Dihydropyrimidine Dehydrogenase (DPYD), 3 Variants

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Dihydropyrimidine dehydrogenase is an enzyme encoded by the *DYPD* gene and is responsible for the metabolism of 5-fluorouracil (5-FU), the most frequently used chemotherapeutic drug in the treatment of colorectal adenocarcinomas. Germline variants in *DPYD* affect enzyme production, which may result in dose-related toxicity or in a reduction of treatment effectiveness.

Disease Overview

Physiology

When 5-FU is metabolized in the body

- Approximately 80% is catabolized by the enzyme dihydropyrimidine dehydrogenase (DPD) into an *inactive* form, dihydro 5-FU, and excreted in urine
- Remaining drug is metabolized into an *active* form which inhibits the synthesis of both DNA and RNA by
  - Direct incorporation of cytotoxic metabolites (5-FUTP and 5-FdUTP) into nucleic acids
  - Competitive inhibition of the thymidylate synthase (TYMS) enzyme

Treatment Issues

- Intravenous 5-FU: Adrucil (5-fluorouracil)
- Oral 5-FU prodrugs: Xeloda (capecitabine), Uftoral (tegafur/uracil)
- Grade III-IV drug toxicity attributed to 5-FU occurs in approximately 16% of individuals
- Germline variants in the *DPYD* gene can lead to reduced 5-FU catabolism and result in grade III-IV 5-FU toxicity
  - Complications include hematologic, gastrointestinal, and dermatologic symptoms as well as toxicity-related death
  - Clinical testing for variants that alter 5-FU metabolism may aid in patient care

Clinical Issues (5-FU Dosing)

- Homozygous or compound heterozygous *DYPD* gene variants
  - Associated with DPD enzyme deficiency
  - Avoidance of fluoropyrimidine therapy is recommended
    - An alternate drug should be selected
- Heterozygous *DYPD* gene variants
  - Associated with 30-70% of normal DPD activity
  - Fluoropyrimidine therapy should be initiated with reduced dosing
    - Approximately 25-50% of a standard dose is recommended
    - Titration of dose based on patient tolerability and therapeutic drug monitoring
- Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing available at www.pharmgkb.org/gene/PA145

Genetics

Gene

DPYD

Variants Tested

DPYD Gene Variants		
***DPYD* Variant**	**Alternative Name(s)**	**Predicted Consequence in Patients Receiving 5-FU**
c.1679T>G	*DPYD**13, rs55886062	No DPD activity; increased toxicity risk
c.1905+1G>A	*DPYD**2A, IVS14+1 G>A, rs3918290	No DPD activity; increased toxicity risk
c.2846A>T	rs67376798	Decreased DPD activity; increased toxicity risk

See www.pharmgkb.org for allele frequency and other data about these variants.

Test Interpretation

Results

Positive

- *DPYD* gene variant detected
  - Predicts decreased DPD enzymatic activity
  - Associated with an increased risk for grade III-IV 5-FU toxicity

Negative

- No variants detected in *DPYD*: predictive of *1 functional alleles

Limitations

- Only targeted variants in the *DPYD* gene will be detected
- Rare diagnostic errors may occur due to rare sequence variations
- Genetic and/or nongenetic factors not detected by this test may affect 5-FU drug metabolism and efficacy and the risk for toxicity
- Genotyping does not replace the need for therapeutic drug monitoring or clinical observation
- Lack of detection of the targeted *DPYD* variants does not rule out risk for 5-FU toxicity or predict degree of responsiveness to 5-FU

Additional Resources

Caudle KE, Thorn CF, Klein TE , et al. Clinical Pharmacogenetics Implementation Consortium guidelines for dihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing. *Clin Pharmacol Ther*. 2013;94(6):640-645.

Related Information

Colorectal (Colon) Cancer
Germline Pharmacogenetics - PGx