Next generation sequencing reveals co-existence of hereditary spherocytosis and Dubin–Johnson syndrome in a Chinese girl: A case report

Yuan Li, Yang Li, Yang Yang, Wen-Rui Yang, Jian-Ping Li, Guang-Xin Peng, Lin Song, Hui-Hui Fan, Lei Ye, You-Zhen Xiong, Zhi-Jie Wu, Kang Zhou, Xin Zhao, Li-Ping Jing, Feng-Kui Zhang, Li Zhang

ORCID number: Yuan Li (0000-0001-8603-011X); Yang Li (0000-0001-8864-6487); Yang Yang (0000-0002-4268-1823); Wen-Rui Yang (0000-0001-9650-3937); Jian-Ping Li (0000-0002-9765-2579); Guang-Xin Peng (0000-0001-6666-7391); Lin Song (0000-0002-5999-3049); Hui-Hui Fan (0000-0001-6446-2376); Lei Ye (0000-0001-6615-9573); You-Zhen Xiong (0000-0002-1569-4872); Zhi-Jie Wu (0000-0003-3984-0819); Kang Zhou (0000-0003-2900-2520); Xin Zhao (0000-0002-5621-0459); Li-Ping Jing (0000-0002-7315-9755); Feng-Kui Zhang (0000-0002-2553-5998); Li Zhang (0000-0002-4702-9658).

Author contributions: Li Y designed and wrote the report; Zhang L and Zhang FK reviewed the manuscript for its intellectual content and revised the entire work; Li Y, Yang Y, and Li JP performed the histological assessments and evaluations; Yang WR, Ye L, and Xiong YZ performed the imaging assessments and evaluations; Zhao X, Wu ZJ, and Zhou K analysed the NGS data and made evaluations; Peng GX, Fan HH, and Song L performed the hemolytic test and flow cytometry analysis; Jing LP reviewed the manuscript for its intellectual content; all authors have read and approved the final manuscript.

Supported by the National Science and Technology Important and Special Project of China, No. 2017ZX09304024.

Abstract

BACKGROUND
Hereditary spherocytosis (HS) is a hereditary disease of hemolytic anemia that occurs due to the erythrocyte membrane defects. Dubin–Johnson syndrome (DJS), which commonly results in jaundice, is a benign hereditary disorder of bilirubin clearance that occurs only rarely. The co-occurrence of HS and DJS is extremely rare. We recently diagnosed and treated a case of co-occurring HS and DJS.

CASE SUMMARY
A 21-year-old female patient presented to our department because of severe jaundice, severe splenomegaly, and mild anemia since birth. We eventually confirmed the diagnosis of co-occurring DJS and HS by next generation sequencing (NGS). The treatment of ursodeoxycholic acid in combination with phenobarbital successfully increased hemoglobin and reduced total bilirubin and direct bilirubin.

CONCLUSION
The routine application of NGS can efficiently render a definite diagnosis when inherited disorders are suspected.

Key words: Hereditary spherocytosis; Dubin–Johnson syndrome; Hemolytic anemia; Jaundice; Next generation sequencing; ABCC2; SPTB; Case report

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.
Informed consent statement: The patient involved in this study gave written informed consent authorizing the use and disclosure of his protected health information. The study protocol was approved without restrictions by the Medical Ethics Committee of Institute of Hematology and Blood Diseases Hospital, CAMS and PUMC.

Conflict-of-interest statement: The authors have no conflicts of interest to disclose.

CARE Checklist (2016) statement: The manuscript was prepared and revised according to the CARE Checklist (2016).

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Unsolicited manuscript

Received: April 19, 2019
Peer-review started: April 22, 2019
First decision: August 1, 2019
Revised: August 21, 2019
Accepted: September 9, 2019
Article in press: September 9, 2019
Published online: October 26, 2019

P-Reviewer: Jeong BH, Devgun M
S-Editor: Zhang L
L-Editor: Wang TQ
E-Editor: Xing YX

Core tip: A rare case of co-occurring Dubin–Johnson syndrome and hereditary spherocytosis, which presented exceptionally severe jaundice, was diagnosed by next generation sequencing.

