Dubin-Johnson Syndrome in twins linked to novel genetic mutations

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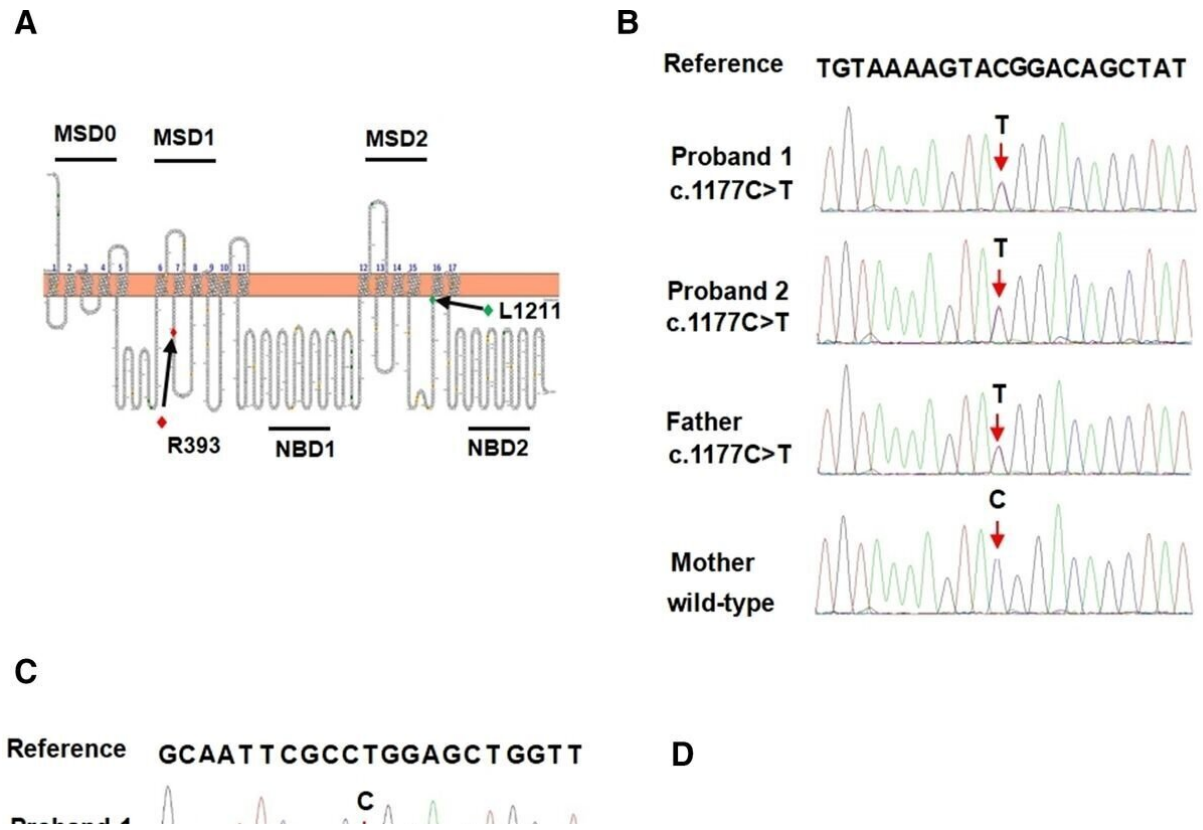


(A) Localization of the R393 and L1211 in a predicted topology model of MRP2 protein. The full-length model was generated by the open-source tool Protter (http://wlab.ethz.ch/protter/start/). (B) Sequencing analysis of the *ABCC2* gene indicates the disease-associated variant of probands (II-2, II-3), the missense mutation 1177C>T predicated to cause the mutation Arg393Trp (R393W) in the amino-acid sequence of the MRP2 protein heredity from the father (I-1) and (C) the missense mutation 3632T>C (L1211P) inherited from the mother (I-2). (D) Pedigree of the family presenting *ABCC2* variants. Circles and squares represent

females and males, respectively. Half-black filled symbols represent heterozygous mutation carriers, and the question mark symbol indicates the normal subject without genetic examination. The black-filled symbols represent the twin probands. MSD, membrane-spanning domain; NBD, nucleotide-binding domain. Credit: Sun R, Chen Y, Zhu M, et al.

Researchers in China and Italy have made a significant breakthrough in understanding Dubin-Johnson syndrome (DJS), a rare inherited liver disorder. The team identified specific genetic mutations responsible for DJS in a pair of dizygotic twins, offering valuable insights into the cause of the disease and potentially improving diagnosis for patients with unclear symptoms.

