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Review Article

Dubin-Johnson and Rotor Syndromes: A Review and Update of Pathophysiological Mechanisms

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Abstract

Dubin-Johnson syndrome (DJS) and Rotor syndrome (RS) are rare, autosomal recessive disorders that result in chronic, predominantly conjugated hyperbilirubinemia without cholestasis or hepatocellular injury. Although both conditions are benign and non-progressive, they reflect distinct molecular defects in hepatocellular transport pathways. DJS arises from mutations in the *ABCC2* gene encoding the canalicular transporter multidrug resistance–associated protein 2, leading to impaired biliary excretion of conjugated bilirubin and organic anions. In contrast, RS results from combined deficiencies of the sinusoidal transporters OATP1B1 and OATP1B3, encoded by *SLCO1B1* and *SLCO1B3* genes, respectively, which mediate hepatic reuptake of conjugated bilirubin from the sinusoidal blood. These defects explain the characteristic biochemical and clinical distinctions between the syndromes, including the black hepatic pigmentation and markedly elevated urinary coproporphyrin I fraction in DJS, and the absence of pigmentation with moderate coproporphyrin I predominance in RS. Recent studies have expanded the understanding of how these transporters influence not only bilirubin handling but also the hepatic disposition of various drugs and endogenous metabolites. Recognition of DJS and RS is essential to prevent misdiagnosis of cholestatic or hepatocellular disease, avoid unnecessary investigations, and anticipate altered pharmacokinetics in affected individuals. This review synthesizes current evidence from molecular, biochemical, and clinical studies to highlight how these syndromes illuminate broader principles of hepatic transporter physiology and its relevance to inherited and acquired disorders of bilirubin metabolism.

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Introduction

Dubin-Johnson syndrome (DJS) and Rotor syndrome (RS) are genetically determined disorders that both result in chronic conjugated hyperbilirubinemia.[1] However, they have different pathophysiological mechanisms. DJS is an autosomal recessive disorder due to mutations in the *ABCC2* gene, which encodes the canalicular (apical) membrane transporter multidrug resistance-associated protein (MRP) 2, also known as canalicular multispecific organic anion transporter.[2,3] RS is also an autosomal recessive condition that is due to defects in organic anion transporter protein B1 and B3 (OATP1B1/1B3) caused by simultaneous mutations in both *SLCO1B1* and *SLCO1B3* genes (*SLCO1B1/1B3*).[3] This results in impaired hepatic uptake and reuptake of conjugated bilirubin.

There is increased interest in these benign conditions since recent studies have demonstrated that the gene mutations responsible for hyperbilirubinemia may also result in increased susceptibility to drug toxicity. Because these syndromes are rare, asymptomatic, and often underdiagnosed, the aim of this review is to update the genetics and pathophysiology and review typical presentations, diagnosis, and management.

Excretion of conjugated bilirubin

Hepatic excretion of conjugated bilirubin is a complicated process. Conjugated bilirubin is primarily excreted from hepatocytes directly into bile by active transport across the canalicular membrane by the transporter MRP2 encoded by the *ABCC2* gene, a member of the ATP-binding cassette subfamily C transporters highly expressed in hepatocytes (Fig. 1A).[1–4] When MRP2 transport capacity has been exceeded, a major compensatory mechanism of conjugated bilirubin excretion occurs indirectly through the activity of the MRP3 encoded by the *ABCC3* gene. MRP3 is localized on the sinusoidal (basolateral) membrane and transports conjugated bilirubin from hepatocytes into the bloodstream, which is eventually reabsorbed into hepatocytes by OATP1B1/1B3 transporters (Fig. 1A).[2,5] Although the delivery of conjugated bilirubin into the sinusoids for excretion seems counter-intuitive, this mechanism has been hypothesized to prevent saturation of detoxification processes in upstream zone 1 hepatocytes by delivery of excess conjugated bilirubin to zone 3 hepatocytes. This concept is consistent with the observation that OATP1B1/1B3 reuptake transporters are primarily found in zone 3 hepatocytes.[6] MRP3 is upregulated in cholestatic states and is the only basolateral transporter shown to efficiently transport conjugated bilirubin[4,7] as well as amphipathic anionic substrates, glutathione conjugates, glucuronide

