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# Rotor Syndrome

## Synonym: Rotor-Type Hyperbilirubinemia

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# Summary

## Clinical characteristics

Rotor syndrome is characterized by mild conjugated and unconjugated hyperbilirubinemia that usually begins shortly after birth or in childhood. Jaundice may be intermittent. Conjunctival icterus may be the only clinical manifestation.

## Diagnosis/testing

The diagnosis of Rotor syndrome is established in a proband with isolated, predominantly conjugated hyperbilirubinemia without cholestasis or liver injury and typical findings on cholescintigraphy. Identification of biallelic pathogenic variants in *SLCO1B1* and *SLCO1B3* on molecular genetic testing can confirm the diagnosis when cholescintigraphy is either not available or not recommended due to risks associated with the procedure.

## Management

*Treatment of manifestations:* No treatment required.

*Agents/circumstances to avoid:* Although no adverse drug effects have been documented in persons with Rotor syndrome, the absence of the hepatic proteins OATP1B1 and OATP1B3 may have serious consequences for liver uptake – and thus for the toxicity of numerous commonly used drugs and/or their metabolites.

*Other:* Because most individuals with Rotor syndrome are born to consanguineous couples, the diagnosis of Rotor syndrome may coincidentally identify such consanguinity. In some centers, this may be an indication for clinical genetics consultation and/or genetic counseling.

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## Genetic counseling

Rotor syndrome is inherited in an autosomal recessive digenic manner. The parents of an affected child are obligate heterozygotes for a pathogenic variant in *SLCO1B1* and a pathogenic variant in *SLCO1B3* or obligate heterozygotes for a large deletion affecting the coding regions of both *SLCO1B1* and *SLCO1B3*. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier of at least one pathogenic variant, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk relatives and prenatal and preimplantation genetic testing are possible if the pathogenic variants have been identified in an affected family member.

# Diagnosis

## Suggestive Findings

Rotor syndrome **should be suspected** in individuals with the following clinical and laboratory features.

**Clinical features**

- Mild jaundice (may be intermittent)
- Conjunctival icterus (in some affected individuals)
- Otherwise normal physical examination

**Laboratory features** (see Table 1)

- Conjugated hyperbilirubinemia with serum total bilirubin concentration is usually between 2 and 5 mg/dL but can be higher. Conjugated bilirubin usually exceeds 50% of total bilirubin.
- Presence of bilirubin in the urine
- Absence of hemolysis*
- Normal serum ALT, AST, ALP, and γ-GT activity*
- Cholescintigraphy
- Total urinary porphyrins: elevated coproporphyrin

* Tests for hemolysis and measurement of ALT, AST, ALP, and γ-GT activity are needed to evaluate for hemolytic anemia and hepatobiliary diseases that are considered in the differential diagnosis of Rotor syndrome.

Note: The liver is histologically normal in persons with Rotor syndrome; therefore, suspicion of hereditary jaundice is not an indication for liver biopsy.

Tests not generally available:

- Urinary porphyrin fractionation
- Immunohistologic study for OATP1B1 and OATP1B3 in archival liver biopsy specimen

**Table 1.** Laboratory Findings in Rotor Syndrome

| Finding | | Rotor Syndrome | Normal |
|---|---|---|---|
| **Serum bilirubin** | **Total** | 2-5 mg/dL [1] | 0.3-1.0 mg/dL [2] |
| | **Conjugated: total** | >50% | <20% |
| **Urine** | **Bilirubin** | Present | Not detected |
| | **Coproporphyrins** | ↑ 2.5-5x normal [3] | |
| **Hemolysis** | | None | None |
| **Disappearance of plasma anionic compounds [4]** | | Delayed | Rapid |

*Table 1. continued from previous page.*

| Finding | | Rotor Syndrome | Normal |
|---|---|---|---|
| **Cholescintigraphy** | | See footnote 5 | Normal |
| **Liver** | **Enzymes** | Normal | Normal |
| | **Appearance** | Normal | Normal |
| | **Histology** | Normal [6] | Normal |
| | **Protein expression** | Absence of OATP1B1 & OATP1B3 [7] | Normal |

