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Pharmacogenomics study finds rare gene variants critical for personalized drug treatment

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The use of genetic tests to predict a patient's response to drugs is increasingly important in the development of personalized medicine. But genetic tests often only look for the most common gene variants. In a pharmacogenomics study published online today in *Genome Research* (www.genome.org), researchers have characterized rare genetic variants in a specific gene that can have a significant influence in disposition of a drug used to treat cancer and autoimmune disease, a finding that will help improve the effectiveness of personalized care.

The drug methotrexate is used to treat cancers such as acute lymphoblastic leukemia, and autoimmune diseases including rheumatoid arthritis. Common genetic variants in the *SLCO1B1* gene, which encodes a transporter in the liver important for clearance of medication from the body, are present in 10-15% of the population and affect the efficiency of methotrexate clearance from the body.

Low clearance of methotrexate results in high levels in the blood and increased side effects. Rare variants could also significantly affect drug clearance, but the influence of rare versus common *SLCO1B1* variants in methotrexate clearance had not yet been explored.

In this report, an international team of researchers sequenced the exons of *SLCO1B1*, the gene regions that code for protein, in a cohort of pediatric patients receiving methotrexate, finding rare genetic variants

that have an effect on the efficiency of clearance of the drug from the body. "We showed that rare inherited genomic variants, present in as few as 1 in 699 people, account for a significant percentage of variability in blood levels of methotrexate," said Dr. Mary Relling of St. Jude Children's Research Hospital, senior author of the study. "This means that the high blood levels present in 2% of people are due to very rare genetic variants."

The research group then utilized computational algorithms to predict the potential negative impact of genomic variants identified in this study on function of the SLCO1B1 protein in the transport of methotrexate. They then tested these predictions in laboratory cell lines, confirming that these genetic variants conferred lower transport of the drug.

"Our discovery of important but rare coding variants in *SLCO1B1* not only has implications for methotrexate, but also possibly for other drugs," explained Dr. Laura Ramsey of St. Jude Children's Research Hospital, primary author of the study. Ramsey noted that SLCO1B1 variants are tested to inform choice of the appropriate dosage of statins, commonly used to treat or prevent high cholesterol.

Ramsey added that clinical genetic tests are currently limited, generally only testing for the most common *SLCO1B1* variants. "Our findings that there are additional rare functional coding variants in this gene suggest that genotyping tests would need to expand to include rare variants in order to avoid false negative test results."

Scientists from St. Jude Children's Research Hospital (Memphis, TN), Aarhus University (Aarhus, Denmark), MD Anderson Cancer Center (Houston, TX), the University of Tennessee Health Science Center (Memphis, TN), the Sidney Kimmel Comprehensive Cancer Center (Baltimore, MD), and the University of California, San Francisco (San Francisco, CA) contributed to this study.

More information: The manuscript will be published online ahead of print on December 6, 2011. Its full citation is as follows: Ramsey LB, Bruun GH, Yang W, Trevino LR, Vattathil S, Scheet P, Cheng C, Rosner GL, Giacomini KM, Fan Y, Sparreboom A, Mikkelsen TS, Corydon TJ, Pui C, Evans WE, Relling MV. Rare versus common variants in pharmacogenetics: SLCO1B1 variation and methotrexate disposition. Genome Res doi: 10.1101/gr.129668.111