TPMT gene

thiopurine S-methyltransferase

Normal Function

The *TPMT* gene provides instructions for making an enzyme called thiopurine S-methyltransferase (TPMT). This enzyme carries out a specific chemical reaction called S-methylation of a group of molecules known as aromatic and heterocyclic sulphydryl compounds. This function is of particular interest because it is critical for breaking down (metabolizing) drugs called thiopurines. These drugs, which include 6-thioguanine, 6-mercaptopurine, and azathioprine, inhibit (suppress) the body's immune system. They are used to treat several forms of cancer and other disorders involving immune system malfunction, such as Crohn's disease and rheumatoid arthritis. Thiopurine drugs are also used in organ transplant recipients to help prevent the immune system from attacking the transplanted organ.

Once inside the body, thiopurine drugs are converted to toxic compounds that kill immune system cells in the bone marrow. The TPMT enzyme "turns off" thiopurine drugs by metabolizing them to inactive, nontoxic compounds.

Health Conditions Related to Genetic Changes

Thiopurine S-methyltransferase deficiency

Changes in the *TPMT* gene cause TPMT deficiency, which is a reduction in the activity of the TPMT enzyme. Without enough of this enzyme, the body cannot "turn off" thiopurine drugs by metabolizing them into inactive compounds. The drugs stay in the body longer and continue to destroy cells unchecked, which leads to bone marrow damage (hematopoietic toxicity). This damage causes myelosuppression, which is an inability of the bone marrow to make enough red blood cells, white blood cells, and platelets. A shortage of these cells can cause a variety of health problems, the most serious of which include abnormal bleeding and an increased risk of potentially life-threatening infections. Although hematopoietic toxicity can occur in anyone who takes thiopurine drugs, people with TPMT deficiency are at highest risk of this complication.

The *TPMT* gene can be classified as either low-activity or high-activity. When the gene is altered in a way that impairs the activity of the TPMT enzyme, it is described as low-activity. When the gene is unaltered and TPMT activity is normal, it is described as high-activity. Because two copies of the gene are present in each cell, each person can have

two low-activity copies, one low-activity copy and one high-activity copy, or two high-activity copies. People with two low-activity copies of the *TPMT* gene in each cell have TPMT deficiency and are at the greatest risk of developing hematopoietic toxicity when treated with thiopurine drugs unless they are given much less than the usual dose. People with one high-activity copy and one low-activity copy have moderately reduced enzyme activity and are also at increased risk of this complication unless given a significantly lower dose of the drug. People with two high-activity copies have normal TPMT activity and do not have an increased risk of hematopoietic toxicity with thiopurine drug treatment.

More than 40 low-activity versions (alleles) of the *TPMT* gene have been found in people with TPMT deficiency. Each of these alleles includes one or more changes in the gene that reduce the stability and activity of the TPMT enzyme. Two particular alleles, *TPMT*3A* and *TPMT*3C*, underlie more than 90 percent of cases of the condition. Studies suggest that *TPMT*3A* is the most common low-activity allele in whites, while *TPMT*3C* is the most common low-activity allele in Asians, Africans, and African Americans.

Other Names for This Gene

- S-adenosyl-L-methionine:thiopurine S-methyltransferase
- thiopurine methyltransferase
- TPMT_HUMAN

Additional Information & Resources

Tests Listed in the Genetic Testing Registry

- Tests of TPMT (https://www.ncbi.nlm.nih.gov/gtr/all/tests/?term=7172[geneid])

Scientific Articles on PubMed

- PubMed (https://pubmed.ncbi.nlm.nih.gov/?term=%28%28TPMT%5BTIAB%5D%29+OR+%28thiopurine+S-methyltransferase%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+720+days%22%5Bdp%5D)

Catalog of Genes and Diseases from OMIM

- THIOPURINE S-METHYLTRANSFERASE; TPMT (https://omim.org/entry/187680)

Gene and Variant Databases

- NCBI Gene (https://www.ncbi.nlm.nih.gov/gene/7172)
- ClinVar (https://www.ncbi.nlm.nih.gov/clinvar?term=TPMT[gene])

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Genomic Location

The *TPMT* gene is found on chromosome 6 (https://medlineplus.gov/genetics/chromosome/6/).

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