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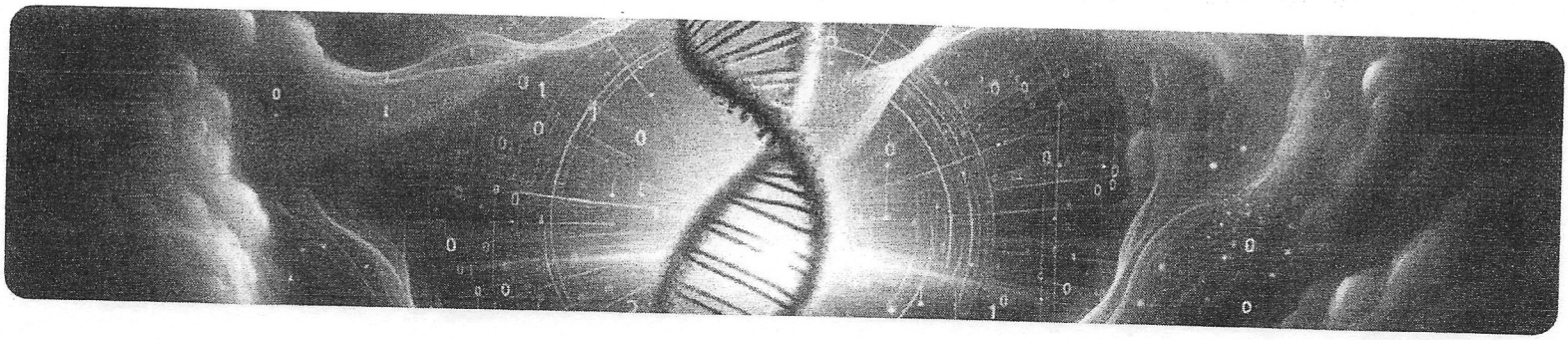
Next-Gen Disease Screen

Summary Report BETA



Genome: **Michael Vaughn**
Report Date: **August 17, 2026**
Analysis: **Next-Gen Disease Screen Premium**
Data: **Whole Genome Sequencing**

Confidential Information

Genome Sequencing Laboratory Information
- CLIA Certification: **45D1102202**
- CAP Accreditation: **7212851**
- Location: **USA** (Houston, Texas)
- Service: **30× Whole Genome Sequencing**

Genome Data Analysis Information
- Analysis Performed By: **Sequencing.com**
- Data Analyzed: **30× Whole Genome Sequencing**
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CYP2C19: Increased Function

Gene: CYP2C19
Variant Identifier: rs12248560 , RCV000782438
Your Data: CT
Risk Status: Medication Carrier

Description: CYP2C19: increased function, sometimes referred to as ultra-rapid metabolizer status, is a genetic variation where the CYP2C19 enzyme in the liver works more quickly than normal. This enzyme is responsible for breaking down certain medications, such as antidepressants, proton pump inhibitors, and some antiplatelet drugs. People with this condition may process these medications too rapidly, which can lead to reduced effectiveness. Treatment options typically involve adjusting medication dosages or selecting alternative drugs that are not primarily metabolized by the CYP2C19 enzyme, under the guidance of a healthcare provider. Genetic testing can help diagnose this condition and inform treatment decisions.

Symptoms: Increased bleeding risk, Reduced response to certain medications, Altered drug metabolism, Increased risk of side effects from some drugs, Altered effectiveness of certain antidepressants, Variation in response to certain blood thinners, Altered response to proton pump inhibitors

CYP2C19: No Function

Gene: CYP2C19
Variant Identifier: rs12769205 , RCV000782431
Your Data: AG
Risk Status: Medication Carrier

Description: The condition "CYP2C19: no function," commonly referred to as being a "poor metabolizer," involves a genetic variation where the CYP2C19 enzyme is nonfunctional, impacting the body's ability to process certain medications. This can affect the effectiveness and safety of drugs like some antidepressants, proton pump inhibitors, and antiplatelet agents. Treatment options often involve adjusting medication types or dosages under medical supervision to ensure therapeutic efficacy and minimize adverse effects, with some individuals requiring alternative medications that do not rely on the CYP2C19 enzyme for metabolism. Genetic testing can help identify this condition and guide personalized treatment plans.

Symptoms: Increased risk of side effects from certain medications, Reduced effectiveness of some drugs, Altered response to antidepressants, Variable response to blood thinners, Increased risk of stomach ulcers

Function of the 2 individual variants

rs12248560 (c.-806C>T) defines CYP2C19*17 — a gain-of-function allele. This promoter-region variant increases *CYP2C19* transcription and enzyme expression, so it enhances (rather than impairs) conversion of prodrugs such as clopidogrel to their active metabolites.[1] It is the SNP used to call the *17 allele in essentially all major genotyping panels.[2][3] On its own, one or two *17 alleles classify a person as a **rapid** (*1/*17) or **ultrarapid** (*17/*17) metabolizer.[1][4]

rs12769205 (an intron 2 branch-point A>G change) tags loss-of-function alleles — most importantly CYP2C19*35, and it also co-occurs on CYP2C19*2. Functionally, rs12769205 disrupts a splice branch point, causing complete inclusion of intron 2 ("exon 2B"), a reading-frame shift, and a premature stop codon — i.e., a **loss-of-function** change that can abolish CYP2C19 protein.[5] Mechanistically it is distinct from the classic *2-defining SNP (rs4244285, c.681G>A). The key population nuance: in individuals of African ancestry, rs12769205 frequently occurs **alone**, defining **CYP2C19*35**, a no-function allele; in most other populations it is in linkage disequilibrium with rs4244285 and is simply part of the ***2** haplotype. *35 is important precisely because a panel that genotypes only rs4244285 will miss it and misclassify a true LOF allele as normal-function.[5]

