

Response to Aghdassi et al., Letter to the editor “Genetic polymorphisms in the UDP-glucuronosyltransferase UGT1A7 gene in patients with acute liver failure after kava–kava consumption”

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Sir,

Diagnosis of drug-induced liver injury (DILI) due to herbal and dietary supplements (HDS) is notoriously difficult and often based on circumstantial evidence and exclusion of other causes. Risk factors are poorly defined, and the spectrum of potential culprit products is changing continuously. Among the well-known precipitators of acute liver injury potentially causing liver failure are products derived from kava (*Piper methysticum rhizoma*) previously used for the treatment of anxiety and depression. Over 100 cases of serious liver damage have been recorded worldwide, with numerous kava products from different manufacturers and no obvious pattern with regard to mode of extraction, dosage, duration of intake, co-medication or patient characteristics. Following numerous cases of fulminant liver failure leading to liver transplantation and death, kava products were banned in the USA, Europe and Australia (Centers for Disease Control and Prevention 2003). Although clinical presentation was considerably variable, causality assessment left little doubt that kava was the cause in a majority of a series of 29 cases of adverse hepatic reactions due to kava in Germany (Stickel et al. 2003). Among these patients, nine developed fulminant liver failure with subsequent liver transplantation in eight of the patients, and three died eventually. Apart from the fact that the majority of individuals were women, likely reflecting consumers' preferences rather than true disposition, no apparent risk factor

could be identified. Russmann et al. (2001) suggested a poor-metabolizer phenotype of cytochrome P450 2D6 as a risk factor for developing kava-related liver damage; however, this observation has not made it into routine diagnostics to identify subjects at risk.

In this issue of the *Archives*, Aghdassi et al. (2015) present an interesting suggestion that there may be a possible additional degradation pathway, and genetic risk factor for kava-related DILI related to the degradation of kavapyrones by a variation of the gene coding for uridine-diphosphate (UDP)-glucuronosyltransferase, *UGT1A7*3*. Authors genotyped four patients with fulminant hepatic failure following kava ingestion and found an *UGT1A7*3* allele frequency of 37.5, and 50 % in those undergoing liver transplantation, but no CYP2D6 poor-metabolizer phenotype. Considering the *UGT1A7*3* allele frequencies among Caucasians between 16 and 36 %, authors felt that the mild overrepresentation in their patients could be a hint for *UGT1A7*3* as a genetic risk factor. In earlier studies, variant *UGT1A7*3* was found in 43 of 59 patients with hepatocellular carcinoma studied by Vogel et al. (2001), but this finding was later revised and attenuated after re-genotyping an enlarged cohort unravelled a PCR amplification bias (Vogel et al. 2011). Although the idea is intriguing, several aspects call for caution in this regard: (1) with such low numbers, the presented series of 4 (!) patients may well be subject to a type I error detecting an association that does not exist; frankly speaking, the *UGT1A7*3* allele frequency of 50 % in transplant liver recipients may simply be a chance finding, and more patients need to be genotyped to generate robust data that withstand statistical scrutiny. For this, it would be interesting to see the *UGT1A7*3* allele frequency in a larger series of patients with unequivocal kava-related liver injury, and networking with databases maintained by international DILI networks is encouraged to find such

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patients (Andrade et al. 2005; Fontana et al. 2009); (2) the UGT1A7 isoenzyme is not expressed in the liver, which renders its importance for liver-related idiosyncratic drug reactions rather low, although it was suggested that may function as a gatekeeper for xenobiotics at their first entry into the human body; (3) among the mutations in the *UGT* gene with a high prevalence in the population is that coding for Gilbert–Meulengracht hyperbilirubinemia, commonly not associated with DILI, but other misadventures. For example, genetic polymorphisms in *UGT1A1*, such as *UGT1A1*28* in Caucasians and Asians and *UGT1A1*6* only in Asians, modify the tolerability of irinotecan, resulting in severe neutropenia in homozygous carriers of one or heterozygosity of either variation (Ichikawa et al. 2015).

In conclusion, there seems to be yet inconclusive evidence that genetic variations in the *UGT* gene have a significant share in the predisposition to kava-related DILI until there is more supportive data. But there may be other genetic variants with a more significant impact, and efforts to their identification are clearly commendable.

And although kava is thankfully off the market, other products are on the rise with unclear risk profiles and the potential to cause life-threatening liver injury (Navarro et al. 2014). Attentive surveillance of their use remains an important task, and thrusting work-up of cases is warranted should toxicities occur.

Compliance with ethical standards

Conflict of interest None.

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