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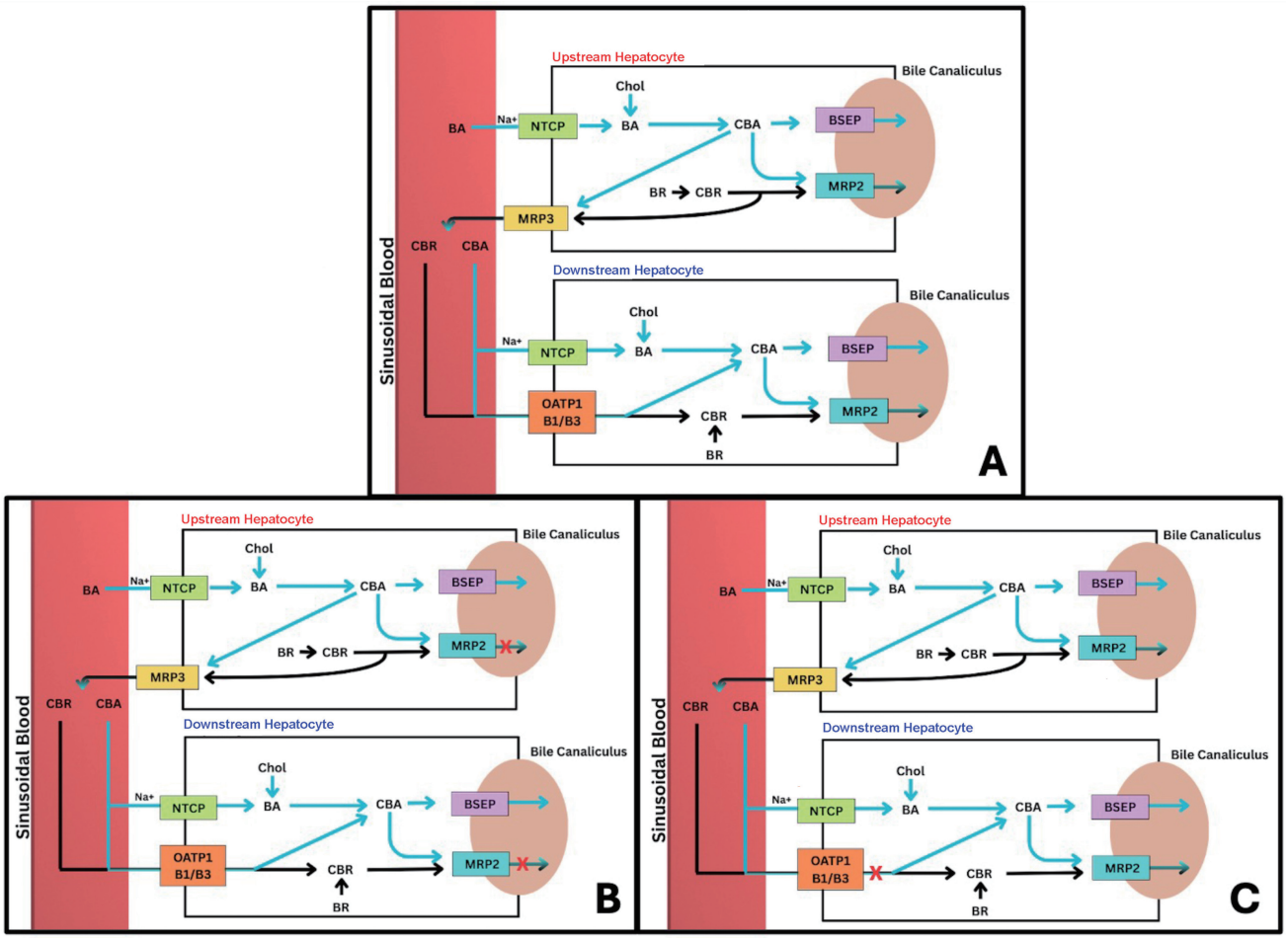

Fig. 1. Hepatocellular transport of conjugated bilirubin and bile acids in Dubin-Johnson syndrome and Rotor syndrome. (A) In normal physiology, conjugated bilirubin is actively excreted into bile through the multidrug resistance–associated protein 2 (MRP2) on the canalicular membrane, while bile acids are secreted via the bile salt export pump (BSEP). Basolateral efflux transporters such as MRP3 allow limited reflux of conjugated bilirubin and bile acids into sinusoidal blood from upstream hepatocytes, serving as an alternative route during cholestasis. Reuptake of conjugated bilirubin and other organic anions from blood back into downstream hepatocytes occurs via OATP1B1 and OATP1B3. (B) In Dubin-Johnson syndrome (DJS), loss-of-function mutations in ABCC2 cause defective MRP2, preventing canalicular excretion of conjugated bilirubin. The diagram denotes this with an "X" over MRP2; there is compensatory MRP3-mediated efflux into the sinusoidal circulation. Bile acid transport via BSEP remains intact. (C) In Rotor syndrome (RS), biallelic mutations in SLCO1B1 and SLCO1B3 impair OATP1B1/B3 function, reducing hepatocellular reuptake of conjugated bilirubin that refluxes into the bloodstream. The diagram shows "X" marks over OATP1B1/B3, while MRP2 and BSEP remain functional. BA, bile acids; CBA, conjugated bile acids; BR, bilirubin; CBR, conjugated bilirubin; Chol, cholesterol; NTCP, sodium taurocholate cotransporting polypeptide; OATP1B1/B3, organic anion transporting polypeptides 1B1 and 1B3; BSEP, bile salt export pump; MRP2, multidrug resistance–associated protein 2; MRP3, multidrug resistance–associated protein 3; Na^+, sodium.

