Titel des Beitrags:

Analysis of the DPYD gene implicated in 5-fluorouracil catabolism in a cohort of Caucasian individuals.

Abstract:

PURPOSE: Complete or partial loss of dihydropyrimidine dehydrogenase (DPD) function has been described in cancer patients with intolerance to fluoropyrimidine drugs like 5-fluorouracil (5-FU) or Xeloda. The intention of this population study is to assess and to evaluate gene variations in the entire coding region of the dihydropyrimidine dehydrogenase gene (DPYD), which could be implicated in DPD malfunction. EXPERIMENTAL DESIGN: A cohort of 157 individuals was genotyped by denaturing high-performance liquid chromatography; 100 of these genotypes were compared with functional studies on DPD activity and mRNA expression. RESULTS: Twenty-three variants in coding and noncoding regions of the DPYD gene were detected, giving rise to 15 common haplotypes with a frequency of>1%. Rare sequence alterations included a frameshift mutation (295-298delTCAT) and three novel point mutations, 1218G>A (Met406Ile), 1236G>A (Glu412Glu), and 3067C>T (Pro1023Ser). DPD enzyme activity showed high variation in the analyzed population and correlated with DPD mRNA expression. In particular, the novel variants were not accompanied with decreased enzyme activity. However, a statistically significant deviation from the median DPD activity of the population was associated with the mutations 1601G>A (Ser534Asn) and
2846A>T (Asp949Val). CONCLUSION: This work presents an analysis of DPYD gene variations in a large cohort of Caucasians. The results reflect the genetic and enzymatic variability of DPD in the population and may contribute to further insight into the pharmacogenetic disorder of DPD deficiency.