ABCB4 Gene

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ATP binding cassette subfamily B member 4

genes

1. Normal Function

The *ABCB4* gene (also known as *MDR3*) provides instructions for making a protein that helps move certain fats called phospholipids across the membranes of liver cells and release the phospholipids into a digestive fluid called bile. Outside the liver cells, phospholipids attach (bind) to bile acids, which are a component of bile that digest fats. Large amounts of bile acids are potentially harmful to cells; when they are bound to phospholipids, bile acids are less toxic.

2. Health Conditions Related to Genetic Changes

2.1 Progressive familial intrahepatic cholestasis

More than 45 mutations in the *ABCB4* gene have been found to cause a severe form of liver disease called progressive familial intrahepatic cholestasis type 3 (PFIC3) that usually leads to liver failure. Affected individuals have a mutation in both copies of the *ABCB4* gene. Mutations that lead to the production of a short, nonfunctional protein or cause no protein to be produced tend to be associated with more severe liver disease that appears earlier in life. *ABCB4* gene mutations that cause PFIC3 impair the movement of phospholipids across cell membranes, leading to a lack of phospholipids available to bind to bile acids. A buildup of free bile acids damages liver cells, which causes the signs and symptoms of liver disease.

2.2 Intrahepatic cholestasis of pregnancy

Women with an *ABCB4* gene mutation are at risk of developing a condition called intrahepatic cholestasis of pregnancy. Affected women typically develop impaired bile secretion and severe itching during the third trimester of pregnancy, and these features disappear after the baby is born. A single mutation in the *ABCB4* gene leads to a mild reduction of the ABCB4 protein. Under most circumstances, though, enough protein is available to move an adequate amount of phospholipids out of liver cells to bind to bile acids. Although the mechanism is unclear, the function of the remaining ABCB4 protein appears to be impaired during pregnancy, which may further reduce the movement of phospholipids into bile. The lack of phospholipids available to bind to bile acids leads to a buildup of

toxic bile acids that can impair liver function, including the regulation of bile flow. Problems with bile flow lead to the signs and symptoms of intrahepatic cholestasis of pregnancy. Many factors, however, likely contribute to the risk of developing this complex disorder.

2.3 Other disorders

Mutations in the *ABCB4* gene are also associated with a rare condition called low phospholipid-associated cholelithiasis (LPAC). This condition is characterized by the formation of small pebble-like deposits of cholesterol in the gallbladder or bile ducts (gallstones). In LPAC, gallstones usually occur in people before age 40, which is young for the appearance of gallstones. In addition, affected individuals may have an accumulation of small crystals of cholesterol (microlithiasis) or a material called biliary sludge in the bile ducts of the liver. Biliary sludge is made up of solid particles that are usually dissolved in bile, including cholesterol crystals and calcium salts. The gallstones, cholesterol crystals, or biliary sludge can cause symptoms, such as pain, fever, nausea, or inflammation of the pancreas (pancreatitis), that can recur even after removal of the gall bladder.

It is thought that mutations in the *ABCB4* gene that are involved in LPAC impair the protein's ability to transfer phospholipids into bile. Because phospholipids help keep cholesterol dissolved in bile, the lack of phospholipids can result in the formation of gallstones or crystals from undissolved cholesterol.

3. Other Names for This Gene

- ATP-binding cassette, sub-family B (MDR/TAP), member 4
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- MDR3
- MDR3_HUMAN
- multidrug resistance protein 3
- multiple drug resistance 3
- P glycoprotein 3/multiple drug resistance 3
- P-glycoprotein-3/multiple drug resistance-3
- PFIC-3
- PGY3

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