Thiopurine S-methyltransferase deficiency

Thiopurine S-methyltransferase (TPMT) deficiency is a condition characterized by significantly reduced activity of an enzyme that helps the body process drugs called thiopurines. These drugs, which include 6-thioguanine, 6-mercaptopurine, and azathioprine, inhibit (suppress) the body’s immune system. Thiopurine drugs are used to treat some autoimmune disorders, including Crohn disease and rheumatoid arthritis, which occur when the immune system malfunctions. These drugs are also used to treat several forms of cancer, particularly cancers of blood-forming tissue (leukemias) and cancers of immune system cells (lymphomas). Additionally, thiopurine drugs are used in organ transplant recipients to help prevent the immune system from attacking the transplanted organ.

A potential complication of treatment with thiopurine drugs is damage to the bone marrow (hematopoietic toxicity). Although this complication can occur in anyone who takes these drugs, people with TPMT deficiency are at highest risk. Bone marrow normally makes several types of blood cells, including red blood cells, which carry oxygen; white blood cells, which help protect the body from infection; and platelets, which are involved in blood clotting. Damage to the bone marrow results in myelosuppression, a condition in which the bone marrow is unable to make enough of these cells. A shortage of red blood cells (anemia) can cause pale skin (pallor), weakness, shortness of breath, and extreme tiredness (fatigue). Low numbers of white blood cells (neutropenia) can lead to frequent and potentially life-threatening infections. A shortage of platelets (thrombocytopenia) can cause easy bruising and bleeding.

Many healthcare providers recommend that patients’ TPMT activity levels be tested before thiopurine drugs are prescribed. In people who are found to have reduced enzyme activity, the drugs may be given at a significantly lower dose or different medications can be used to reduce the risk of hematopoietic toxicity.

TPMT deficiency does not appear to cause any health problems other than those associated with thiopurine drug treatment.

Frequency

Studies suggest that less than 1 percent of individuals in the general population have TPMT deficiency. Another 11 percent have moderately reduced levels of TPMT activity that increase their risk of hematopoietic toxicity with thiopurine drug treatment.

Causes

TPMT deficiency results from changes in the TPMT gene. This gene provides instructions for making the TPMT enzyme, which plays a critical role in breaking down (metabolizing) thiopurine drugs. Once inside the body, these drugs are converted to
toxic compounds that kill immune system cells in the bone marrow. The TPMT enzyme "turns off" thiopurine drugs by breaking them down into inactive, nontoxic compounds. Changes in the *TPMT* gene reduce the stability and activity of the TPMT enzyme. Without enough of this enzyme, the drugs cannot be "turned off," so they stay in the body longer and continue to destroy cells unchecked. The resulting damage to the bone marrow leads to potentially life-threatening myelosuppression.

**Inheritance Pattern**

The activity of the TPMT enzyme is inherited in a pattern described as autosomal codominant. Codominance means that two different versions of the gene are active (expressed), and both versions influence the genetic trait.

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.

**Other Names for This Condition**

- poor metabolism of thiopurines
- thiopurine methyltransferase deficiency
- TPMT deficiency

**Diagnosis & Management**

**Genetic Testing Information**

- What is genetic testing? [primer/testing/genetictesting](https://www.ncbi.nlm.nih.gov/gtr/conditions/C0342801/)
Research Studies from ClinicalTrials.gov

- ClinicalTrials.gov
  https://clinicaltrials.gov/ct2/results?cond=%22thiopurine+S-methyltransferase+deficiency%22+OR+%22thiopurine%22

Other Diagnosis and Management Resources

- MedlinePlus Drug: Azathioprine
  https://medlineplus.gov/druginfo/meds/a682167.html
- MedlinePlus Drug: Mercaptopurine
  https://medlineplus.gov/druginfo/meds/a682653.html
- MedlinePlus Drug: Thioguanine
  https://medlineplus.gov/druginfo/meds/a682099.html

Additional Information & Resources

Health Information from MedlinePlus

- Drug: Azathioprine
  https://medlineplus.gov/druginfo/meds/a682167.html
- Drug: Mercaptopurine
  https://medlineplus.gov/druginfo/meds/a682653.html
- Drug: Thioguanine
  https://medlineplus.gov/druginfo/meds/a682099.html
- Encyclopedia: Anemia
  https://medlineplus.gov/ency/article/000560.htm
- Encyclopedia: Low White Blood Cell Count and Cancer
  https://medlineplus.gov/ency/patientinstructions/000675.htm
- Encyclopedia: Thrombocytopenia - Drug-Induced
  https://medlineplus.gov/ency/article/000556.htm
- Health Topic: Bone Marrow Diseases
  https://medlineplus.gov/bonemarrowdiseases.html
- Health Topic: Drug Reactions
  https://medlineplus.gov/drugreactions.html
- Medical Tests: Pharmacogenetic Tests
  https://medlineplus.gov/lab-tests/pharmacogenetic-tests/

Genetic and Rare Diseases Information Center

- Thiopurine S methyltransferase deficiency
  https://rarediseases.info.nih.gov/diseases/5173/thiopurine-s-methyltransferase-deficiency
Educational Resources

- MalaCards: thiopurines, poor metabolism of, 1
  https://www.malacards.org/card/thiopurines_poor_metabolism_of_1
- MalaCards: thiopurines, poor metabolism of, 2
  https://www.malacards.org/card/thiopurines_poor_metabolism_of_2
- Orphanet: Orphanet: Thiopurine S-methyltransferase deficiency
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=3315
- St. Jude’s Children’s Research Hospital: Thiopurine Methyltransferase (TPMT)
  https://www.stjude.org/research/clinical-trials/pg4kds-pharmaceutical-science/
  implemented-genes/thiopurine-methyltransferase-tpmt.html
- The Leukemia & Lymphoma Society: Normal Blood and Marrow
  https://www.lls.org/managing-your-cancer/understanding-blood-marrow-and-the-
  lymphatic-system/normal-blood-and-marrow

Patient Support and Advocacy Resources

- American Autoimmune Related Diseases Association
  https://www.aarda.org/
- The Leukemia & Lymphoma Society
  https://www.lls.org/
- Transplant Living from the United Network for Organ Sharing
  https://transplantliving.org/after-the-transplant/preventing-rejection/post-transplant-
  medications/

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28thiopurine+S-methyltrans-
  sferase+deficiency%5BTIAB%5D%29+OR+%28TPMT+deficiency%5BTIAB%5D
  %29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+
  3600+days%22%5Bdp%5D

Catalog of Genes and Diseases from OMIM

- THIOPURINES, POOR METABOLISM OF, 1
  http://omim.org/entry/610460
Sources for This Summary

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/9841604

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/18303966

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/16267626

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/11304783

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/20096268

  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/23962279 
  Free article on PubMed Central: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3971986/

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