Dihydropyrimidine Dehydrogenase (DPYD), 3 Variants

Dihydropyrimidine dehydrogenase is an enzyme encoded by the *DPYD* 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

- ~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 ~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 *DPYD* gene variants
  - Associated with DPD enzyme deficiency
  - Avoidance of fluoropyrimidine therapy is recommended
    - An alternate drug should be selected
- Heterozygous *DPYD* gene variants
  - Associated with 30-70% of normal DPD activity
  - Fluoropyrimidine therapy should be initiated with reduced dosing
    - ~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](http://www.pharmgkb.org/gene/PA145)
Genetics

Gene

*DPYD*

Variants Tested

<table>
<thead>
<tr>
<th><em>DPYD</em> Variant</th>
<th>Alternative Name(s)</th>
<th>Predicted Consequence in Patients Receiving 5-FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.1679T&gt;G</td>
<td><em>DPYD</em>13, rs55886062</td>
<td>Decreased DPD activity</td>
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<tr>
<td></td>
<td></td>
<td>Increased toxicity risk</td>
</tr>
<tr>
<td>c.1905+1G&gt;A</td>
<td><em>DPYD</em>2A, IVS14+1 G&gt;A, rs3918290</td>
<td>Abolished DPD activity</td>
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<tr>
<td></td>
<td></td>
<td>Greatly increased toxicity risk</td>
</tr>
<tr>
<td>c.2846A&gt;T</td>
<td>rs67376798</td>
<td>Decreased DPD activity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased toxicity risk</td>
</tr>
</tbody>
</table>

See [www.pharmgkb.org](http://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

References

Related Information

Colorectal Cancer
Germline Pharmacogenetics - PGx