Dihydropyrimidine Dehydrogenase Deficiency

Subjects: Genetics & Heredity

Contributor: Nicole Yin

Dihydropyrimidine dehydrogenase deficiency is a disorder characterized by a wide range of severity, with neurological problems in some individuals and no signs or symptoms in others.

genetic conditions

1. Introduction

In people with severe dihydropyrimidine dehydrogenase deficiency, the disorder becomes apparent in infancy. These affected individuals have neurological problems such as recurrent seizures (epilepsy), intellectual disability, a small head size (microcephaly), increased muscle tone (hypertonia), delayed development of motor skills such as walking, and autistic behaviors that affect communication and social interaction. Other affected individuals are asymptomatic, which means they do not have any signs or symptoms of the condition. Individuals with asymptomatic dihydropyrimidine dehydrogenase deficiency may be identified only by laboratory testing.

People with dihydropyrimidine dehydrogenase deficiency, including those who otherwise exhibit no symptoms, are vulnerable to severe, potentially life-threatening toxic reactions to certain drugs called fluoropyrimidines that are used to treat cancer. Common examples of these drugs are 5-fluorouracil and capecitabine. These drugs are not broken down efficiently by people with dihydropyrimidine dehydrogenase deficiency and build up to toxic levels in the body (fluoropyrimidine toxicity). Severe inflammation and ulceration of the lining of the gastrointestinal tract (mucositis) may occur, which can lead to signs and symptoms including mouth sores, abdominal pain, bleeding, nausea, vomiting, and diarrhea. Fluoropyrimidine toxicity may also lead to low numbers of white blood cells (neutropenia), which increases the risk of infections. It can also be associated with low numbers of platelets in the blood (thrombocytopenia), which impairs blood clotting and may lead to abnormal bleeding (hemorrhage). Redness, swelling, numbness, and peeling of the skin on the palms and soles (hand-foot syndrome); shortness of breath; and hair loss may also occur.

2. Frequency

Severe dihydropyrimidine dehydrogenase deficiency, with its early-onset neurological symptoms, is a rare disorder. Its prevalence is unknown. However, between 2 and 8 percent of the general population may be vulnerable to toxic reactions to fluoropyrimidine drugs caused by otherwise asymptomatic dihydropyrimidine dehydrogenase deficiency.

3. Causes

Dihydropyrimidine dehydrogenase deficiency is caused by mutations in the *DPYD* gene. This gene provides instructions for making an enzyme called dihydropyrimidine dehydrogenase, which is involved in the breakdown of molecules called uracil and thymine. Uracil and thymine are pyrimidines, which are one type of nucleotide. Nucleotides are building blocks of DNA, its chemical cousin RNA, and molecules such as ATP and GTP that serve as energy sources in the cell.

Mutations in the *DPYD* gene result in a lack (deficiency) of functional dihydropyrimidine dehydrogenase. Dihydropyrimidine dehydrogenase deficiency interferes with the breakdown of uracil and thymine, and results in excess quantities of these molecules in the blood, urine, and the fluid that surrounds the brain and spinal cord (cerebrospinal fluid). It is unclear how the excess uracil and thymine are related to the specific signs and symptoms of dihydropyrimidine dehydrogenase deficiency. Mutations that result in the absence (complete deficiency) of dihydropyrimidine dehydrogenase generally lead to more severe signs and symptoms than do mutations that lead to a partial deficiency of this enzyme.

Because fluoropyrimidine drugs are also broken down by the dihydropyrimidine dehydrogenase enzyme, deficiency of this enzyme leads to the drug buildup that causes fluoropyrimidine toxicity.

3.1. The Gene Associated with Dihydropyrimidine Dehydrogenase Deficiency

- DPYD

4. Inheritance

Dihydropyrimidine dehydrogenase deficiency is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. Depending on the severity of these mutations, people with two mutated copies of the *DPYD* gene in each cell may exhibit the signs and symptoms of this disorder, or they may be generally asymptomatic but at risk for toxic reactions to fluoropyrimidine drugs.

