Identification of mutation-prone points in bile salt export pump

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Abstract

Background. The bile salt export pump mediates uphill canalicular bile acid secretion. Inherited dysfunction of the bile salt export pump causes a progressive and a benign form of familial intrahepatic cholestasis. Mutations within the bile salt export pump gene are reported. Presently, prediction of protein nanostructure and function is a great challenge in the proteomics and structural genomics era. Identification of the point vulnerable to mutation is a new trend to expand knowledge on disorders at the genomic and proteomic level of diseases. Materials and methods. A bioinformatic analysis was performed to study the positions that determine peptide motifs in the amino acid sequence of the bile salt export pump. To identify the weak linkage in bile salt export pump, a new bioinformatic tool named GlobPlot was used. Results. The positions 16/34, 119/127, 451/459, 550/561, 1084/1099, 1108-1118, 1135-1140, 1211-1217, and 1314-1321 were identified as the positions prone to mutation. Conclusion. Based on this study, the weak linkages in the bile salt export pump can be identified and can provide good information for expectation of possible new mutations that can lead to cross species jumping. In addition, the results from this study provide useful information for further research on the bile salt export pump.

Key Words: bile salt export pump, weak linkage, mutation

Introduction

Recent progress in liver cell biology and molecular genetics revealed that a number of familial and congenital cholestatic disorders are caused by mutations in genes coding for hepatobiliary transporter or for signaling proteins involved in morphogenesis [1]. The status of the field has been reviewed in the light of its impact on current diagnostic and clinical practice [1]. The powerful techniques of molecular biology have enabled cloning of the transporters involved in biliary secretion and the enterohepatic circulation of bile acids [2]. The bile salt export pump mediates uphill canalicular bile acid secretion [2]. Inherited dysfunction of the bile salt export pump causes a progressive and a benign form of familial intrahepatic cholestasis, denominated as PFIC2 and BRIC2, respectively [3]. Inborn defects in its function cause intrahepatic cholestasis in infants; inhibition of its function by drugs causes hepatotoxicity [2].

Mutations within the bile salt export pump gene are reported. Presently, prediction of protein nanostructure and function is a great challenge in the proteomics and structural genomics era. The quest to identify the point vulnerable to mutation is a new trend to expand knowledge on disorders at the genomic and proteomic level of diseases [4,5]. Generally, disordered regions in proteins often contain short linear peptide motifs that are important for protein function. Identification of the peptide motifs in the amino acid sequence can give a good prediction for the weak linkages in a protein [4,5]. Here, the author performed a bioinformatic analysis to study the positions that determine peptide motifs in the amino acid sequence of the bile salt export pump.

Materials and methods

Obtaining the sequence

The database PubMed was used to search for the amino acid sequence of polymerase of bile salt export pump of Homo sapiens. Then the derived sequences were used for further study on weak linkage.
Identification of weak linkage in bile salt export pump

To identify the weak linkage in bile salt export pump, a new bioinformatic tool, i.e. GlobPlot [6], was used. GlobPlot is a web service that allows the user to plot the tendency within the query protein for order/globularity and disorder [6]. It successfully identifies inter-domain segments containing linear motifs, and also apparently ordered regions that do not contain any recognized domain [6].

Results

In this work, derived bile salt export pump sequence (AAD28285) was used for further study. The positions identified for the bile salt export pump are presented in Figure 1. The positions 16/C134, 119/C1127, 451/C1459, 550/C1561, 1084/C11099, 1108/C11118, 1140/C11217, and 1314/C11321 were identified as the positions prone to mutation.

Discussion

Identification of the transport systems involved in bile secretion and of the genes codifying these systems has allowed the etiology of familial intrahepatic cholestasis to be determined in most affected children [7]. Recent studies reveal that bile acids are signaling molecules that activate several nuclear receptors and regulate many physiological pathways and processes to maintain bile acid and cholesterol homeostasis [8]. Analysis of orphan receptor expression patterns in enterohepatic tissues identified bile acids as ligands for farnesoid X receptor (FXR) [9]. Basically, bile acid-activated FXR directly induces expression of small heterodimer partner (SHP), a nuclear receptor that suppresses bile acid biosynthesis down-regulates the Na+/taurocholate cotransport peptide (NTCP), a pump depicted to transport bile acids from the lumen into hepatocytes, and induces expression of the bile salt export pump, the principal bile acid efflux transporter in the liver [9].

In the liver, the sodium-dependent taurocholate transporter at the basolateral (sinusoidal) membrane and the bile salt export pump at the canalicular membrane mediate hepatic uptake and hepatobiliary secretion of bile salts [10]. Canalicular secretion is the driving force for the enterohepatic cycling of bile salts and most genetic diseases are caused by defects of canalicular secretion [10]. A genetic defect of the bile salt export pump is believed to be the underlying factor in many cholestatic diseases. Here, the author used an algorithm to identify the positions in the amino acid sequences of the bile salt export pump that can be mutated. In this work, the author can identify many positions. Some are known positions and the others are newly discovered. Based on this study, the weak links in the bile salt export pump can be identified and can provide useful information for expectation of possible new mutations that can lead to cross species jumping. In addition, the results from this study can provide valuable information for further research on the bile salt export pump.

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References