Citation: Li Y, Li Y, Yang Y, Yang WR, Li JP, Peng GX, Song L, Fan HH, Ye L, Xiong YZ, Wu ZJ, Zhou K, Zhao X, Jing LP, Zhang FK, Zhang L. Next generation sequencing reveals co-existence of hereditary spherocytosis and Dubin–Johnson syndrome in a Chinese girl: A case report. World J Clin Cases 2019; 7(20): 3303-3309
URL: https://www.wjgnet.com/2307-8960/full/v7/i20/3303.htm
DOI: https://dx.doi.org/10.12998/wjcc.v7.i20.3303

INTRODUCTION
Hereditary spherocytosis (HS) is a hereditary disease of hemolytic anemia that occurs due to the erythrocyte membrane defects caused by the gene mutation in the erythrocyte membrane protein, and its common clinical manifestations include hemolysis, anemia, jaundice, splenomegaly, etc. Dubin–Johnson syndrome (DJS), which commonly results in jaundice, is a benign hereditary disorder of bilirubin clearance that occurs only rarely. The co-occurrence of HS and DJS is extremely rare[1] and leads to severe jaundice. We recently diagnosed and treated a case of co-occurring HS and DJS in a patient who had severe jaundice and moderate anemia intensified by the infection of the upper respiratory tract. We applied next generation sequencing (NGS) to arrive at a definite diagnosis. The case is reported as follows.

CASE PRESENTATION

Chief complaints
A 21-year-old female patient presented to our department on November 10, 2017 because of severe jaundice, severe splenomegaly, and mild anemia since birth (Table 1).

History of past illness
She did not undergo irradiation treatment. When she was two years old, the yellow staining was intensified in her skin and sclera and she started having dark brown urine. Other clinical manifestations included anemia, splenomegaly, and elevated bilirubin, but her transaminases were normal. All later clinicians that she visited could not clarify her situation any further except for giving the diagnosis of “hemolytic anemia” and did not advise any treatment either. Her history of past illness was negative. She did not receive blood transfusion or surgery. Her regular blood routine testing showed the following: WBC 8.4–10.8 × 10^9/L (normal: 4-10 × 10^9/L), hemoglobin (HGB) 106–111 g/L (110-150 g/L), platelets (PLT) 186–241 × 10^9/L (100-300 × 10^9/L), percentage of neutrophils (NE%) 56.9%–60.5% (normal: 50%-70%), percentage of lymphocytes (LY%) 33.1%–34.7% (normal: 20%-40%), and percentage of reticulocytes (RET%) 7.8%–11.3% (normal: 0.5%-1.5%). Her liver function results were: Total bilirubin (TBIL) 132–162.8 μmol/L (normal: 5.0-21.0 μmol/L), direct bilirubin (DBIL) 34.4–40 μmol/L (normal: 0-3.4 μmol/L), and indirect bilirubin (IBIL) 98.6–137 μmol/L (normal: 0-13.6 μmol/L). She experienced intensified anemia and jaundice upon fatigue or infection. She sought further diagnosis of her situation in her current visit to our clinic.

Personal and family history
She was the only child of her family and her parents had no similar clinical manifestations including anemia, splenomegaly, and elevated bilirubin.

Physical examination
On physical examination, the patient demonstrated obvious anemic appearance and intense yellowing of the skin, without any edema. The liver was not palpable, but the spleen was palpable at 6 cm below the rib margin.