conjugates, sulfate conjugates, leukotriene C4, and bilirubin, as well as a broad range of hormones and drugs to the sinusoids in humans. [4,8]

Excretion of conjugated bile salts

Bile salts are secreted by hepatocytes through a coordinated process involving uptake from blood and export into bile primarily mediated by four key transporters: sodium taurocholate cotransporting polypeptide (NTCP), OATP1B1/1B3, bile salt export pump (BSEP), and MRP2 (Fig. 1A).[9,10] NTCP (sodium-dependent transporter) and OATP1B1/1B3 (sodium-independent transporter) are located on the sinusoidal membrane of hepatocytes and are responsible for the uptake of bile salts from portal blood into the hepatocyte; once inside the cell, bile acids are transported to the canalicular membrane.[9,10] BSEP (encoded by the *ABCB11* gene) is the main transporter on the canalicular membrane exporting bile acids from hepatocytes into bile canaliculi.[9,11] This is an ATP-dependent process and represents the rate-limiting step in bile salt secretion. BSEP is highly specific for bile acids and is tightly regulated to prevent intracellular accumulation and toxicity.[9,11] MRP2 also exports some conjugated bile salts (especially dianionic forms, such as glucuronidated or sulfated bile acids) into bile at the canalicular membrane.[9,10] As discussed above, MRP2 is not as specific for bile salts and is also responsible for primary conjugated bilirubin excretion as well as various substrates and drugs. MRP3 can transport some bile acids, specifically conjugated forms, out of hepatocytes into the blood, providing an alternative route for excretion when canalicular transport via MRP2 or BSEP is impaired.[12]

Dubin-Johnson syndrome

Epidemiology: DJS is a rare autosomal recessive disorder characterized by chronic predominantly conjugated hyper-

bilirubinemia.[1,13] The global prevalence is unknown. It has been most reported with high frequency among Iranian and Moroccan Israeli (Sephardic) Jews, with an estimated prevalence of 1 in 1,300 individuals in these populations.[3,12] It is less common in other ethnic groups, although cases have been reported in Japan and China as well as sporadically worldwide.[14,15] The disorder occurs in both genders equally but has an earlier onset in males. There are no clinically significant gender differences in the presentation, severity, or outcomes of DJS.[14–16] The disorder is rarely detected within the first decade of life.[17] Patients usually present in the second decade of life; however, males tend to manifest earlier.[16] The disease may occur at any age, sometimes as late as the sixth decade of life, and has been described to occur during pregnancy or on the administration of hormonal contraceptives.[18]

Pathophysiology: DJS is inherited in an autosomal recessive manner, resulting in the absence or functional deficiency of MRP2 usually due to homozygous or compound heterozygous mutations in the *ABCC2* gene on chromosome 10q24.[8] These mutations may include nonsense, missense, or deletion variants often affecting the domains critical for transporter function and maturation.[7,19,20]

These pathogenic variants in the *ABCC*2 gene result in loss or dysfunction of the canalicular transporter MRP2 (Fig. 1B).[3] Impaired MRP2 function leads to intrahepatocellular accumulation of bilirubin glucuronides, which are subsequently redirected across the sinusoidal membrane by efflux pumps, primarily MRP3.[4,21] This adaptive response facilitates the efflux of conjugated bilirubin and bile acid conjugates into the sinusoidal circulation, resulting in conjugated hyperbilirubinemia.[4,22]

Besides bilirubin transport, MRP2 also contributes to the canalicular excretion of conjugated bile salts. Consequently, MRP2 dysfunction leads to partial retention of bile salts within hepatocytes, which may increase intracellular bile acid concentrations, resulting in cholestasis. To mitigate potential hepatocellular toxicity, compensatory upregulation of MRP3 promotes basolateral bile salt efflux into the systemic circulation.[10,23] This mechanism helps prevent severe hepatocellular injury but can result in elevated serum bile salts in addition to conjugated bilirubin,[22] although clinically significant cholestasis is rare.[24]

DJS has been reported to be precipitated by stress, infection, pregnancy, oral contraceptives, or drugs.[25] During physiological stressors, there is often increased hemolysis or hepatocellular turnover, leading to increased bilirubin load. When MRP2 activity is deficient, the liver cannot increase canalicular excretion of conjugated bilirubin, resulting in jaundice.[26] In addition, increased estrogen levels, as occurs during pregnancy or with exogenous estrogens, can further impair hepatic excretory function by downregulating NTCP and OATP1B1/1B3, which are responsible for the sinusoidal uptake of bile acids and organic anions into hepatocytes.[10,27] Additionally, estrogens can reduce the expression of basolateral efflux transporters such as MRP3, which normally compensate for MRP2 deficiency by exporting conjugated bilirubin and bile acids back into the blood.[28] This results in a heightened susceptibility to cholestasis and more severe hyperbilirubinemia in individuals with DJS who have altered levels of stress, hormones, or active infection.