The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition. However, people with one mutated copy of the *DPYD* gene in each cell may still experience toxic reactions to fluoropyrimidine drugs.

5. Other Names for This Condition

- dihydropyrimidinuria
- DPD deficiency
- familial pyrimidemia
- hereditary thymine-uraciluria

References

1. Al-Sanna'a NA, Van Kuilenburg AB, Atrak TM, Abdul-Jabbar MA, Van Gennip AH.Dihydropyrimidine dehydrogenase deficiency presenting at birth. J Inherit MetabDis. 2005;28(5):793-6.
2. Caudle KE, Thorn CF, Klein TE, Swen JJ, McLeod HL, Diasio RB, Schwab M.Clinical Pharmacogenetics Implementation Consortium guidelines fordihydropyrimidine dehydrogenase genotype and fluoropyrimidine dosing. ClinPharmacol Ther. 2013 Dec;94(6):640-5. doi: 10.1038/clpt.2013.172.
3. Ciccolini J, Gross E, Dahan L, Lacarelle B, Mercier C. Routinedihydropyrimidine dehydrogenase testing for anticipating 5-fluorouracil-relatedsevere toxicities: hype or hope? Clin Colorectal Cancer. 2010 Oct;9(4):224-8.doi: 10.3816/CCC.2010.n.033. Review.
4. Mattison LK, Fourie J, Desmond RA, Modak A, Saif MW, Diasio RB. Increasedprevalence of dihydropyrimidine dehydrogenase deficiency in African-Americanscompared with Caucasians. Clin Cancer Res. 2006 Sep 15;12(18):5491-5.
5. Saif MW, Mattison L, Carollo T, Ezzeldin H, Diasio RB. Dihydropyrimidinedehydrogenase deficiency in an Indian population. Cancer Chemother Pharmacol.2006 Sep;58(3):396-401.
6. van Kuilenburg AB, De Abreu RA, van Gennip AH. Pharmacogenetic and clinicalaspects of dihydropyrimidine dehydrogenase deficiency. Ann Clin Biochem. 2003Jan;40(Pt 1):41-5. Review.
7. van Kuilenburg AB, Dobritzsch D, Meinsma R, Haasjes J, Waterham HR, NowaczykMJ, Maropoulos GD, Hein G, Kalhoff H, Kirk JM, Baaske H, Aukett A, Duley JA, WardKP, Lindqvist Y, van Gennip AH. Novel disease-causing mutations in thedihydropyrimidine dehydrogenase gene interpreted by analysis of thethree-dimensional protein structure. Biochem J. 2002 May 15;364(Pt 1):157-63.
8. van Kuilenburg AB, Meijer J, Mul AN, Hennekam RC, Hoovers JM, de Die-Smulders CE, Weber P, Mori AC, Bierau J, Fowler B, Macke K, Sass JO, Meinsma R, HennermannJB, Miny P, Zoetekouw L, Vijzelaar R, Nicolai J, Ylstra B, Rubio-Gozalbo ME.Analysis of severely affected patients with dihydropyrimidine dehydrogenasedeficiency reveals large intragenic rearrangements of DPYD and a de novointerstitial deletion del(1)(p13.3p21.3). Hum Genet. 2009 Jun;125(5-6):581-90.doi: 10.1007/s00439-009-0653-6.
9. Van Kuilenburg AB, Vreken P, Abeling NG, Bakker HD, Meinsma R, Van Lenthe H,De Abreu RA, Smeitink JA, Kayserili H, Apak MY, Christensen E, Holopainen I,Pulkki K, Riva D, Botteon G, Holme E, Tulinius M, Kleijer WJ, Beemer FA, Duran M,Niezen-Koning KE, Smit GP, Jakobs C, Smit LM, Van Gennip AH, et al. Genotype and phenotype in patients with dihydropyrimidine dehydrogenase deficiency. Hum Genet.1999 Jan;104(1):1-9. Review.

Retrieved from https://www.encyclopedia.pub/entry/history/show/11350