Laboratory examinations
Blood tests gave the following results: WBC 4.58 × 10^9/L (normal: 4-10 × 10^9/L),
Table 1  The characteristics of the patient

| Gender       | Age   | Onset age   | Symptoms and signs                      |
|--------------|-------|-------------|----------------------------------------|
| Female       | 21 years | Since birth | Anemia, severe jaundice, splenomegaly   |

**Laboratory examination**

| before treatment | after treatment |
|------------------|-----------------|
| HGB (g/L)        | 105             | 114           |
| ARC (×10^12/L)   | 0.2083          | N/E           |
| TBIL (μmol/L)    | 111.8           | 88.69         |
| DBIL (μmol/L)    | 35.4            | 29.9          |
| IBIL (μmol/L)    | 76.4            | 58.79         |
| DBIL/TBIL (%)    | 31.7            | 33.7          |

**NGS results**

A *de novo* heterozygous mutation of the SPTB gene, c.2413 C > T (p.Gln805*)

The mutation of the ABCC2 gene from the father: c.4313+1 G > T

The mutation of the ABCC2 gene from the mother: c.3629 G > A (R1210H)

Absolute neutrophil count (ANC) 3.22 × 10^9/L (normal: 2.7-7.0 × 10^9/L), red blood cells (RBC) 2.64 × 10^12/L (normal: 3.5-5.0 × 10^12/L), HGB 85 g/L (normal: 110-150 g/L), mean corpuscular volume 87.9 fl (normal: 80-100 fl), mean corpuscular hemoglobin 32.2 pg (normal: 27-34 pg), mean corpuscular hemoglobin concentration 366 g/L (normal: 320-360 g/L), PLTs 170 × 10^12/L (normal: 100-300 × 10^12/L), RET% 7.89% (normal: 0.5%-1.5%), and ARC 0.2083 × 10^12/L (normal: 0.024-0.084 × 10^12/L). The urine test gave all normal results except for elevated urobilinogen (+). The liver and kidney function tests showed: total protein 69.4 g/L (normal: 66-83 g/L), albumin 42.2 g/L (normal: 35-52 g/L), globulin 27.2 g/L (normal: 20-35 g/L), alanine aminotransferase 9.7 U/L (normal: 0-35 U/L), aspartate aminotransferase 11.6 U/L (normal: 0-35 U/L), alkaline phosphatase 50.4 U/L (normal: 30-120 U/L), γ-glutamyl transpeptidase 9.5 U/L (normal: 8-57 U/L), TBIL 111.8 μmol/L (normal: 5.0-21.0 μmol/L), DBIL 35.4 μmol/L (normal: 0-3.4 μmol/L), DBIL/TBIL ratio 31.7% (normal: 20%), UCB 76.4 μmol/L (normal: 0-13.6 μmol/L), blood urea nitrogen 2.54 mmol/L (normal: 8-7.6 mmol/L), creatinine 58.3 μmol/L (normal: 49-90 μmol/L), uric acid 362 μmol/L (normal: 154-357 μmol/L), and lactate dehydrogenase 189.6 U/L (normal: 0-248 U/L). Hemolysis test showed reduced plasma haptoglobin (0.375 g/L; normal: 0.5-2.0 g/L), and plasma-free hemoglobin was 37.1 mg/L (normal: 0-40 mg/L). Eosin-5’-maleimide (EMA) flow cytometry showed that the mean fluorescence intensity attenuation of the RBC EMA was 23.41% (normal: <16%). The RBC osmotic fragility (EOF) test showed that hemolysis started at 0.6% (normal: 0.44%) and completed at 0.36% (normal: 0.32%). The acidified glycerol lysis test (AGLT50) gave a result of 60 s (normal: >290 s).

