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LETTER TO THE EDITOR, NEWS AND VIEWS

Liver injury and genetic polymorphisms in the cytochrome P450 and UDP-glucuronosyltransferase genes

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Sir,

We thank Dr. Stickel for his insightful comments on our recent letter (Aghdassi et al. 2015). He and Dr. Shouval had originally compiled detailed evidence that drug-induced liver injury associated with non-prescription herbal dietary supplements can, to a certain extent, be attributed to polymorphisms in the cytochrome P450 gene (Stickel and Shouval 2015). One of these agents is a pharmaceutical extract of the herbal antidepressant kava–kava, which was withdrawn from international markets by regulatory authorities because of a significant number of reported cases with severe kava-associated liver injury (Kraft et al. 2001; Stickel et al. 2003). We had collected four such cases and found that half of those requiring transplantation had a polymorphism in the uridine-diphosphate (UDP)-glucuronosyltransferase (UGT) gene that had previously been found to account for a reduced detoxification capacity (Vogel et al. 2001). We also found that none of the patients carried the poor metabolizer CYP2D6 genotype. Other UGT polymorphisms had already been found to be associated with an increased risk of gallstone formation (Buch et al. 2010) or pancreatic injury (Ockenga et al. 2003), but Dr. Stickel correctly points out that the initial association studies were fraught by a PCR amplification bias and subsequent reanalyses resulted in much less prominent associations.

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For drug-induced pancreatic injury, very little is known about potential genetic associations (Grady et al. 1992; Keim et al. 2001). Even more regrettably, neither consented definitions nor drug injury consortia exist that would permit an analysis of underlying genetic and environmental factors, all of which are well-established features of liver injury networks (Navarro et al. 2014).

Dr. Stickel points out that our evidence for an association between drug-induced liver injury and UGT polymorphisms is weak at best, and we do agree with his assessment. After much confusion resulting from the PCR amplification bias that weakened initial studies (Vogel et al. 2001; Ockenga et al. 2003), more recent studies have improved in robustness, but investigations conducted by established liver injury networks are urgently needed before any definite conclusions about the role of UGT can be made. Our letter was meant to encourage such investigations and is clearly insufficient to establish a UGT gene association with kava-induced liver injury.

Dr. Stickel further points to a female predominance among patients with kava-related liver injury and suggests that consumer preference for mild herbal antidepressant may account for this skewed gender ratio. In this context, it is interesting that kava–kava originates from Polynesian islands where it is used in ceremonial (and sometimes recreational) drinking rituals, and its mild sedative, anaesthetic and anxiolytic properties are much appreciated. Unlike for pharmaceutical extracts, cases of liver injury have not been reported in connection with ceremonial use of fresh kava potions. One possible reason may be that women are traditionally excluded from kava-consuming rituals in the island societies of Vanuatu, Fiji and others, and sex-linked factor for liver injury may be a worthwhile target for further investigations. Dr. Stickel rightly indicates that kava extracts may no longer pose a medical problem because of

its withdrawal from the markets. However, the liver toxicity of other herbal extracts like St. John's Wort, *Teucrium chamaedrys* and certain types of green tea is still incompletely understood. We agree with Dr. Stickel that for these compounds drug-induced liver injury repositories and biobanks ought to play a much greater role in identifying the underlying mechanism of damage.

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