

# Clopidogrel Resistance

Subjects: Genetics & Heredity

Contributor: Peter Tang

Clopidogrel resistance is a condition in which the drug clopidogrel is less effective than normal in people who are treated with it. Clopidogrel (also known as Plavix) is an antiplatelet drug, which means that it prevents blood cells called platelets from sticking together (aggregating) and forming blood clots. This drug is typically given to prevent blood clot formation in individuals with a history of stroke; heart attack; a blood clot in the deep veins of the arms or legs (deep vein thrombosis); or plaque buildup (atherosclerosis) in the blood vessels leading from the heart, which are opened by placement of a small thin tube (stent).

Keywords: genetic conditions

---

## 1. Introduction

People with clopidogrel resistance who receive clopidogrel are at risk of serious, sometimes fatal, complications. These individuals may have another heart attack or stroke caused by abnormal blood clot formation; those with stents can develop blood clots (thromboses) within the stents, impeding blood flow.

People with clopidogrel resistance can be divided into two categories: intermediate metabolizers and poor metabolizers. Intermediate metabolizers are able to process some clopidogrel, so they receive partial benefit from the treatment but are not protected from developing a harmful blood clot. Poor metabolizers process little or no clopidogrel, so they receive very limited benefit from the treatment and are at risk of forming a harmful blood clot.

Clopidogrel resistance does not appear to cause any health problems other than those associated with clopidogrel drug treatment.

## 2. Frequency

Clopidogrel resistance is a common condition, and its incidence can vary depending on ancestry. About half of individuals with Asian ancestry have clopidogrel resistance, with 10 percent of these individuals classified as poor metabolizers. Among people from western countries, nearly 30 percent are estimated to have clopidogrel resistance, with about 3 percent classified as poor metabolizers.

## 3. Causes

Many genes are involved in converting clopidogrel to its active form and in determining the drug's effects in the body. The *CYP2C19* gene is particularly important for the activation of clopidogrel, and certain common variations (polymorphisms) in this gene have been associated with clopidogrel resistance. *CYP2C19* gene polymorphisms account for most of the variation in clopidogrel activation due to genetic factors. Polymorphisms in other genes likely have smaller effects on clopidogrel activation.

The *CYP2C19* gene provides instructions for making an enzyme that is found primarily in liver cells. It is active in a cell structure called the endoplasmic reticulum, which is involved in protein processing and transport. The *CYP2C19* enzyme plays a role in the processing of many drugs, including clopidogrel. The *CYP2C19* enzyme helps to convert clopidogrel to its active form, which is necessary for the drug to function in the body. In its active form, clopidogrel prevents (inhibits) the function of a receptor protein known as P2RY12 that is found on the surface of platelets. During clot formation, the P2RY12 receptor protein helps platelets cluster together to form a clot to seal off damaged blood vessels and prevent blood loss. By inhibiting the function of the P2RY12 receptor, clopidogrel decreases the formation of blood clots, including clots that can cause heart attack, stroke, and deep vein thrombosis.

The two most common *CYP2C19* gene polymorphisms associated with clopidogrel resistance (known as *CYP2C19*\*2 and *CYP2C19*\*3) result in the production of a nonfunctional *CYP2C19* enzyme that cannot convert clopidogrel to its active form. Without active clopidogrel to interfere, the P2RY12 receptor continues to promote platelet aggregation and blood clot formation, which can lead to heart attacks, strokes, and thromboses in individuals with a history of these conditions.

In addition to changes in specific genes, many other factors, including sex, age, weight, diet, and other medications, play a role in how the body reacts to clopidogrel.

### 3.1. The gene associated with Clopidogrel resistance

- *CYP2C19*

## 4. Inheritance

Clopidogrel resistance is inherited in an autosomal codominant pattern. Codominance means that two different versions of the gene are active (expressed), and both versions influence the genetic trait. Some people with clopidogrel resistance have a reduced ability to convert the drug to its active form because of a polymorphism in one copy of the *CYP2C19* gene that results in decreased enzyme activity. These individuals are described as intermediate metabolizers. Other individuals with clopidogrel resistance convert very little or none of the drug to its active form because of polymorphisms in both copies of the *CYP2C19* gene, which results in a lack of enzyme activity. These individuals are described as poor metabolizers.

It is important to note that not all individuals with *CYP2C19* gene mutations have clopidogrel resistance. These individuals who are at increased risk for developing clopidogrel resistance may or may not have a bad reaction when treated with the drug.

## 5. Other Names for This Condition

- *CYP2C19*-related poor drug metabolism
- poor metabolism of clopidogrel
- resistance to clopidogrel

---

## References

1. Hirota T, Eguchi S, Ieiri I. Impact of genetic polymorphisms in *CYP2C9* and *CYP2C19* on the pharmacokinetics of clinically used drugs. *Drug Metab Pharmacokinet*. 2013;28(1):28-37. Epub 2012 Nov 20. Review. Citation on PubMed
2. Niu X, Mao L, Huang Y, Baral S, Li JY, Gao Y, Xia YP, He QW, Wang MD, Li M, Zou L, Miao XP, Hu B. *CYP2C19* polymorphism and clinical outcomes among patients of different races treated with clopidogrel: A systematic review and meta-analysis. *J Huazhong Univ Sci Technolog Med Sci*. 2015 Apr;35(2):147-156. doi: 10.1007/s11596-015-1404-7. Epub 2015 Apr 16. Review. Citation on PubMed
3. Scott SA, Sangkuhl K, Stein CM, Hulot JS, Mega JL, Roden DM, Klein TE, Sabatine MS, Johnson JA, Shuldiner AR; Clinical Pharmacogenetics Implementation Consortium. Clinical Pharmacogenetics Implementation Consortium guidelines for *CYP2C19* genotype and clopidogrel therapy: 2013 update. *Clin Pharmacol Ther*. 2013 Sep;94(3):317-23. doi: 10.1038/clpt.2013.105. Epub 2013 May 22. Citation on PubMed or Free article on PubMed Central
4. Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons; Writing Committee Members, Holmes DR Jr, Dehmer GJ, Kaul S, Leifer D, O'Gara PT, Stein CM. ACCF/AHA Clopidogrel clinical alert: approaches to the FDA "boxed warning": a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the American Heart Association. *Circulation*. 2010 Aug 3;122(5):537-57. doi: 10.1161/CIR.0b013e3181ee08ed. Epub 2010 Jun 28. Citation on PubMed
5. Uppugunduri CR, Daali Y, Desmeules J, Dayer P, Krajcinovic M, Ansari M. Transcriptional regulation of *CYP2C19* and its role in altered enzyme activity. *Curr Drug Metab*. 2012 Oct;13(8):1196-204. Review. Citation on PubMed