*1.* Rarely may be up to 5-10 mg/dL [Author, personal observation] or up to 20 mg/dL [Chowdhury et al 2001]
*2.* For total and direct bilirubin in persons older than age one year. Note: Although normal levels of total and direct bilirubin may be higher in the neonatal period and infancy, Rotor syndrome is not usually diagnosed in this age group.
*3.* Coproporphyrinuria is frequently observed in those with parenchymal liver diseases, and thus is not specific to Rotor syndrome.
*4.* Includes bromosulfophthalein and indocyanin green
*5.* Radiotracers ($^{99m}$Tc-HIDA/$^{99m}$Tc-N [2,6-dimethylphenyl-carbamoylmethyl] iminodiacetic acid, $^{99m}$Tc-DISIDA/disofenin, $^{99m}$Tc-BrIDA/mebrofenin) are taken up slowly by the liver and the liver is scarcely visualized; however, there is persistent visualization of the cardiac blood pool and prominent excretion by the kidneys.
*6.* Note that suspicion of hereditary jaundice is not an indication for liver biopsy.
*7.* Immunohistologic staining does not detect OATP1B1 and OATP1B3 at the sinusoidal membrane of hepatocytes. Note: Expression of MRP2, frequently absent in Dubin-Johnson syndrome (see Differential Diagnosis), is normal [Hrebícek et al 2007].

## Establishing the Diagnosis

The diagnosis of Rotor syndrome **is established** in a proband with isolated, predominantly conjugated hyperbilirubinemia without cholestasis or liver injury and typical findings on cholescintigraphy (Table 1). Identification of biallelic pathogenic variants in *SLCO1B1* and *SLCO1B3* on molecular genetic testing can confirm the diagnosis when cholescintigraphy is either not available or not recommended due to risks associated with the procedure (see Table 2).

Molecular genetic testing approaches can include a combination of **concurrent gene testing** and **multigene panel**:

- **Concurrent gene testing.** Sequence analysis of *SLCO1B1* and *SLCO1B3* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If biallelic pathogenic variants in *SLCO1B1* and *SLCO1B3* are not found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.
- **A multigene panel** that includes *SLCO1B1*, *SLCO1B3*, and other genes of interest (see Differential Diagnosis) can be considered to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 2).

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

**Table 2.** Molecular Genetic Testing Used in Rotor Syndrome

| Gene [1, 2] | Proportion of Rotor Syndrome Attributed to Pathogenic Variants in Gene | Proportion of Pathogenic Variants [3] Detectable by Test Method | |
|---|---|---|---|
| | | Sequence analysis [4] | Gene-targeted deletion/ duplication analysis [5] |
| *SLCO1B1* | 100% [6] | ~75% [7, 8] | ~25% [7] |
| *SLCO1B3* | | ~50% [7, 8] | ~50% [7] |

*1.* Genes are listed in alphabetic order.
*2.* See Table A. Genes and Databases for chromosome locus and protein.
*3.* See Molecular Genetics for information on allelic variants detected in this gene.
*4.* Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
*5.* Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
*6.* The Rotor syndrome locus comprises both *SLCO1B1* and *SLCO1B3*, which lie very close together on the same chromosome. All individuals with Rotor syndrome who have undergone molecular testing have had biallelic inactivating pathogenic variants in both *SLCO1B1* and *SLCO1B3* [van de Steeg et al 2012].
*7.* A biallelic whole-gene deletion spanning both *SLCO1B1* and *SLCO1B3* was present in four families. A biallelic nonsense variant in *SLCO1B1* and a biallelic deletion of exon 12 in *SLCO1B3* were present in three families. A nonsense variant in *SLCO1B1* and a biallelic splice site variant in *SLCO1B3* were present in one family [van de Steeg et al 2012].
*8.* Of the seven individuals reported by Kagawa et al [2015] with biallelic *SLC01B1* and *SLC01B3* pathogenic variants, six individuals of Japanese ancestry were homozygous for an insertion of a ~6.1-kb L1 retrotransposon in intron 5 of *SLCO1B1* resulting in aberrant splicing. The L1 retrotransposon insertion is not detected by routine sequence analysis but can be detected by allele-specific PCR designed to amplify and sequence the insertion breakpoint.

