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My46 Trait Profile

Thiopurine response

Other Names: Select U.S. brand names of thiopurines: Azasan®, Imuran®, Lanvis®, Purinethol®, Tabloid®

An individual's response to thiopurines (a group of medications that are used to suppress the body's immune system) is in part due to variants in the TPMT gene. Individuals with variants in this gene react more strongly to thiopurines and may have a higher chance of experiencing serious side effects from an average dose of thiopurines.

Characteristics of Thiopurine response

Thiopurines are a group of medications that are used to suppress the body's immune system. Healthcare providers often prescribe thiopurine medications for a variety of conditions including autoimmune disorders such as rheumatoid arthritis and lupus; and inflammatory bowel disorders such as Crohn's disease and ulcerative colitis. Thiopurines can also be used as anti-cancer medications to treat lymphoma and leukemia. They are also often prescribed for organ transplant recipients to help prevent organ rejection. Thiopurine medications, just like other medications, can cause a range of side effects. The same dose of the medication may cause nausea in one person or more serious complications such as damaging or suppressing the bone marrow (myelosuppresion) in another person. Myelosuppression can result in low production of white blood cells, which in turn can make someone more susceptible to illnesses and infections. Myelosuppresion can also result in low production of red blood cells, causing anemia. The amount of thiopurine (i.e., the dose) a person needs varies between individuals: too little medication may have no clinical effect (i.e., not treat what it was initially prescribed for), but too much medication can lead to serious side effects such as myelosuppression. The differences in thiopurine response for each individual are largely due to variants in the TPMT gene. An individual who has low or reduced TPMT activity requires a lower dose than the average thiopurine dose. However, variation in thiopurine response is influenced by many other factors as well, including its interaction with other medications.

Diagnosis/Testing

Many factors influence an individual's ideal dose of thiopurines, but changes or variants in the TPMT gene play an important role. The TPMT gene makes the S-methyltransferase enzyme. This enzyme helps to metabolize (break down or process) thiopurine medications in the body. Variants in the TPMT gene (e.g., TPMT*2, TPMT*3A, TPMT*3B, TPMT*3C, TPMT*4) cause this enzyme to not work as well. Thus, for an individual who is taking a thiopurine medication and has a TPMT variant, the thiopurine medication is metabolized at a much slower rate (i.e. slow metabolizer), and in turn, the medication stays in the body longer.

The TPMT variants an individual has can determine how rapidly the thiopurine medication is metabolized and cleared from the body. Accordingly, knowing an individual's TPMT variant status can be used to help guide what is the best dose of thiopurine to give an individual.

Management/Surveillance

Individuals with variants in the TPMT gene may require a reduced thiopurine dose. The level of dose reduction depends on how many variants an individual carries. Individuals with multiple variants in the gene often require a large reduction in thiopurine dose. It is important to know that regardless of genetic test results, response to thiopurines still requires monitoring with regular blood tests (e.g., complete blood count) or other appropriate clinical monitoring.

Mode of inheritance

Response to thiopurines is a complex condition, which means that it is caused by a combination of many different factors. These factors can be genetic or non-genetic (such as environmental factors). Complex conditions are inherited in a multifactorial pattern. This means that the chance for an individual to develop a serious side effect from the use of thiopurine medications is influenced by the number and type of genetic and non-genetic factors to which an individual is exposed. In other words, no single gene, and no single environmental factor causes an undesired response to thiopurines. Not all of these genetic factors and environmental factors are known.

Risk to family members

Complex conditions, like response to thiopurines, tend to recur in families, because they are partly influenced by genetic variants.

Special considerations

None

Resources

PharmGKB: The Pharmacogenomics Knowledgebase
http://www.pharmgkb.org
Genetic Home Reference: TPMT
http://ghr.nlm.nih.gov/gene/TPMT

References

McDonagh, EM. et al. (2011)."From pharmacogenomic knowledge acquisition to clinical applications: the PharmGKB as a clinical pharmacogenomic biomarker resource." Biomarkers in Medicine 5(6): 795-806.
Relling, MV. et al. (2013)."Clinical Pharmacogenetics Implementation Consortium Guidelines for Thiopurine Methyltransferase Genotype and Thiopurine Dosing: 2013 Update." Clinical Pharmacology & Therapeutics 93(4): 324-325.

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