Although clinically significant cholestasis is rare in DJS, neonatal cholestasis is the most well-documented form of overt cholestasis in DJS. In neonates with DJS, immaturity of alternative hepatic transporters, such as MRP3, amplifies the functional consequences of MRP2 deficiency, resulting in clinically significant cholestasis and conjugated hyperbilirubinemia. With hepatic maturation, compensatory upregulation of transporters and the development of alternative excretory pathways mitigate these effects.[14,16,29]

In addition to bilirubin and bile acids, many drugs and medications are dependent on MRP2 for excretion. The loss of MRP2 function can affect their absorption, tissue distribution, and clearance. This increases the risk of drug accumulation, renal toxicity, and drug-drug interactions.[30] Heterozygous carriers of MRP2 mutants typically maintain normal serum bilirubin levels, although urinary excretion of coproporphyrin isomer I may be increased, reflecting subtle disturbances in metabolite handling and elimination.[31]

Clinical presentation: DJS typically presents most commonly in adolescence or early adulthood,[32] with intermittent episodes of self-limited jaundice and dark urine.[33] The frequency and duration of jaundice episodes demonstrate considerable variability among affected individuals. Most patients experience one to several episodes per year, although some may remain asymptomatic for years between recurrences.[33] More recent data from a multicenter genetic cohort study found that approximately 70% of genetically confirmed DJS patients exhibited recurrent jaundice, with recurrence intervals ranging from annually to once every few years.[34] Each episode typically lasts from several days to four weeks and resolves spontaneously without specific treatment (Table 1).[2,3,8,14–16,29,32,34–40]

Because DJS in adults does not typically cause clinically significant cholestasis, bile duct obstruction, or accumulation of bile acids, pruritus is not considered a symptom of this condition.[41] However, rare cases of overt cholestasis have been reported, particularly in neonates or in adults precipitated by stress, infection, pregnancy, oral contraceptives, or drugs.[25] Case series and reports have described infants presenting with prolonged jaundice, acholic stools, and elevated direct bilirubin, consistent with cholestasis.[14–16,42] Togawa *et al*. reported that all 10 neonates with DJS in their multicenter study exhibited cholestasis, with some showing acholic stools and elevated bile acids.[16] In another retrospective study reviewing a database of 533 cases of neonatal cholestasis, defined as jaundice with a conjugated bilirubin of >17 mg/dL, 28 of 533 cases (5.3%) were diagnosed with DJS.[43] Similarly, another study evaluated 101 patients referred for evaluation of jaundice with concomitant pregnancy or oral contraceptive use, of which 27 were found to have DJS: 18 were using oral contraceptives, and 9 were pregnant.[35] Despite these reports, the overall incidence of clinically apparent cholestasis remains exceedingly low. Most affected individuals exhibit a benign, non-progressive conjugated hyperbilirubinemia with preserved hepatic synthetic function.[44]

A distinctive but clinically silent feature is black pigmentation of the liver, which is usually discovered incidentally during surgery or imaging and does not cause symptoms.[45] Black pigmentation of the liver is thought to be secondary to defective secretion of epinephrine metabolites caused by MRP2 dysfunction. These metabolites undergo oxidation to form polymerized, melanin-like pigments that are insoluble, producing a dark brown to black liver on gross inspection. In one experimental study, normal rats and mutant rats with defective bile canalicular secretion were administered epinephrine. Mutant rats excreted only 0.19% of the administered dose in bile, compared with 2.80% in control rats over the same period. The livers of mutant rats became markedly dark, whereas the livers of normal rats maintained their typical color.[46]

Laboratory findings: The laboratory abnormalities found in DJS include elevation of conjugated and total bilirubin in the serum but normal aspartate aminotransferase (AST),

Table 1. Comparative clinical, biochemical, and genetic features of Dubin-Johnson and Rotor syndromes

