Intragenic deletions and a deep intronic mutation affecting pre-mRNA splicing in the dihydropyrimidine dehydrogenase gene as novel mechanisms causing 5-fluorouracil toxicity.

Dihydropyrimidine dehydrogenase (DPD) is the initial enzyme acting in the catabolism of the widely used antineoplastic agent 5-fluorouracil (5FU). DPD deficiency is known to cause a potentially lethal toxicity following administration of 5FU. Here, we report novel genetic mechanisms underlying DPD deficiency in patients presenting with grade III/IV 5FU-associated toxicity. In one patient a genomic DPYD deletion of exons 21-23 was observed. In five patients a deep intronic mutation c.1129-5923C>G was identified creating a cryptic splice donor site. As a consequence, a 44 bp fragment corresponding to nucleotides c.1129-5967 to c.1129-5924 of intron 10 was inserted in the mature DPD mRNA. The deleterious c.1129-5923C>G mutation proved to be in cis with three intronic polymorphisms (c.483 + 18G>A, c.959-51T>G, c.680 + 139G>A) and the synonymous mutation c.1236G>A of a previously identified haplotype. Retrospective analysis of 203 cancer patients showed that the c.1129-5923C>G mutation was significantly enriched in patients with severe 5FU-associated toxicity (9.1%) compared to patients without toxicity.
(2.2%). In addition, a high prevalence was observed for the c.1129-5923C>G mutation in the normal Dutch (2.6%) and German (3.3%) population. Our study demonstrates that a genomic deletion affecting DPYD and a deep intronic mutation affecting pre-mRNA splicing can cause severe 5FU-associated toxicity. We conclude that screening for DPD deficiency should include a search for genomic rearrangements and aberrant splicing.

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