# Clinical Characteristics

## Clinical Description

The only clinical feature of Rotor syndrome is mild jaundice due to conjugated and unconjugated hyperbilirubinemia that usually begins shortly after birth or in childhood.

Jaundice may be intermittent. Conjunctival icterus may be the only clinical manifestation.

## Genotype-Phenotype Correlations

Hyperbilirubinemia develops only in persons with biallelic inactivating pathogenic variants in both *SLCO1B1* and *SLCO1B3* [van de Steeg et al 2012]. Presence of at least one wild type (functional) allele of either *SLCO1B1* or *SLCO1B3* prevents Rotor-type hyperbilirubinemia.

A combination of a mild variant in one allele of either *SLCO1B1* or *SLCO1B3* with deleterious variants affecting the remaining three alleles has not been documented.

## Prevalence

The prevalence of Rotor syndrome is unknown but is very low (<1:1,000,000).

No information is available regarding specific populations in which the prevalence may be greater or lower than expected.

## Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with mutation of *SLCO1B1* or *SLCO1B3*.

Of note, sequence variants that predict an amino acid change in *SLCO1B1* or *SLCO1B3* resulting in reduced activity of the encoded transporters have been associated with altered sensitivity to some drugs.

## Differential Diagnosis

Inherited disorders of bilirubin clearance can present with either conjugated or unconjugated hyperbilirubinemia. Dubin-Johnson syndrome, a benign conjugated hyperbilirubinemia similar to Rotor syndrome, is caused by decreased secretion of conjugated bilirubin into bile. Defects in bilirubin conjugation resulting in increased levels of unconjugated bilirubin are represented by:

- Gilbert syndrome, which is benign and common;
- Crigler-Najjar syndrome type II, which is benign and rare; and
- Crigler-Najjar syndrome type I, a rare, severe, life-threatening disease associated with kernicterus typically manifesting within the first days after birth.

Since Rotor syndrome is usually diagnosed after the neonatal period, only benign forms of hereditary jaundice are included in the differential diagnosis.

**Dubin-Johnson syndrome** (DJS) (OMIM 237500), an autosomal recessive disorder of secretion of conjugated bilirubin into bile, is more common than Rotor syndrome. The findings in DJS are summarized in Table 3. In addition to jaundice, abdominal pain and hepatomegaly may be present in some persons with DJS – although, like Rotor syndrome, DJS is typically benign. DJS is caused by pathogenic variants in *ABCC2*.

**Table 3.** Comparison of Findings in Dubin-Johnson Syndrome and Rotor Syndrome

| Finding | | Rotor Syndrome | Dubin-Johnson Syndrome | Normal |
|---|---|---|---|---|
| **Serum bilirubin** | **Total** | 2-5 mg/dL [1] | 2-5 mg/dL [2] | 0.3-1.0 mg/dL [3] |
| | **Conjugated: total** | >50% | >50% | <20% |
| **Urine** | **Bilirubin** | Present; urine may be dark | Present; urine may be dark | Not detected |
| | **Porphyrins** | Total porphyrin output ↑; coproporphyrin ↑2.5-5x normal | Total porphyrin output normal [4] | <200 µg/24h [5] |
| **Hemolysis** | | None | None | None |
| **Disappearance of plasma anionic compounds [6]** | | Severely delayed | Delayed | Rapid |
| **Cholescintigraphy** | | See footnote 7 | See footnote 8 | Normal |

*Table 3. continued from previous page.*

| Finding | | Rotor Syndrome | Dubin-Johnson Syndrome | Normal |
|---|---|---|---|---|
| **Liver** | **Enzymes** [9] | Normal | Normal | Normal |
| | **Appearance** | Normal | Dark [10] | Normal |
| | **Histology** | Normal | See footnote 11 | Normal |
| | **Protein expression** | Absence of OATP1B1, OATP1B3 [12, 13] | Absence of MRP2 [14, 15] | Normal |

