Automated Identification of Novel Dehydrogenase Mutations Linked to Chemotherapy Sensitivity by Integrating Computational Mutation Predictions

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5-Fluorouracil (5-FU), a common chemotherapy for solid tumors, is metabolized primarily by dihydropyrimidine dehydrogenase (DPD), encoded by the DPYD gene. With > 200 known variants, individuals with nonfunctional DPYD alleles exhibit impaired 5-FU metabolism and are at risk of severe toxicity. Approximately 3-5% of the population has partial DPD deficiency, and 0.2% completely lack enzymatic activity. Despite this, DPYD genotyping is not standard practice. This study uses computational methods to search for novel variants within DPYD coding region. cBioPortal was utilized to search the TCGA database for studies involving colon cancer patients with novel DPYD mutations exhibiting a total FIS score of at least 2 or identified through 3D modeling of DPD using PyMol based on their proximity to or within the active site. Putative pathogenic mutations were analyzed using AlphaMissense and ChimeraX to assign a RSMD score, assessing their potential negative impact on DPD function. Seven mutations were identified with possible pathogenicity. Of these seven identified mutations, four (c.198G > C/T, c.2161G > A, c.2185G > A, c.2909C > A) were found to have high enough pathogenic possibilities to be considered for treatment procedures. An automated procedure of this assessment is available via a public online notebook. By combining computational modeling with analysis of naturally occurring mutations in colon cancer patients, we have successfully identified potentially pathogenic mutations in the DPYD gene. This information can enhance existing clinical diagnostic tests, providing a more comprehensive assessment of DPYD mutations, including novel variants.

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