Published in final edited form as:

Hepatology. 2016 July ; 64(1): 305. doi:10.1002/hep.28249.

Role of ABCG2 in liver injury associated with erythropoietic protoporphyria

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Dear Editor,

We argue against the opinion in the article by Hagiwara et al that decreased ABCG2 expression might be associated with severe liver damage in erythropoietic protoporphyria (EPP) ⁽¹⁾. Cholestasis is the major type of liver injury in EPP patients, and is dependent on protoporphyrin IX (PPIX)-mediated bile duct blockage ⁽²⁾. The authors documented cholestatic injury in the elder brother by observing high levels of alkaline phosphatase (690 U/L) and total bilirubin (7 mg/dL) in serum ⁽¹⁾. The authors also observed PPIX accumulation in hepatocytes, but not in the biliary system, in the same patient ⁽¹⁾. These observations do not match each other, because less PPIX in bile ducts should cause fewer bile duct blockage and less cholestatic injury. Actually, the data in this study contradict a previous study using genetically engineered EPP mouse models, in which PPIX accumulation in hepatocytes attenuates liver damage ⁽³⁾.

The current study determined PPIX location together with ABCG2 expression using the same fluorescence method ⁽¹⁾. It is unknown whether this fluorescence method is specific for PPIX detection. In addition, liver biopsy of the elder brother showed bile thrombi ⁽¹⁾, which should be the PPIX plugs, because PPIX is highly hydrophobic and is the cause of bile duct blockage ⁽²⁾. We suggest that the authors reevaluate PPIX distribution in the liver by using the standard methods for PPIX analysis ⁽⁴⁾. Furthermore, because the authors reported ABCG2 downregulation in only one EPP patient and measured ABCG2 expression after liver injury ⁽¹⁾, it is difficult to determine whether ABCG2 downregulation is a cause or an effect of EPP-associated liver injury. Finally, the risk of liver injury increases in EPP patients with increased age ⁽⁵⁾. The current study showed liver injury in the elder brother but did not provide the age of the younger brother ⁽¹⁾. In summary, the facts do not support the assertion that decreased ABCG2 expression is the cause of liver damage in EPP.

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