	Dubin-Johnson syndrome	Rotor syndrome
Inheritance	Autosomal recessive due to pathogenic variants in *ABCC2* (encodes MRP2/cMOAT transporter)[2,3]	Autosomal recessive digenic disorder requiring biallelic pathogenic variants in *SLCO1B1* and *SLCO1B3* (encode OATP1B1 and OATP1B3 transporters)[3]
Mechanism	Loss or dysfunction of MRP2 on the canalicular (apical) membrane leads to impaired canalicular excretion[2,3]	Loss of OATP1B1/OATP1B3 on the sinusoidal (basolateral) membrane leads to impaired hepatic uptake/reuptake from blood[3]
Bilirubin levels	Mean serum bilirubin: ~2-5 mg/dL with conjugated bilirubin >50%[32] (rarely as high as 10-20 mg/dL in adults)[15,16]	Mean serum bilirubin: ~2-5 mg/dL with conjugated bilirubin >50%[32]
Neonatal cholestasis	Documented: neonatal cholestasis occurs rarely (thought to be due to decreased BSEP and possibly other bile acid transporter activity in neonatal liver); spontaneous resolution with neonatal maturation[14,16,29]	Not reported: no neonatal or adult cholestasis[38]
Pregnancy & hormonal effects	Worsening of jaundice and risk of cholestasis during pregnancy or with oral contraceptives; estrogens can downregulate transporters and reduce compensatory MRP3 expression[35]	Not associated with pregnancy-induced cholestasis; bilirubin levels tend to be stable and not exacerbated by pregnancy/ estrogens in reported cases[38]
Uroporphobilinogen levels	Total urinary coproporphyrin output is normal but the fraction due to coproporphyrin I is markedly increased (80–90% of total)[36]	Total urinary coproporphyrin output is increased (2.5-5x normal) with coproporphyrin I fraction comprises about 65% of total[3,32,40]
Drug-induced jaundice	Defective MRP2 impairs excretion of conjugated bilirubin and certain drugs into bile; can also lead to mild increases in drug-induced jaundice but clinically significant drug toxicity is uncommon[3,8]	Defective OATP1B1 and OATP1B3 transporters impairs hepatic uptake; substantially increased risk of drug toxicity and drug-induced jaundice, especially for medications that rely on these transporters for hepatic clearance[3,8]
Hepatobiliary scintigraphy	Hepatobiliary scintigraphy using 99mTc-HIDA, 99mTc-DISIDA, or 99mTc-mebrofenin can show characteristically delayed uptake of the radiotracer, with visualization of the liver parenchyma and extremely poor elimination, resulting in persistent hepatic enhancement[37–39]	Due to OATP1B1 and OATP1B3 deficiency, impaired hepatic uptake of technetium-labeled radiotracers can result in minimal or absent visualization of the liver parenchyma with prominent renal excretion of the tracer[37–39]
Gross liver appearance	The liver is characteristically black due to pigment deposition[32]	Liver appears normal[32]

The table contrasts their inheritance patterns, biochemical profiles, diagnostic workup, imaging findings, hormonal influences, and distinguishing histopathologic features to aid in clinical differentiation. ABCC2, ATP-binding cassette subfamily C member 2; MRP2, multidrug resistance–associated protein 2; cMOAT, canalicular multispecific organic anion transporter; SLCO1B1, solute carrier organic anion transporter family member 1B1; SLCO1B3, solute carrier organic anion transporter family member 1B3; OATP1B1, organic anion transporting polypeptide 1B1; OATP1B3, organic anion transporting polypeptide 1B3; BSEP, bile salt export pump; MRP3, multidrug resistance–associated protein 3; 99mTc-HIDA, technetium-99m–labeled hepatobiliary iminodiacetic acid; 99mTc-DISIDA, technetium-99m–labeled diisopropyl iminodiacetic acid; 99mTc-mebrofenin, technetium-99m–labeled mebrofenin.

alanine aminotransferase (ALT), alkaline phosphatase (ALP), and γ-glutamyltransferase (GGT) levels.[47] Albumin levels and prothrombin time are typically normal.[18] Total bilirubin typically ranges from 2–5 mg/dL, with conjugated bilirubin constituting more than 50% of the total.[32] Levels of conjugated (direct) bilirubin in patients with DJS have been as high as 10–20 mg/dL, with rare cases in neonates reaching up to 30 mg/dL.[15,16]

A classic diagnostic feature is the urinary coproporphyrin isomer pattern: patients with DJS typically have normal total urine coproporphyrin levels, but markedly increased coproporphyrin I isomer levels, constituting over 80% of total urinary coproporphyrins. This is in contrast to the normal predominance of coproporphyrin III in urine.[36] In normal individuals, 75% of coproporphyrins are excreted via bile, and 25% are excreted in urine. Coproporphyrin III is preferentially excreted into urine, while coproporphyrin I is mainly secreted into bile.[3] The MRP2 transporter is responsible for the biliary excretion of coproporphyrin I. In DJS, dysfunctional or deficient MRP2 transporters result in decreased excretion into bile and increased quantities of coproporphyrin I excreted in the urine.[48] This finding is highly specific and can help distinguish DJS from other causes of conjugated hyperbilirubinemia.