The patient was found negative in the hemoglobin A2 test, anti-alkaline hemoglobin test, heat instability test, hemoglobin acetate membrane electrophoresis, direct Coombs test, cold agglutinin test, denatured globin corpuscle test, isopropanol test, methemoglobin reduction test, and acid hemolysis test. The patient had normal activities of erythrocyte pyruvate kinase, erythrocyte pyrimidine 5’-nucleotidase, 6-phosphatase glucose dehydrogenase, and erythrocyte glucose phosphate isomerase, and there was no anomaly in immunoglobulin quantification, antinuclear antibody, etc. Iliac marrow smear showed obviously active hyperplasia, with 44% (normal: 40%-60%) of granulocytes and 48.5% (normal: 15%-25%) of erythrocytes. The peripheral blood smear was rich in small spherical RBC, which accounted for 70% of the mature RBC. Bone marrow autopsy showed relatively normal (50%) myeloproliferation based on HE and PAS staining, as well as escalated erythrocytes/granulocytes ratio. The reticular fiber dyeing result was MF-0. The karyotype was 46. An abdominal CT scan showed enlarged spleen with minor effusion. The liver had normal size, proportionate lobes, and parenchyma of uniform density. The intrahepatic and extrahepatic bile ducts showed no sign of dilation, and the hepatic portal had a clear structure. No anomaly was observed for the gallbladder, pancreas, kidneys, or abdominal cavity. Abdominal ultrasound examination showed hyperechogenic liver parenchyma, moderately enlarged spleen, as well as normal gallbladder and pancreas. Hence, as a result of the preceding clinical findings, the patient was diagnosed with HS.

**Imaging examinations**
However, because of the extraordinary jaundice of the patient, whole exome sequencing was carried out additionally after the diagnosis of HS. DNA for NGS was extracted from peripheral blood of the patient and her parents. Agarose electrophoresis, Qubit 2.0 fluorometer dsDNA HS Assay (Thermo Fisher Scientific), and 2100 Bioanalyzer and Herculase II Fusion DNA Polymerase (Agilent) were used for DNA library preparation according to the instructions. Targeted fragments were captured with exome capture probes (Agilent) and sequenced on the Illumina HiSeq X platform following Illumina-provided protocols. The sequencing quality was determined with FastQC software. After data filtration, the clean reads were mapped to human reference genome (hg19) using SentieonBWA software. Then, the mapped reads were used to detect SNV and InDel with Sentieon (the same algorithm with GATK), and annotated using ANNOVAR/VEP software. All the variants were annotated with VEP software and the pathogenic variants were screened by ClinVar, OMIM, and HGMD. Function prediction of missense mutations and annotation of non-coding sequences were performed with PolyPhen-2 and Sorting Intolerant from Tolerant (SIFT).

Blood (2 mL) was drawn for Sanger sequencing from the patient and her healthy parents. All the suspicious pathogenic variants were validated in the patient and her parents using Sanger sequencing. Primers were designed with Primer 3 software, and BLAST in NCBI database was used to confirm specificity. PCR amplification product was sequenced with an ABI 3500D x DNA Analyser (Applied Biosystems, Foster City, CA, United States) and analyzed with sequencing analysis software (Thermo Fisher).

The sequencing results revealed a de novo heterozygous mutation of the SPTB gene (NM_000347.5), c.2413C > T (p.Gln805*), as well as two inherited novel heterozygous mutations of the ABCC2 gene (NM_000392.4), c.4313+1 G > T from the father and c.3629G > A (R1210H) from the mother (Figure 1). Neither of these mutations had been observed in the Clin Var, OMIM, and HGMD databases, indicating that these variants are very rare. All three mutations were predicted to be harmful and pathogenic with PolyPhen-2 and SIFT. These mutations were identified as pathogenic variants following the 2013 ACMG guidelines.

**FINAL DIAGNOSIS**

The final diagnosis was co-existence of HS and DJS.

**TREATMENT**

The patient was recommended to receive oral doses of ursodeoxycholic acid and phenobarbital in addition to splenectomy. She refused splenectomy and was then discharged.

**OUTCOME AND FOLLOW-UP**

The patient first took ursodeoxycholic acid in combination with phenobarbital for three months. The treatment successfully increased HGB to 114 g/L (normal: 110-150 g/L) and reduced TBIL to 88.69 μmol/L (normal: 5.0-21.0 μmol/L), DBIL to 29.9 μmol/L (normal: 0-3.4 μmol/L), DBIL/TBIL to 33.7% (normal: 20%), and IBIL to 58.79 μmol/L (normal: 0-13.6 μmol/L).

