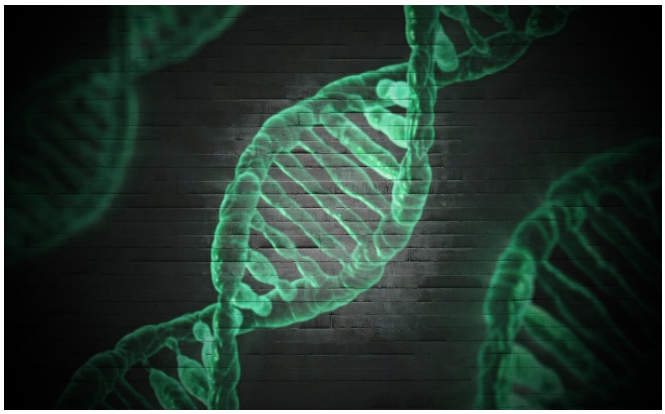
Rare gene mutations lead to greatly increased risk of fatal chemotherapy toxicity

23 September 2021



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Patients with abnormal variants (mutations) in the *DPYD* gene are known to be at risk for severe toxicity from treatment with 5-fluorouracil or capecitabine—chemotherapies commonly used to treat colorectal cancer, as well as pancreatic, breast, gastroesophageal and other cancers. But previous studies have not reported the extent to which these *DPYD* gene variants are linked to fatal chemotherapy toxicity, as fatal toxicity is rare in any individual study. Pooling studies is needed to examine the association of *DPYD* gene variants with this severe outcome.

In a meta-analysis of previously published studies, researchers at Dartmouth's and Dartmouth-Hitchcock's Norris Cotton Cancer Center (NCCC), led by Gabriel A. Brooks, MD, MPH, found that uncommon variants in the *DPYD* gene, present in 4% of all cancer patients, were associated with a 25-times increased risk of fatal toxicity after treatment with standard doses of either chemotherapy drug. The absolute risk of fatal toxicity was 0.1% in patients without DPYD gene variants, and as high as 3.7% in patients with any of the three most severe *DPYD* gene variants.

The team's study is newly published online in*The Oncologist.*

Though *DPYD* and other gene testing has been recommended by the European Medicines Agency since spring of 2020, gene testing is not widely done in the US before patients are administered chemotherapy with 5-fluorouracil or capecitabine. Brooks' study suggests that adding pre-treatment screening may help prevent avoidable chemotherapy-related deaths without interrupting standard of care, as most patients who carry abnormal gene variants can still be treated with reduced doses of these chemotherapies. NCCC has already implemented routine screening for *DPYD* gene variants in most gastrointestinal cancer patients.

"US organizations such as the Food & Drug Administration (FDA), the American Society of Clinical Oncology, or the National Comprehensive Cancer Network should consider recommending this testing. The FDA is currently considering a citizen's petition advocating for more widespread genetic testing, of which I am a cosigner," says Brooks.

More information: Bhavina B. Sharma et al, Pathogenic DPYD variants and treatment?related mortality in patients receiving fluoropyrimidine chemotherapy: A systematic review and meta?analysis, *The Oncologist* (2021). DOI: 10.1002/ONCO.13967

Provided by Dartmouth-Hitchcock Medical Center