Patients with DJS have impaired hepatobiliary excretion of certain drugs and drug metabolites that are substrates of the MRP2 transporter. This defect can lead to altered pharmacokinetics, including increased plasma levels and prolonged half-life of drugs and metabolites that rely on MRP2 for biliary excretion, such as some antibiotics, chemotherapeutics, and other organic anions (Table 2).[3,8,33,49]

Imaging: Abdominal ultrasound, CT, and MRI imaging are not recommended as diagnostic tools for DJS but may be helpful in excluding biliary ductal disease. Hepatobiliary scintigraphy (cholescintigraphy) using technetium-labeled radiotracers such as 99mTc-HIDA, 99mTc-DISIDA, or 99mTc-mebrofenin can show characteristically delayed uptake of the radiotracer and visualization of the liver parenchyma with ex-

Table 2. Drugs and pharmacologic classes affected by transporter deficiencies in Dubin-Johnson and Rotor syndromes

Dubin-Johnson syndrome	Rotor syndrome
Chemotherapeutics: Methotrexate, tamoxifen, docetaxel, vinblastine, vincristine, paclitaxel, cisplatin, doxorubicin, etoposide, irinotecan[3,8]	Chemotherapeutics: Cisplatin, flavopiridol, methotrexate, oxaliplatin, paclitaxel, vincristine[49]
Antiepileptic drugs: Carbamazepine, valproic acid[3]	Antidiabetic: Troglitazone sulfate, repaglinide[3,49]
Antibiotics: Ampicillin, amoxicillin, azithromycin, cephalosporins, erythromycin, moxifloxacin, rifampin[3,8]	Antibiotics: Benzylpenicillin, cefazolin, erythromycin, nafcillin, rifampicin[3,49]
NSAIDs: Salicylates, ibuprofen, naproxen[3]	Antiarrhythmics: Digoxin[49]
HIV: Tenofovir, indinavir, ritonavir, saquinavir[3,8]	HIV: Tenofovir (OATP1B1 substrate)[3]
Antihypertensives: Olmesartan, valsartan, telmisartan, fosinopril[8]	Antihypertensives: Atrasentan, bosetan, enalapril, olmesartan, temocapril, telmisartan, valsartan[49]
3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors: Simvastatin, pravastatin, pitavastatin, fluvastatin, atorvastatin, lovastatin and rosuvastatin[8,49]	3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors: Pravastatin (OATP1B1 and OATP1B3 substrate), simvastatin (OATP1B1 substrate), atorvastatin (OATP1B1 substrate)[33,49]
Analgesics: Acetaminophen, morphine[49]	Tyrosine kinase inhibitors: Sorafenib, regorafenib[49]

Dubin-Johnson syndrome results from loss of the canalicular efflux transporter MRP2 (*ABCC2* gene defect), leading to impaired biliary excretion of conjugated drug metabolites such as glucuronides, sulfates, and glutathione conjugates, which can increase systemic exposure or hepatic accumulation. Rotor syndrome is caused by deficiency of the hepatic uptake transporters OATP1B1 and OATP1B3 (encoded by the *SLCO1B1/SLCO1B3* genes), resulting in reduced hepatocellular uptake and altered clearance of many anionic drugs that are substrates of one or both of these transporters. NSAIDs, nonsteroidal anti-inflammatory drugs; HIV, human immunodeficiency virus; HMG-CoA, 3-hydroxy-3-methylglutaryl–coenzyme A; OATP1B1, organic anion transporting polypeptide 1B1; OATP1B3, organic anion transporting polypeptide 1B3.

tremely poor elimination.[37–39]

Histopathology: Liver biopsy is not needed in the vast majority of cases. If liver biopsy is performed, the hallmark histopathological feature is accumulation of coarse brown-black granules typically seen on hematoxylin and eosin staining, predominantly within the cytoplasm of centrilobular (zone 3) hepatocytes, sparing the periportal areas.[3,50] The pigment consists of polymers of epinephrine metabolites, which accumulate due to defective excretion of organic anions. Special stains (e.g., Fontana-Masson) may be positive, but the pigment is resistant to bleaching and does not stain for iron, distinguishing it from hemosiderin and other pigments.[51,52] Although this pigment accumulation is histologically and macroscopically evident, it does not result in hepatocellular injury, liver dysfunction, or systemic catecholamine toxicity.[3,47]

On electron microscopy, membrane-bound, electron-dense lysosomal granules are observed within hepatocytes, especially near the biliary pole, corresponding to the pigment seen on light microscopy. Additional ultrastructural changes may rarely include dilated granular endoplasmic reticulum, paracrystalline mitochondrial inclusions, and dilation of bile canaliculi, which is a result of impaired excretion of conjugated bilirubin and other organic anions from hepatocytes into the bile canaliculi. This leads to accumulation and impaired flow of these substances within the hepatocyte and canalicular lumen, causing distension and dilation.[51,53] Kupffer cells may also show increased phagocytic activity and contain similar pigment deposits.[51]

Clinical course: DJS in adults follows a benign, non-progressive clinical course.[3] Most adults remain asymptomatic aside from jaundice.[3,32] In adults with DJS, the intensity and frequency of jaundice are stable over time. Long-term follow-up studies and case reports consistently show that hyperbilirubinemia remains unchanged, and jaundice does not worsen with age or disease duration.[3,54] Females with DJS remain at risk for recurrent jaundice and cholestasis during pregnancy and oral contraceptive use.[10,27]

Management: The management of DJS is supportive and does not require specific therapy. Patient education and reassurance regarding the excellent prognosis are central to management.[3,32]

Medication regimens should be reviewed and adjusted to avoid drugs known to cause toxicity or result in increased serum levels in DJS.[55,56] This is especially relevant during periods of physiological stress or when new medications are introduced.