**DISCUSSION**

The diagnosis of HS was straightforward. Hemolytic anemia could be readily inferred since the patient experienced the symptoms since birth. Anemia, jaundice, enlarged spleen, increased reticulocytes in peripheral blood, and marrow morphology all pointed to proliferative anemia. The key evidence of HS included notable increase in the small spherical mature RBC in the peripheral blood smear, escalated RBC osmotic fragility in the EOF and AGLT50 tests, and notable defect of erythrocyte membrane protein in the EMA test. The genome sequencing revealed heterozygous mutation of the SPTB gene and thus verified the diagnosis of HS.

Although the patient was clearly diagnosed with moderate HS, this could not convincingly account for the severe jaundice and the significantly elevated levels of TBIL, DBIL, and IBIL. Since the imaging results clearly excluded any obstruction of intrahepatic and extrahepatic bile ducts, and the activities of all liver enzymes were
Figure 1  Sanger sequencing confirmed a de novo heterozygous mutation of the SPTB gene (NM_000347.5), c.2413 C > T (p.Gln805*), and two inherited novel heterozygous mutations of the ABCC2 gene (NM 000392.4), c.4313+1 G > T from the father and c.3629 G > A (R1210H) from the mother, are shown.

found normal, the observed degree of hemolysis did not suffice to reasonably explain the severity of jaundice. Consequently, we suspected that another disease aside from HS was likely, and we naturally turned our attention to two hereditary disorders of bilirubin clearance, i.e., DJS and the Rotor syndrome (RS), because the patient had experienced elevated DBIL since birth and showed normal liver enzymes without abnormality in the liver and bile duct images.

DJS, first reported in 1954[3], is a rare, chronic, benign, autosomal recessive disorder characterized by elevated DBIL along with normal liver function. Its pathogenesis has been largely clarified and could be accounted by the mutation of the ABCC2 gene.

The human ABCC2 gene is located at chromosome 10q24, and its introns and exons have been well sequenced. The ABCC2 gene has 32 exons that encode the ABCC2 transporter, i.e., the multidrug resistance-associated protein 2. The ABCC2 transporter is an ATP-binding cassette transporter at the apical membrane of hepatocytes consisting of 1545 amino acids. It is the major carrier that is responsible for transporting bilirubin into bile, and it becomes activated by the ATP hydrolysis of two ATP-binding regions to expel the substrate outside the cell via an energy dissipation process. Mutation of the ABCC2 gene in the DJS patients leads to defected ABCC2 transporter and thus impaired ability to transport DBIL into the bile, and the high serum DBIL in turn results in jaundice.

To date, 34 kinds of ABCC2 mutations have been found in DJS patients[4-17], including 6 kinds of nonsense mutations (17.4%), 14 kinds of missense mutations (41.2%), 4 kinds of small deletions (11.8%), 4 kinds of splice mutations (11.8%), and 6 kinds of large deletions (17.4%). At least 23 mutations (67.6%) of the total 34 are predicted to be harmful. The mutations may result in the maturity disorder or positioning error of the ABCC2 transporter and reduce the protein...
Li Y et al. HS coexisting with DJS diagnosed by NGS

In summary, to the best of our knowledge, the current case is probably the first case that was definitively diagnosed with the co-occurrence of HS and DJS by NGS. We suggest that inherited disorders of bilirubin clearance should be investigated if patients with inherited hemolytic anemia present with severe hyperbilirubinemia. The
routine application of NGS is also recommended to efficiently render a definite diagnosis when inherited disorders are suspected.