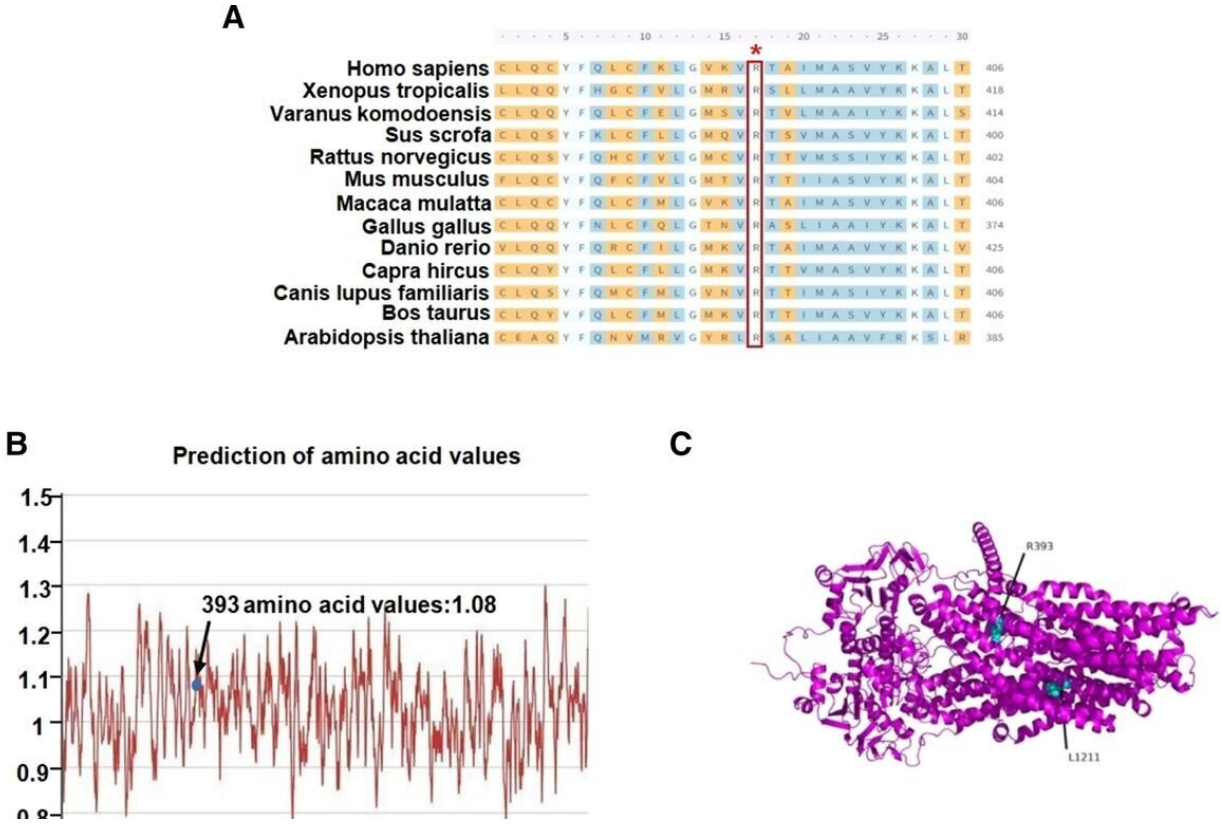
DJS disrupts the liver's ability to eliminate waste products, leading to a buildup of bilirubin, a yellow pigment in the blood. This can cause jaundice, a condition characterized by yellowing of the skin and whites of the eyes. However, symptoms of DJS are often mild and easily overlooked, making diagnosis challenging.

The study, published in *eGastroenterology*, employed whole exome sequencing (WES), a powerful genetic analysis technique. WES allowed researchers to examine the protein-coding regions of all human genes in the twins' DNA. This detailed analysis revealed two critical mutations in the ABCC2 gene, which provides instructions for building a protein called MRP2. MRP2 acts as a transporter, eliminating waste products from liver cells.

One of the mutations identified was previously reported to be associated with DJS. This mutation significantly reduces the overall amount of MRP2 protein produced by the liver cells.

The research team also discovered a novel mutation in the ABCC2 gene, not previously linked to DJS. This newly identified mutation alters the MRP2 protein itself, hindering its ability to function properly on the cell membrane.

The combined effect of these mutations is thought to disrupt the normal flow of waste products out of the liver cells. This impaired waste processing system is thought to be the underlying cause of DJS in these twins.