While classic clinical features and non-invasive tests such as urine coproporphyrin analysis are supportive of a diagnosis of DJS, genetic testing is recommended for confirmation, particularly in cases with early onset, atypical presentation, or diagnostic uncertainty.[15,34] Genetic testing also aids in expanding the known mutation spectrum and guides family counseling regarding inheritance and prognosis.[15,16]

RS

Epidemiology: RS is a rare disorder inherited in an autosomal recessive digenic manner, requiring biallelic pathogenic variants in both *SLCO1B1/1B3* genes.[1,57] It is more likely to occur in offspring of consanguineous couples and is characterized by mild, predominantly conjugated and unconjugated hyperbilirubinemia.[38] The prevalence is extremely low, estimated to be less than 1 per 1,000,000 individuals globally. Most descriptions appear in the literature as sporadic case reports.[38] Certain pathogenic variants have a much higher carrier frequency in East Asian populations. For example, the carrier frequency of one variant was reported to be approximately 10.1% in East Asians and up to 18.5% in Southern Han Chinese but was almost absent in other populations.[58] This population-specific genetic predisposition has led to a higher number of reported cases in East Asia, including Japan, China, and Taiwan.[58–60]

Pathophysiology: RS is caused by complete deficiency of the hepatic transporters OATP1B1/B3 encoded by the *SLCO1B1/B*3 genes, respectively.[57] These transporters are located on the basolateral membrane of downstream hepatocytes and are responsible for the reuptake of conjugated bilirubin and other organic anions, including bile acids, coproporphyrins, steroids, thyroid hormones, and numerous

drugs and toxins from the blood and transport into the liver.[2,5] These defects result in accumulation of conjugated and unconjugated bilirubin and organic anions in the blood. The result is a predominantly conjugated hyperbilirubinemia,[5,6] and elevated conjugated bile acids, as the defect affects the hepatic reuptake of conjugated but not unconjugated bile acids, which are not substrates for OATP1B1/1B3 (Fig. 1C).[6,8]

Unlike DJS, cholestasis does not occur in RS because the canalicular excretion pathway for conjugated bilirubin into bile via MRP2 remains intact. Thus, bile flow and excretion of bilirubin into the intestine are normal, and there is no intrahepatic retention or impaired bile flow, which are the hallmarks of cholestasis.[5] Additionally, the kidney excretes the excess conjugated bilirubin from the serum, leading to an increased amount of urinary coproporphyrin excretion (as discussed below), with dark urine as a result.[39]

Clinical presentation: The clinical presentation of RS is mild, non-hemolytic, predominantly conjugated hyperbilirubinemia, most often manifesting as intermittent jaundice and dark urine,[38] in the absence of pruritus, with otherwise normal physical examination.[3,61] The jaundice is often subtle, and conjunctival icterus may be the only visible manifestation in some individuals. Physical examination is otherwise unremarkable, with no evidence of hepatomegaly, splenomegaly, or other stigmata of chronic liver disease. Unlike DJS, symptoms are not episodic, are not triggered by stressors, and do not change with time or age.[40] There is no pigmentation of the liver (Table 1).[40]

Laboratory findings: The primary laboratory abnormality seen in RS is total bilirubin, typically ranging from 2–5 mg/dL, with conjugated bilirubin constituting more than 50% of the total.[8,32,38] ALT, AST, ALP, and GGT are within normal limits.[8,32,38] There is no evidence of hemolysis, and red blood cell indices are normal.[38]

Bilirubinuria is present due to the renal excretion of conjugated bilirubin.[38] A hallmark of RS is increased total urinary coproporphyrin excretion with a predominance of coproporphyrin isomer I. Total urinary coproporphyrin excretion is elevated 2.5–5 times above normal, and the isomer I fraction is consistently around 65% of the total, compared to normal controls (about 25%) and DJS (about 85–90%).[3,32,40,62] Unlike DJS, RS results in increased total urinary coproporphyrin excretion because of the simultaneous absence of OATP1B1 and OATP1B3, which are responsible for the sinusoidal uptake of conjugated bilirubin and coproporphyrins from the blood into hepatocytes.[39] Conjugated bilirubin and coproporphyrins remain in the circulation and are excreted in urine at higher levels.[3,5,47,63] Recent studies have also identified glucuronidated bile acidemia as a laboratory feature, with substantial accumulation of bile acids glucuronidated at the C-3 position, further reflecting the defective OATP1B1/1B3-mediated hepatic reuptake pathway.[6] However, total bile acid levels are not elevated, and cholestasis is not present.[38]

