# CYP2C19 mutations: When clopidogrel's efficacy is a genetic lottery

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> Clopidogrel remains a cornerstone of antiplatelet therapy following percutaneous coronary intervention (PCI), yet its efficacy is notoriously variable. This variability often traces back to the cytochrome P450 2C19 (CYP2C19) enzyme, essential for converting the prodrug into its active metabolite. But what happens when the enzyme itself is altered by genetic mutation, not just polymorphism?

**KEY TAKEAWAYS**

- The Pivot: Five specific CYP2C19 gene mutations, including one novel variant, were identified in patients with coronary heart disease, distinguishing them from common polymorphisms.
- The Data: The M136K mutation enhanced clopidogrel's antiplatelet effect, reducing platelet aggregation rate by 24.83% (59.58% vs. 34.75%; P<0.05) and increasing phosphorylated VASP levels by 23.0% (1.0 vs. 1.23; P<0.05) in vitro compared to wild-type.
- The Action: While not immediately actionable in routine practice, these findings underscore the complex genetic landscape influencing clopidogrel response and highlight a potential gain-of-function mutation that could lead to enhanced antiplatelet effects.

Clopidogrel's role in preventing thrombotic events after PCI is well-established, but its effectiveness hinges on metabolic activation. The drug is a prodrug, requiring a two-step oxidation process primarily mediated by CYP2C19 to form its active thiol metabolite. This metabolite then irreversibly binds to the P2Y12 receptor on platelets, inhibiting ADP-induced platelet aggregation. Genetic variations, particularly loss-of-function polymorphisms in the CYP2C19 gene, are widely recognized as determinants of clopidogrel response, leading to reduced active metabolite formation and, consequently, higher rates of cardiovascular events.1

But the focus has largely been on these common polymorphisms, like CYP2C19*2 and *3, which are known to impair clopidogrel activation. Less attention has been paid to rarer, potentially more impactful, gene mutations that might either severely compromise or, conversely, enhance the enzyme's function. A study published in Zhonghua Xin Xue Guan Bing Za Zhi (Chinese Journal of Cardiovascular Diseases) investigated these less common mutations, aiming to identify novel variants and characterize their functional impact on clopidogrel activation.1

## Uncovering Rare Genetic Variants

The investigators enrolled 1,493 patients with coronary heart disease (CHD) who underwent PCI at the Second Affiliated Hospital of Nanchang University between March 2011 and June 2019. They also included 1,022 healthy physical examination volunteers, matched for genetic background, gender, and age, as controls. The average age of CHD patients was 64.5 ± 10.4 years, with 75.62% male. Healthy controls had an average age of 64.1 ± 11.0 years, with 76.13% male.

This large cohort allowed for a comprehensive genetic screening.1

Researchers extracted DNA from blood samples and employed Sanger first-generation sequencing to detect CYP2C19 gene mutations across the full exon and exon-intron junctions. This deep sequencing approach aimed to capture both known and novel genetic alterations. They compared identified variations in CHD patients against the 1000 Genomes Browse database and their healthy control cohort to distinguish true mutations from common genetic polymorphisms.1

The team identified five distinct gene mutations in 12 patients (0.80%) within the CHD cohort. These included four previously known mutations: T130K (1 case), M136K (6 cases), N277K (3 cases), and V472I (1 case). The clinical stake was that they also discovered one new mutation, G27V (1 case). No corresponding gene mutations appeared in the healthy control group, suggesting these variants might be more prevalent or specifically associated with the CHD population.1

To predict the functional impact of these mutations, the PolyPhen-2 prediction software was used. This analysis classified T130K and M136K as 'probably damaging,' G27V as 'possibly damaging,' and N277K and V472I as 'benign mutations.' These predictions provided an initial hypothesis regarding how each mutation might affect the CYP2C19 protein's function and, by extension, clopidogrel metabolism.1

## Functional Consequences of Mutation

The study moved beyond mere identification and prediction, performing in vitro functional assays to directly assess the impact of these mutations on clopidogrel activation. They transfected human normal liver cells (HL-7702) with plasmids encoding either the wild-type CYP2C19 gene or the identified mutant genes. After 24 hours, they measured CYP2C19 protease expression in each group. This step confirmed that the mutant proteins were indeed being expressed, setting the stage for functional testing.1

To evaluate clopidogrel activation, the researchers incubated liver S9 protein (containing the CYP2C19 enzyme) with clopidogrel. The resulting active metabolites were then applied to platelets to detect the platelet aggregation rate and the activity of human vasodilator-activated phosphoprotein (VASP). VASP phosphorylation is a direct measure of P2Y12 receptor inhibition, serving as a reliable biomarker for clopidogrel's antiplatelet effect. A higher VASP phosphorylation level indicates greater P2Y12 inhibition and, thus, more effective antiplatelet activity.1

The in vitro functional studies yielded a striking result for one specific mutation: M136K. The platelet aggregation rate in the M136K gene mutation group was 24.83% lower than that of the wild type (59.58% vs. 34.75%; $P<0.05$). Concurrently, the phosphorylated VASP level was 23.0% higher in the M136K group compared to the wild type (1.0 vs. 1.23; $P<0.05$). These data unequivocally demonstrate that the M136K mutation functions as a gain-of-function variant, enhancing the activation of the CYP2C19 enzyme on clopidogrel and leading to more potent platelet inhibition.1