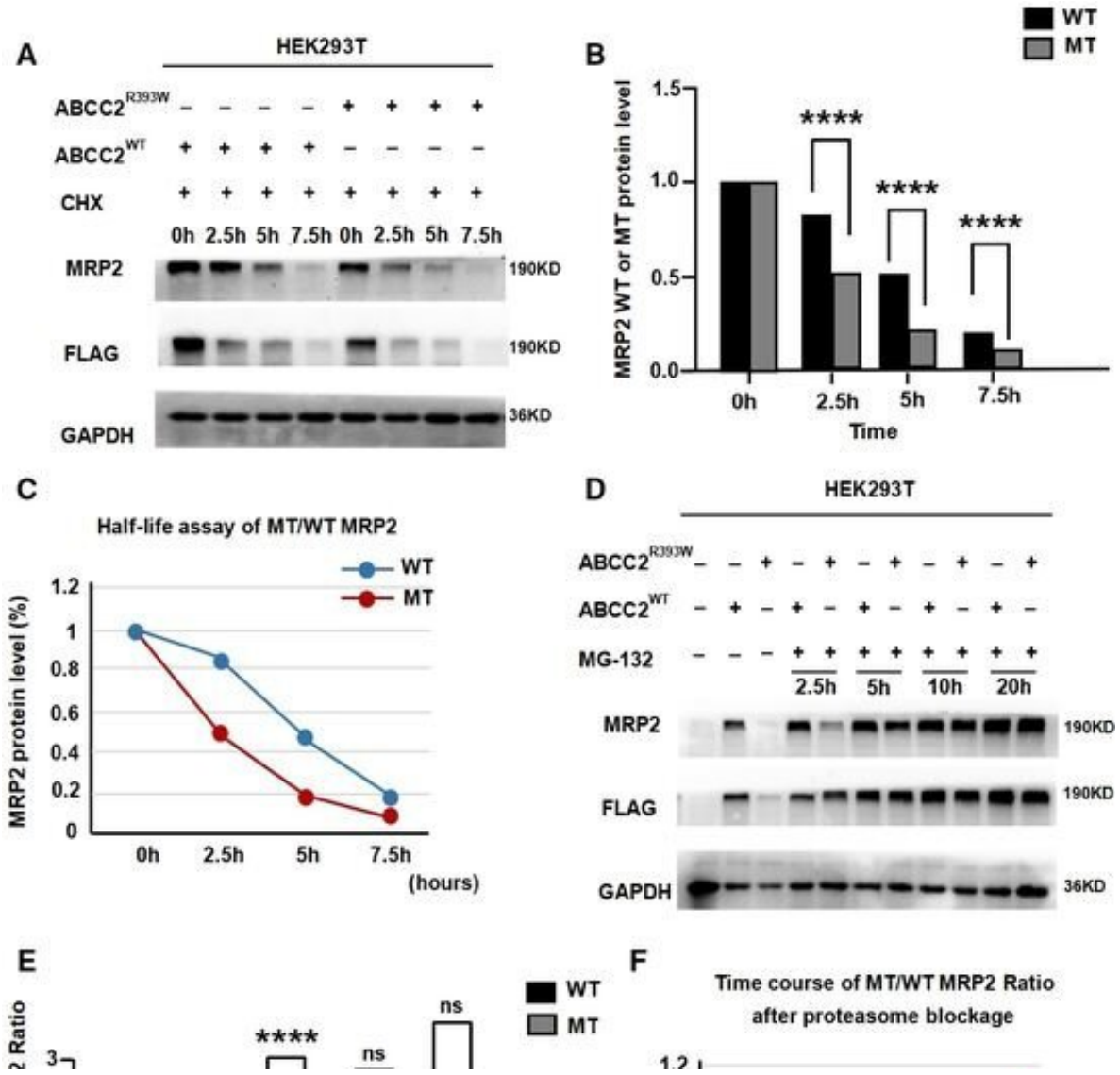
The ABCC2 c.1177C>T resulted in an R393W substitution in MRP2 protein in the conserved amino acid region in different species. *Represents the position of the R393 is indicated by the red box. (B) Prediction of amino acid values. Arrow and blue dot indicate the position of R393. (C) Localization of R393 and L1211 in MRP2 by SWISS_MODEL. (D) In wild-type MRP2 protein, R393 forms

hydrogen bonds with G389, M397, Q429 and N1193. In mutant MRP2 protein, the hydrogen bond between W393 and Q429, and N1193 were broken, and a new hydrogen bond was formed between W393 and M424. (E) In wild-type MRP2 protein, L1211 forms hydrogen bonds with L1207 and G1215. In mutant MRP2 protein, the hydrogen bond between P1211 and L1207 were broken. Credit: Sun R, Chen Y, Zhu M, et al.

The study highlights the effectiveness of WES in diagnosing DJS, particularly for patients with atypical presentations or mild symptoms. Traditionally, diagnosing DJS relied on clinical symptoms, liver biopsies, and specific tests. However, these methods may not always be conclusive, especially in the early stages of the disease.

WES offers a more precise and objective approach to diagnosing DJS. By identifying the specific genetic mutations responsible for the disease, doctors will be able to confidently diagnose patients and guide their future management.

While this study focused on a single case involving twins, the findings have broader implications. The researchers believe these mutations may be present in other individuals diagnosed with DJS, potentially explaining some variability in observed disease severity. Further research involving a larger patient population is necessary to confirm these initial findings.



(A–C) Half-life assay of the MRP2^{WT} and MRP2^{R393W} by using cycloheximide (CHX) to block protein synthesis and chase the remaining protein level by western blot at 0, 2.5, 5 and 7.5 hours. The half-life of MRP2^{WT} was around 5 hours, whereas the MRP2^{R393W} was almost depleted within 2.5 hours. Western blot (D–F) and immunofluorescence (G, H) results of MRP2^{WT} and the MRP2^{R393W} expression after MG132 treatment indicated that proteasome blockage MG132 accumulated MRP2^{R393W} expression and attenuated the difference between the wild-type and mutant MRP2. (I, J) Whereas lysosome blockage chloroquine (CHL) failed to elevate the mutant MRP2 protein level. All data are expressed as mean±SEM Asterisks (*) represent statistically significant differences (**p