*1.* Rarely may be up to 5-10 mg/dL [Author, personal observation] or up to 20 mg/dL [Chowdhury et al 2001]
*2.* May be higher
*3.* For total and direct bilirubin in persons older than age one year. Note: Although normal levels of total and direct bilirubin may be higher in the neonatal period and infancy, Rotor syndrome is not usually diagnosed in this age group.
*4.* Total urinary porphyrin output is normal; however, predominance of coproporphyrin isomer I among urinary porphyrin species is observed on chromatography.
*5.* Total urinary porphyrin output
*6.* Includes bromosulfophthalein (BSP), indocyanin green, and cholescintigraphy radiotracers (99mTc-HIDA/99mTc-N [2,6-dimethylphenyl-carbamoylmethyl] iminodiacetic acid, $^{99m}$Tc-DISIDA/disofenin, $^{99m}$Tc- BrIDA/mebrofenin). Note: In Dubin-Johnson syndrome, BSP conjugates reappear in the blood after administration of unconjugated BSP; this is not the case in Rotor syndrome.
*7.* Scarcely visualized on cholescintigraphy, with slow liver uptake, persistent visualization of the cardiac blood pool, and prominent kidney excretion
*8.* Visualization of the liver is normal or somewhat delayed but filling of the gallbladder is absent or delayed.
*9.* Serum ALT, AST, ALP, and γ-GT activity
*10.* The liver is macroscopically dark (sometimes black).
*11.* Liver histopathologic findings are characterized by accumulation of dark melanin-like pigment in lysosomes of hepatocytes. The pigment is PAS- and Masson-Fontana-reactive; however, in contrast to melanin it does not reduce neutral silver ammonium solution. Autofluorescence is another characteristic feature of the pigment. The pigment may be almost absent in infancy and in persons recovering from acute liver injury. Liver architecture is otherwise normal.
*12.* Immunohistologic staining does not detect OATP1B1 and OATP1B3 at the sinusoidal membrane of hepatocytes. Note: Expression of MRP2, which is typically absent in Dubin-Johnson syndrome, is normal [Hrebícek et al 2007].
*13.* Expression of MRP2 in Rotor syndrome is unremarkable [Hrebícek et al 2007].
*14.* Absence of multidrug resistance-associated protein 2 (MRP2) from the canalicular membrane of hepatocytes, observed in most but not all cases of DJS, is the consequence of pathogenic variants in *ABCC2*. *ABCC2* encodes MRP2, which serves as the canalicular export pump for conjugated bilirubin and numerous other anionic compounds.
*15.* The older name of MRP2 (OMIM 601107) is cMOAT – *c*analicular *m*ultispecific *o*rganic *a*nion *t*ransporter. Immunohistologic detection of MRP2 can be performed in archival paraffin-embedded liver specimens.

**Gilbert syndrome** (OMIM 143500) is an autosomal recessive disorder of bilirubin metabolism caused by pathogenic variants in *UGT1A1* that decrease the rate of bilirubin conjugation catalyzed by UGT1A1. The variants include the promoter TATA repeat variation A(TA)$_7$TAA (normal A(TA)$_6$TAA), which is often combined with the promoter SNP c.-3279T>G), or missense variants in the coding region of *UGT1A1*, which are frequent in the Japanese population but rare in Europeans.

Hyperbilirubinemia <6 mg/dL is predominantly unconjugated, with conjugated bilirubin less than 20% of total serum bilirubin. Gilbert syndrome is the most frequently occurring form of hereditary jaundice, affecting about 5%-10% of all Europeans.

**Crigler-Najjar syndrome type II** (or Arias syndrome) (OMIM 606785) is an autosomal recessive benign disorder similar to Gilbert syndrome, caused by pathogenic variants in the coding region of *UGT1A1* and characterized by predominantly unconjugated hyperbilirubinemia ranging from 6 to 20 mg/dL.

Gilbert syndrome and Crigler-Najjar syndrome type II represent two phenotypes caused by pathogenic variants with quantitatively different consequences on the UGT1A1 enzyme activity. Since plasma bilirubin level is not stable, the two phenotypes may overlap in the same individuals. However, unconjugated hyperbilirubinemia

associated with homozygous A(TA)$_7$TAA genotype but no pathogenic variants in the coding regions of *UGT1A1* should always be diagnosed as Gilbert syndrome.

