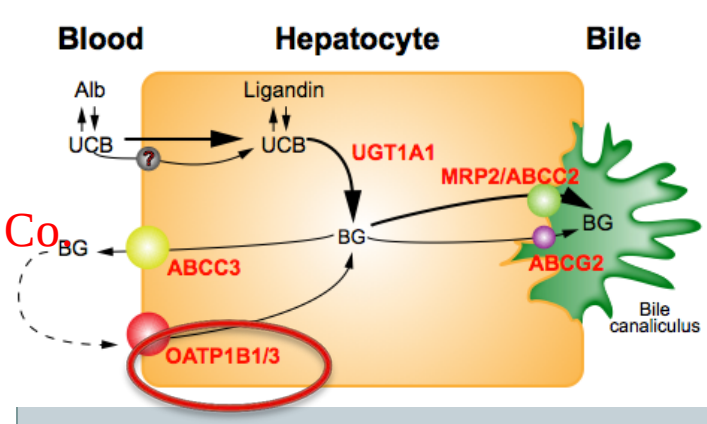
Conjugated Hyperbilirubinemia Diagnosis: Measuring Corproporphyin Isomers (Co. I and III)

- Mayo Clinic Lab Test: Inherited Conjugated Hyperbilirubinemias, Urine
- Patients abstain from alcohol for 24 hours prior to testing, then collect 24 hour urine, refrigerated and protected from light



Test	Normal	Dubin-Johnson's	Rotor's
Urine Coproporphyrin (Co) Level	Normal Level	Normal Level	Elevated 2-5 Fold
Co. I / Total	20-45%	80% of total	65% of total

http://www.mayomedicallaboratories.com/test-catalog/Overview/8652

Hereditary Hyperbilirubinemia: Summary

- In general: all are autosomal recessive; rule out hemolytic anemia and other liver disease
- Unconjugated: Gilbert's, Crigler-Najjar Types I and II
  - CN Type I is usually fatal without early transplant, CN Type II can be treated with phenobarbital
- Conjugated: Dubin-Johnson and Rotor's
  - Distinguish with Urine Coproporphyin Isomers (high total in Rotor's, high I/III ratio in DJ)

Table 20-2 Hereditary Disorders of Bilirubin Metabolism and Transport

	Syndrome				
PARAMETER	**GILBERT'S**	**CRIGLER-NAJJAR TYPE I**	**CRIGLER-NAJJAR TYPE II**	**DUBIN-JOHNSON**	**ROTOR'S**
Incidence	6%-12%	Very rare	Uncommon	Uncommon	Rare
Gene affected	*UGT1A1*	*UGT1A1*	*UGT1A1*	*MRP2*	Unknown
Metabolic defect	↓Bilirubin conjugation	No bilirubin conjugation	↓↓Bilirubin conjugation	Impaired canalicular export of conjugated bilirubin	Impaired canalicular export of conjugated bilirubin

OATP1B1/3

Questions for the doctor?

Many thanks to Dr. Luis Marsano and to my son Oliver, or as the hepatologist like to say...

oLIVER