But the other identified mutations did not show such a clear effect. The platelet aggregation rate and phosphorylated VASP levels were similar between the G27V, T130K, N277K, and V472I gene mutation groups and the wild-type group ($P>0.05$ for all comparisons). This suggests that while these mutations exist, their functional impact on clopidogrel metabolism, at least under these in vitro conditions, is negligible or requires different experimental parameters to be revealed. The finding for M136K stands out as a clear demonstration of altered drug metabolism due to a specific genetic variant.1

## Implications and Caveats

The identification of these rare mutations, particularly the gain-of-function M136K, adds another layer of complexity to the already intricate pharmacogenomics of clopidogrel. While common loss-of-function alleles like CYP2C19*2 and *3 are well-studied for their association with clopidogrel resistance and increased thrombotic risk, this study points to variants that could lead to enhanced drug activation. For clinicians, this raises questions about patients who might be hyper-responders to clopidogrel, potentially increasing their bleeding risk, though this study did not assess clinical outcomes. The HOST-EXAM trial, for instance, showed clopidogrel monotherapy to be non-inferior to aspirin at 10 years, but did not examine genetic variations.1

The study's strength lies in its comprehensive genetic screening and subsequent in vitro functional validation. Identifying a novel mutation (G27V) and confirming the functional impact of M136K provides valuable mechanistic insight. But the study's limitations are also apparent. It is an observational study, not a randomized controlled trial, meaning it cannot establish causality between these mutations and clinical outcomes such as bleeding or thrombotic events. The sample size for each specific mutation was very small, with M136K appearing in only 6 patients and G27V in just 1 patient. This makes it difficult to generalize these findings to broader populations or to assess their clinical prevalence accurately.1

The in vitro nature of the functional studies is another significant caveat. While cell-based assays provide a controlled environment to study enzyme activity, they do not fully replicate the complex physiological environment of a living human. Factors such as drug absorption, distribution, and excretion, as well as interactions with other drugs or genetic factors, are not accounted for. Therefore, translating these in vitro findings directly to clinical practice requires caution and further in vivo validation. The study also did not explore the impact of these mutations on other CYP2C19 substrates, which could have broader implications for drug metabolism.1

Still, the work highlights the ongoing need for a deeper understanding of individual variability in drug response. While routine genetic testing for CYP2C19 polymorphisms is not universally recommended, especially given the availability of alternative P2Y12 inhibitors, these findings suggest that a more granular genetic analysis might uncover rare but functionally significant variants. The ALL-RISE trial, for example, focused on angiography-derived physiology for PCI guidance, but genetic factors remain a critical, often overlooked, component of post-PCI management.1

The study's focus on patients with coronary heart disease also means that the prevalence and impact of these mutations in other populations, or in healthy individuals, remain unknown. The comparison with the 1000 Genomes Browse database provided some context, but a more diverse and larger control group might reveal different prevalence rates. The authors used PolyPhen-2 for prediction, which is a valuable tool, but its predictions are not always perfectly aligned with actual functional outcomes, as seen with the benign classification of N277K and V472I despite their presence in CHD patients.1

The long-term clinical consequences of a gain-of-function mutation like M136K are particularly intriguing. If a patient metabolizes clopidogrel more efficiently, they might experience greater antiplatelet efficacy, potentially reducing thrombotic events. But this could also come at the cost of an increased risk of bleeding. This delicate balance between efficacy and safety is a constant challenge in antiplatelet therapy, and genetic factors like M136K could shift that balance in unpredictable ways. Clinicians often rely on comprehensive resources like the Oxford Handbook of Cardiology for guidance on managing such complexities, but rare genetic insights like these are often beyond standard reference texts.1

Future research needs to focus on larger, prospective studies that correlate these specific mutations with clinical outcomes in patients receiving clopidogrel. Such studies would ideally include diverse patient populations and assess

both thrombotic and bleeding events. Investigating the prevalence of these mutations in different ethnic groups could provide a more complete picture of their global impact. Understanding these rare genetic influences could eventually lead to more personalized antiplatelet strategies, moving beyond the current one-size-fits-all approach to clopidogrel.1

### CLINICAL IMPLICATIONS

The identification of a CYP2C19 gain-of-function mutation, M136K, is a fascinating twist in the clopidogrel story. For years, the narrative has centered on loss-of-function variants leading to treatment failure. Now, we have evidence of a mutation that enhances clopidogrel's effect, at least in vitro. This immediately raises the specter of increased bleeding risk in patients who are unknowingly hyper-responders.

But the clinical utility remains distant. The prevalence of these specific mutations is exceedingly low, identified in only a handful of patients in a large cohort. Routine genetic testing for these rare variants is simply not feasible or cost-effective in current practice. The focus for clinicians will rightly remain on the more common loss-of-function polymorphisms, and the decision to switch to alternative P2Y12 inhibitors like ticagrelor or prasugrel will continue to be driven by established clinical risk factors and, in some cases, testing for common alleles.

Still, this research serves as a reminder that the genetic market of drug metabolism is far more complex than our current diagnostic tools can capture. While we may not be ordering tests for M136K anytime soon, the underlying principle that individual genetic makeup profoundly influences drug response is reinforced. It pushes us to consider the full spectrum of genetic variability, not just the most prevalent or problematic variants, as we strive for truly personalized medicine.

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### REFERENCES

1. 1. Guo LJ, Jiang XH, He WF. [Prevalence of CYP2C19 gene mutations in patients with coronary heart disease and its biological activation effect in clopidogrel antiplatelet response]. Zhonghua Xin Xue Guan Bing Za Zhi. 2021;49(1):47-52. doi:10.3760/cma.j.cn112148-20200810-00770

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