See Hyperbilirubinemia: OMIM Phenotypic Series to view genes associated with this phenotype in OMIM.

**Cholestatic liver diseases** and/or **bile duct obstruction** should be suspected whenever hyperbilirubinemia is accompanied by clinical signs other than jaundice and by elevation of serum activity of ALT, AST, ALP, or γ-GT. The same holds true for any abnormal findings in the gallbladder and the biliary tree obtained by imaging and/or endoscopy techniques.

**Hemolytic jaundice** is characterized by predominantly unconjugated hyperbilirubinemia and signs of increased hemolysis.

# Management

## Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with Rotor syndrome, the evaluations summarized in this section (if not performed as part of the evaluation that led to the diagnosis) are recommended:

In most cases an individual diagnosed with Rotor syndrome is the child of a consanguineous couple. Thus, the diagnosis of Rotor syndrome may coincidentally identify such consanguinity. In some centers, this may be an indication for clinical genetics consultation and/or genetic counseling.

## Treatment of Manifestations

No treatment is required.

## Agents/Circumstances to Avoid

No adverse drug effects have been documented in Rotor syndrome; however, the absence of the hepatic proteins OATP1B1 and OATP1B3 may have serious consequences for liver uptake and toxicity of numerous commonly used drugs and/or their metabolites, which enter the liver via either of the two OATP1B transporters.

A list of drugs that enter the liver mainly via OATP1B1 and whose pharmacokinetics are known to be influenced by genetic variability in *SLCO1B1* has been published [Niemi et al 2011]. Some of these drugs are also taken up by OATP1B3 [Shitara 2011].

- Statins – simvastatin, atorvastatin, pravastatin, pitavastatin, rosuvastatin
- Ezetimibe
- Anticancer drugs – methotrexate and irinotecan
- Sartans – olmesartan and valsartan
- Rifampicin
- Mycophenolic acid
- Torsemide
- Thiazolidine diones – pioglitazone and rosiglitazone
- Glinides – nateglinide and repaglinide
- Lopinavir
- Fexofenadine
- Cyclosporin A

## Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

## Pregnancy Management

No special pregnancy management issues from the perspective of either an affected mother or an affected fetus are known.

Of note, during pregnancy the hyperbilirubinemia of Rotor syndrome may complicate the diagnosis and management of liver disease related to pregnancy (e.g., intrahepatic cholestasis of pregnancy) and liver disease not related to pregnancy.

## Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

# Genetic Counseling

*Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional.* —ED.

## Mode of Inheritance

Rotor syndrome, inherited in an autosomal recessive digenic manner, requires biallelic pathogenic variants in both *SLCO1B1* and *SLCO1B3* that result in complete functional deficiencies of both protein products (OATP1B1 and OATP1B3, respectively) [van de Steeg et al 2012].

Note: Although Rotor syndrome is a digenic disorder, pathogenic variants in *SLCO1B1* and *SLCO1B3* do not segregate independently and, consequently, the pattern of inheritance of Rotor syndrome is similar to that of monogenic autosomal recessive disorders.

## Risk to Family Members

**Parents of a proband**

- The parents of an affected child are typically heterozygotes (i.e., carriers) for a pathogenic variant in *SLCO1B1* and a pathogenic variant in *SLCO1B3* or heterozygotes for a large deletion affecting the coding regions of both *SLCO1B1* and *SLCO1B3.*
- Heterozygotes (carriers of one, two, or three pathogenic variants) are asymptomatic and are not at risk of developing Rotor syndrome.

**Sibs of a proband**

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier of at least one pathogenic variant, and a 25% chance of being unaffected and not a carrier.
  - Carriers may have one, two, or three pathogenic variants
  - Carriers with one pathogenic variant in one gene and carriers with two pathogenic variants in one gene (and none in the other gene) are not at risk of having affected children.

- Carriers are asymptomatic and are not at risk of developing Rotor syndrome.

**Offspring of a proband.** The offspring of an individual with Rotor syndrome are obligate heterozygotes (carriers) for a pathogenic variant in *SLCO1B1* and a pathogenic variant in *SLCO1B3*.

**Other family members.** Each sib of the proband's parents is at increased risk of being a carrier of one or more Rotor syndrome-causing pathogenic variants.

## Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the *SLCO1B1* and *SLCO1B3* pathogenic variants in the family.

## Related Genetic Counseling Issues

Because most individuals with Rotor syndrome are born to consanguineous couples, the diagnosis of Rotor syndrome may coincidentally identify such consanguinity. In some centers, this may be an indication for clinical genetics consultation and/or genetic counseling.

**Family planning**

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.

**DNA banking** is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

## Prenatal Testing and Preimplantation Genetic Testing

Once the Rotor syndrome-causing pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Requests for prenatal testing for benign, clinically unimportant conditions such as Rotor syndrome are not expected to be common. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

# Resources

*GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.*

- **National Library of Medicine Genetics Home Reference**
  Rotor syndrome

# Molecular Genetics

*Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information.* —ED.

**Table A.** Rotor Syndrome: Genes and Databases

| Gene | Chromosome Locus | Protein | HGMD | ClinVar |
|---|---|---|---|---|
| *SLCO1B1* | 12p12.1 | Solute carrier organic anion transporter family member 1B1 | SLCO1B1 | SLCO1B1 |
| *SLCO1B3* | 12p12.2 | Solute carrier organic anion transporter family member 1B3 | SLCO1B3 | SLCO1B3 |

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

**Table B.** OMIM Entries for Rotor Syndrome (View All in OMIM)

| | |
|---|---|
| 237450 | HYPERBILIRUBINEMIA, ROTOR TYPE; HBLRR |
| 604843 | SOLUTE CARRIER ORGANIC ANION TRANSPORTER FAMILY, MEMBER 1B1; SLCO1B1 |
| 605495 | SOLUTE CARRIER ORGANIC ANION TRANSPORTER FAMILY, MEMBER 1B3; SLCO1B3 |

## Molecular Pathogenesis

In Rotor syndrome, liver histology is normal; however, expression of OATP1B1 and OATP1B3 is completely absent. The functional consequence of this is that liver uptake of bilirubin mono- and diglucuronides is hampered, causing increased plasma bilirubin-glucuronide levels and jaundice.

Deficiency of OATP1B1 and OATP1B3 also explains the poor uptake by the liver of unconjugated bilirubin and anionic dyes such as bromosulfophthalein, indocyanin green, rose bengal, and cholescintigraphy radiotracers ($^{99m}$Tc-HIDA and related compounds). It also supports the earlier observations that in Rotor syndrome conjugated bromosulfophthalein does not appear in the blood after intravenous administration of its unconjugated precursor.

Reduced hepatic (re)uptake of coproporphyrin isomers probably underlies the increased urinary excretion of coproporphyrins.

**Mechanism of disease causation.** Loss of function

**Table 4.** Gene-Specific Laboratory Considerations

| Gene [1] | Special Consideration |
|---|---|
| *SLCO1B1* | |
| *SLCO1B3* | Failure to amplify exon 5 may indicate the intronic LINE-1 insertion reported by Kagawa et al [2015]. |

*1.* Genes are in alphabetic order.

**Table 5.** Notable Pathogenic Variants by Gene

| Gene [1] | Reference Sequences | DNA Nucleotide Change | Predicted Protein Change | Comment [Reference] |
|---|---|---|---|---|
| *SLCO1B1* | NM_006446.4 | c.1738C>T | p.Arg580Ter | van de Steeg et al [2012], Kagawa et al [2015] |
| *SLCO1B1* & *SLCO1B3* | Assembly NCBI36/hg18 | Chr12: g.20898911_21303509delCAins | No SLCO1B proteins formed due to lacking ORFs | Large digenic deletion [van de Steeg et al 2012] |

*Table 5. continued from previous page.*

| Gene [1] | Reference Sequences | DNA Nucleotide Change | Predicted Protein Change | Comment [Reference] |
|---|---|---|---|---|
| *SLCO1B3* | NG_032071.1 | g.50456_50457insL1 | Frameshift + premature stop | Kagawa et al [2015] |

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
*GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
*1.* Genes are in alphabetic order.

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# Chapter Notes

## Revision History

- 11 July 2019 (sw) Comprehensive update posted live
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