REFERENCES

1. Korkmaz U, Duman AE, Oğütmen Koç D, Gürbüz Y, Dündar G, Ersaroglu F, Sener SY, Sentürk O, Hülägii S. Severe jaundice due to coexistence of Dubin-Johnson syndrome and hereditary spherocytosis: a case report. Turk J Gastroenterol 2011; 22: 422-425 [PMID: 21948575 DOI: 10.4318/tjg.2011.02.061]

2. Rehm HL, Bale SJ, Bayrakt-Toydemir P, Berg JS, Brown KK, Deiglan JL, Fries MJ, Funke BH, Hegde MR, Lyon E; Working Group of the American College of Medical Genetics and Genomics Laboratory Quality Assurance Committee. ACMG clinical laboratory standards for next-generation sequencing. Genet Med 2013; 15: 733-747 [PMID: 23887774 DOI: 10.1038/gim.2013.92]

3. Dubin IN, Johnson FB. Chronic idiopathic jaundice with unidentified pigment in liver cells; a new clinicopathologic entity with a report of 12 cases. Medicine (Baltimore) 1954; 33: 155-197 [PMID: 13193390 DOI: 10.1097/00005792-195409000-00001]

4. Wada M, Toh S, Taniguchi K, Nakamura T, Uchiyumi T, Kohn K, Yoshida I, Kimura A, Sakioka S, Adachi Y, Kuwano M. Mutations in the canalicular multispecific organic anion transporter (cMOAT) gene, a novel ABC transporter, in patients with hyperbilirubinemia II/Dubin-Johnson syndrome. Hum Mol Genet 1996; 7: 203-207 [PMID: 9425327 DOI: 10.1093/hmg/7.2.203]

5. Toh S, Wada M, Uchiyumi T, Itohki A, Makino Y, Horie Y, Adachi Y, Sakioka S, Kuwano M. Genomic structure of the canalicular multispecific organic anion-transporter gene (MRP2/cMOAT) and mutations in the ATP-binding-cassette region in Dubin-Johnson syndrome. Am J Hum Genet 1999; 64: 739-746 [PMID: 10053008 DOI: 10.1086/302292]

6. Mor-Cohen R, Zivelin A, Rosenberg N, Shani M, Muallem S, Seligsohn U. Identification and functional analysis of two novel mutations in the multidrug resistance protein 2 gene in Israeli patients with Dubin-Johnson syndrome. J Biol Chem 2001; 276: 36923-36930 [PMID: 11477083 DOI: 10.1074/jbc.M105047200]

7. Tate G, Li M, Suzuki T, Mitsuya T. A new mutation of the ATP-binding cassette, sub-family C member 2 (ABCC2) gene in a Japanese patient with Dubin-Johnson syndrome. Genet Med 2002; 77: 117-121 [PMID: 12087194 DOI: 10.1266/ggs.77.117]

8. Wakisawa I, Machida I, Suzuki S, Hayashi H, Yano M, Yoshikawa K. Identification of a novel 2026G-C mutation of the MRP2 gene in a Japanese patient with Dubin-Johnson syndrome. J Hum Genet 2003; 48: 425-429 [PMID: 12884082 DOI: 10.1007/s10038-003-0052.0]

9. Shudo J, Suzuki H, Suzuki Y, Hiyama Y, Hiroi T, Utsunomiya F, Oda K, Kawanoto T, Matsuzaki Y, Tanaka N. Novel mutations identified in the human multidrug resistance-associated protein 2 (MRP2/ABCC2) gene in a Japanese patient with Dubin-Johnson syndrome. Hepatol Res 2003; 27: 323-326 [PMID: 14662121 DOI: 10.1016/S1386-6346(03)00267-5]

10. Cebeceauerova D, Jirasek T, Budisova L, Mandy S, Volf V, Novotna Z, Subhanova I, Hrebicek M, Elleder M, Jirscha M. Dual hereditary jaundice: simultaneous occurrence of mutations causing Gilbert’s and Dubin-Johnson syndrome. Gastroenterology 2005; 129: 315-320 [PMID: 16012956 DOI: 10.1053/j.gastro.2004.10.009]

