Strong association of a common dihydropyrimidine dehydrogenase gene polymorphism with fluoropyrimidine-related toxicity in cancer patients.

BACKGROUND: Cancer patients carrying mutations in the dihydropyrimidine dehydrogenase gene (DPYD) have a high risk to experience severe drug-adverse effects following chemotherapy with fluoropyrimidine drugs such as 5-fluorouracil (5-FU) or capecitabine. The pretreatment detection of this impairment of pyrimidine catabolism could prevent serious, potentially lethal side effects. As known deleterious mutations explain only a limited proportion of the drug-adverse events, we systematically searched for additional DPYD variations associated with enhanced drug toxicity.

METHODOLOGY/PRINCIPAL FINDINGS: We performed a whole gene approach covering the entire coding region and compared DPYD genotype frequencies between cancer patients with good (n = 89) and with poor (n = 39) tolerance of a fluoropyrimidine-based chemotherapy regimen. Applying logistic regression analysis and sliding window approaches we identified the strongest association with fluoropyrimidine-related grade III and IV toxicity for the non-synonymous polymorphism c.496A>G (p.Met166Val). We then confirmed our initial results using an independent sample of 53 individuals suffering from drug-adverse-effects. The combined odds ratio calculated for 92 toxicity cases was 4.42 [95% CI 2.12-9.23]; p
(trend)G with toxicity was particularly present in patients with gastroesophageal and breast cancer, but did not reach significance in patients with colorectal malignancies. CONCLUSION: Our results show compelling evidence that, at least in distinct tumor types, a common DPYD polymorphism strongly contributes to the occurrence of fluoropyrimidine-related drug adverse effects. Carriers of this variant could benefit from individual dose adjustment of the fluoropyrimidine drug or alternate therapies.