The impact of ABCC11 polymorphisms on the risk of early-onset fluoropyrimidine toxicity

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A missense variant (c.1637C>T, T546M) in ABCC11 encoding the MRP8 (multidrug resistance protein 8), a transporter of 5-fluorodeoxyuridine monophosphate, has been associated with an increased risk of 5-fluorouracil-related severe leukopenia. To validate this association, we investigated the impact of the ABCC11 variants c.1637C>T, c.538G>A and c.395+1087C>T on the risk of early-onset fluoropyrimidine-related toxicity in 514 cancer patients. The ABCC11 variant c.1637C>T was strongly associated with severe leukopenia in patients carrying risk variants in DPYD, encoding the key fluoropyrimidine-metabolizing enzyme dihydropyrimidine dehydrogenase (odds ratio (OR): 71.0; 95% confidence interval (CI): 2.5-2004.8; Pc.1637C>T*DPYD=0.013). In contrast, in patients without DPYD risk variants, no association with leukopenia (OR: 0.95; 95% CI: 0.34-2.6) or overall fluoropyrimidine-related toxicity (OR: 1.02; 95% CI: 0.5-2.1) was observed. Our study thus suggests that c.1637C>T affects fluoropyrimidine toxicity to leukocytes particularly in patients with high drug exposure, for example, because of reduced fluoropyrimidine catabolism.The Pharmacogenomics Journal advance online publication, 22 March 2016; doi:10.1038/tpj.2016.23.

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