11. Machida I, Wakisawa I, Sanai F, Hayashi H, Kasakabe A, Nimomiya H, Yano M, Yoshikawa K. Mutational analysis of the MRP2 gene and long-term follow-up of Dubin-Johnson syndrome in Japan. J Gastroenterol 2005; 40: 366-370 [PMID: 15870973 DOI: 10.3138/jsg.0055-0014.1555-y]

12. Lee JH, Chen HL, Chen HL, Yi YH, Hsu HY, Chang MH. Neonatal Dubin-Johnson syndrome: long-term follow-up and MRP2 mutations study. Pediatr Res 2006; 59: 584-589 [PMID: 16549354 DOI: 10.1203/01.pdr.0000203093.10908.6b]

13. Pacifico L, Carducci C, Poggiofalle E, Caravona F, Antonozzi I, Chiesa C, Maggiore G. Mutational analysis of ABCC2 gene in two siblings with neonatal-onset Dubin-Johnson syndrome. Clin Genet 2010; 78: 598-600 [PMID: 21044052 DOI: 10.1111/j.1399-0004.2010.01497.x]

14. Devgun MS, El-Nujumi AM, O'Dowd GJ, Barbu V, Poupon R. Novel mutations in the Dubin-Johnson syndrome gene ABCC2 and associated biochemical changes. Ann Clin Biochem 2012; 49: 609-612 [PMID: 23065530 DOI: 10.1258/ach.2012.011279]

15. Uchiyumi T, Tanamachi H, Kuchikawa T, Najita M, Saito I, Kimura K, Taniguchi K, Kato K, Nagai M, Kato S. Mutational and functional analysis of ABCC2/multidrug resistance protein 2 in a Japanese patient with Dubin-Johnson syndrome. Hepatol Res 2013; 43: 569-575 [PMID: 23049960 DOI: 10.1111/1872-034X.12110.x]

16. Sticova E, Elleder M, Huikova L, Lukasova S, Sauer M, Wunschowa-Moudra I, Novotny J, Jirscha M, Dubin-Johnson syndrome coinciding with colon cancer and atherosclerosis. World J Gastroenterol 2013; 19: 946-950 [PMID: 23429660 DOI: 10.3748/wjg.v19.6.946]

17. Baranquag Sastro ML, Garcia Romero R, Miramar Gallard MD. Conjugated hyperbilirubinemia after surgery. A diagnosis of Dubin-Johnson syndrome confirmed by genetic testing. Rev Esp Enferm DIG 2017; 109: 801-802 [PMID: 29032691 DOI: 10.17235/revmed2017.09.2017]

18. Erlinger S, Arias IM, Dhumeaux D. Inherited disorders of bilirubin transport and conjugation: new insights into molecular mechanisms and consequences. Gastroenterology 2014; 146: 1625-1638 [PMID: 24704527 DOI: 10.1053/j.gastro.2014.03.047]

19. Strassburg CP. Hyperbilirubinemia syndromes (Gilbert–Meuleuengracht, Crigler–Najjar, Dubin–Johnson, and Rotor syndrome). Best Pract Res Clin Gastroenterol 2010; 24: 555-571 [PMID: 20955959 DOI: 10.1016/j.bpg.2010.07.007]

20. van de Steeg E, Strancuský V, Hartmannová H, Nosková L, Hřebíček M, Wagenara E, van Esch A, de Waart DR, Oude Elferink RP, Kenworthy KE, Sticova E, al-Edreesi M, Knisely AS, Knoch M, Jirscha M, Schinkel AH. Complete OATP1B1 and OATP1B3 deficiency causes human Rotor syndrome by interrupting conjugated bilirubin reuptake into the liver. J Clin Invest 2012; 122: 519-528 [PMID: 22232210 DOI: 10.1172/JCI19526]