There is evidence that genetic variability or absence of OATP1B1/1B3 function, as seen in RS, can substantially increase plasma concentrations of drugs including statins, ezetimibe, angiotensin II receptor blockers, methotrexate, mycophenolic acid, cyclosporin A, rifampicin, thiazolidinediones, glinides, antiretrovirals, antihistamines, and several anticancer agents (Table 2).[3,49]

Imaging: Hepatobiliary scintigraphy (cholescintigraphy) using technetium-labeled radiotracers such as 99mTc-HIDA, 99mTc-DISIDA, or 99mTc-mebrofenin can show characteristically delayed or poor hepatic uptake of the radiotracer, resulting in minimal or absent visualization of the liver parenchyma, with persistent visualization of the cardiac blood pool and prominent renal excretion of the tracer.[37–39] This pattern reflects the impaired hepatic uptake of anionic compounds due to OATP1B1/1B3 deficiency. This is distinctly different from DJS, where hepatic uptake is preserved but excretion is impaired.[37–39]

CT abdominal and ultrasound are not necessary, as findings in RS are normal. They can help rule out structural abnormalities of the liver and biliary tree.[38]

Histopathology: Liver biopsy is not required to make the diagnosis, as the histopathological findings in RS are normal liver architecture without pigment deposition or other abnormalities.[38]

Clinical course: The clinical course of RS is benign and non-progressive, with only mild fluctuations, and is not associated with episodic exacerbations, unlike DJS.[3,38] Unlike DJS, where bilirubin excretion can be decreased by pregnancy, estrogens, or stress, RS maintains a consistent level of impaired uptake, leading to stable bilirubin levels.[38] There have been no reports of cholestasis in infants or during pregnancy.[38] The condition does not impact life expectancy or quality of life.[5,38,64]

Management: No treatment is required for RS. The clinical course is benign, and patients do not develop liver dysfunction or complications.[3,32] No dietary restrictions, lifestyle modifications, or invasive procedures are indicated for RS.[3]

Molecular genetic testing for RS involves targeted analysis for biallelic pathogenic variants in the *SLCO1B1*/*SLCO1B3* genes. The most widely used methods are next-generation sequencing panels, whole-exome sequencing, and confirmatory Sanger sequencing to detect point mutations, small insertions/deletions, and population-specific structural variants such as LINE-1 retrotransposon insertions in *SLCO1B3*.[59,65] When both parents are heterozygous for *SLCO1B1*/*SLCO1B3* pathogenic variants on the same chromosome, each sibling has a 25% risk of inheriting biallelic variants in both genes and manifesting RS, a 50% risk of being an asymptomatic carrier, and a 25% likelihood of being unaffected and non-carrier. Carriers, defined as individuals harboring only one of the three pathogenic variants, remain asymptomatic and are not at risk of developing disease. Once the causative variants are established in a proband, carrier testing of at-risk relatives and options for prenatal or preimplantation genetic testing become available.[38]

A key consideration in clinical management is the avoidance of drugs that are substrates for OATP1B1/1B3, as deficiency of these hepatic transporters can lead to elevated serum levels and increased risk of toxicity for certain medications.[3,5,66]

Conclusions

RS and DJS are benign genetic causes of conjugated hyperbilirubinemia due to defects in hepatocellular transport of conjugated bilirubin and organic anions. DJS arises from MRP2 mutations that impair canalicular efflux of bilirubin glucuronides, producing conjugated hyperbilirubinemia. RS results from reduction or loss of function of the sinusoidal uptake transporters OATP1B1 and OATP1B3, leading to impaired hepatic clearance of conjugated bilirubin and increased urinary coproporphyrin excretion. In adults, both disorders follow a benign course, with fluctuating jaundice, preserved hepatic function, and no risk of progression to chronic liver disease. In DJS, some newborns have been reported to develop cholestasis, which was self-limited and resolved spontaneously with hepatic maturity. Importantly, impaired transporter activity may influence drug disposition, underscoring the need for clinical awareness to prevent misdiagnosis and to anticipate drug–disease interactions.

Extensive liver testing, biopsy, and genetic analysis are typically unnecessary and should be reserved for atypical cases or diagnostic uncertainty. Management requires no specific therapy. Reassurance of benign outcomes is important, and genetic counseling may be appropriate for families with confirmed mutations or when there is concern for inheritance.

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Conflict of interest

GYW has been an Editor-in-Chief of *Journal of Clinical and Translational Hepatology* since 2013. He has no role in the publisher's decisions regarding this manuscript. GYW and BT have no other conflicts of interest related to this publication.

Author contributions

Review concept (GYW), information collection, drafting of the manuscript (BT), and revision of the manuscript (GYW, BT). All authors have approved the final version and publication of the manuscript.

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