Interpreting the two variants together

Because these are the defining SNPs for ***17 (gain-of-function)** and a ***35/*2-type loss-of-function** allele respectively, a genotype positive for both variants most parsimoniously represents a ***17 / (*35 or *2) diplotype** — one increased-function and one no-function allele. Both the AHA scientific statement and the JACC review classify the combination of one no-function and one increased-function allele (e.g., *2/*17) as an **intermediate metabolizer**, because the gain-of-function *17 allele does not reliably compensate for the loss-of-function allele.[1][4] For clopidogrel specifically this predicts **reduced active-metabolite formation and a reduced antiplatelet response**, with increased risk of adverse cardiovascular/stent-thrombosis events in ACS/PCI populations.[1][4]

Two important caveats apply to that phenotype call:

- Phase and linkage matter. If both variants sit on the *same* chromosome (as they do when rs12769205 is simply riding on a *2 haplotype in strong LD with the *17 promoter change), the alleles are not independent and the diplotype interpretation differs from a true *trans* *17/*35 configuration. The AHA statement explicitly notes that *17's apparent effect largely disappears once the *2 allele it is linked to is accounted for. Accurate calling

therefore requires knowing phase and the full panel of SNPs tested, not just these two positions.[1]

Assuming the two variants lie on opposite chromosomes (a true *17 / *35-or-*2 diplotype), the expected phenotype is intermediate metabolizer — one increased-function and one no-function allele, with the gain-of-function *17 not compensating for the LOF allele.[1][4] Clinically, this predicts a **reduced clopidogrel response**, and current genotype-guided guidelines favor an alternative $P2Y_{12}$ inhibitor (prasugrel or ticagrelor, which are unaffected by CYP2C19 status) in ACS/PCI patients with this phenotype.[4][7][8] Confirming **which** LOF allele is present (*35 vs *2) and the **phase** of the two variants is essential before finalizing the call, since same-chromosome linkage changes the interpretation.[1][5]

* A phenotype call requires knowing which variants are in *cis* (defining one allele) versus *trans* (defining two separate alleles).. You are looking at **one chromosome carrying a compound haplotype** and a second chromosome whose identity must be specified separately to make any phenotype call. **Star-allele calling** assigns one allele per chromosome. A phenotype call requires knowing which variants are in *cis* (defining one allele) versus *trans* (defining two separate alleles).[1] With rs12248560 (gain-of-function, *17) and rs12769205 (a splice-disrupting loss-of-function change) both on the same strand, you are no longer looking at a two-allele* "17 / LOF" diplotype. You are looking at **one chromosome carrying a compound haplotype** and a second chromosome whose identity must be specified separately to make any phenotype call.

The critical mechanistic point is that these two variants are not additive when in cis. rs12769205 disrupts the intron 2 branch point, causing aberrant splicing, a frameshift, and a premature stop codon that can **abolish CYP2C19 protein entirely** — and this happens downstream of, and independent of, the promoter *17 variant. A gain-of-function promoter change only increases transcription of a message that is subsequently mis-spliced into a nonfunctional, truncated product.* [2]*In cis,* ***the loss-of-function splicing defect is epistatic to (dominates) the* 17 promoter up-regulation — you cannot make more functional enzyme by up-regulating transcription of an allele that produces no functional protein. Functionally, therefore, a chromosome carrying both variants behaves as a** [2]**no-function allele****, *not as an increased-function allele.*

Because cis-orientation collapses these two variants onto one no-function chromosome, the metabolizer phenotype is set by the **second, unstated allele**:

Other (trans) chromosome	Resulting diplotype	Predicted phenotype
Normal-function (*1)	one no-function haplotype / *1	**Intermediate metabolizer** (1 no-function + 1 normal-function)[3]
No-function (e.g., *2, *3)	two no-function alleles	**Poor metabolizer**[3]
Increased-function (*17, i.e., rs12248560 also present in trans)	one no-function / one increased-function	**Intermediate metabolizer** (*17 does not compensate)[3], [4]

Under the current AHA genotype–phenotype table, an intermediate metabolizer has "1 no-function and 1 normal-function allele ... or no-function and 1 increased-function allele," while two no-function alleles define a poor metabolizer.[3] So in the most common scenario — the compound cis-haplotype paired with a normal-function *1 on the other chromosome — the expected phenotype is intermediate metabolizer, with reduced clopidogrel active-metabolite formation.*[3]

The key contrast with the trans case

This is the substantive difference from the prior answer. In **trans** (rs12248560 on one chromosome, rs12769205 on the other), you genuinely have a *17 increased-function allele opposite a 2/35-type no-function allele — a* "17 / LOF" diplotype that the AHA and JACC tables classify as intermediate metabolizer because *17 fails to compensate. In* [3][5]*cis, the* 17 promoter variant is physically attached to the dead allele and contributes essentially nothing, because you cannot rescue a frameshifted, prematurely truncated transcript by transcribing more of it.[2] The functional consequence is that the *17 -806T change is effectively "wasted," and the phenotype is driven by the branch-point LOF haplotype plus the opposite allele.*

Importantly, real-world genotyping panels that interrogate only rs4244285 (for *2) plus rs12248560 (for* 17) **cannot resolve phase** and will not detect a rs12769205-defined *35 allele at all — this is precisely the misclassification risk Chaudhry et al. flagged, where a true no-function allele is read as normal-function. Resolving cis vs. trans in compound heterozygotes generally requires allele-specific/long-range PCR or family/trio data, as demonstrated by Skierka and Black.*[2][1]

Bottom line

In cis, rs12248560 and rs12769205 describe a single chromosome, so no phenotype can be assigned from these two variants alone — the second allele must be specified. Because the branch-point splicing defect (rs12769205) abolishes functional protein and is epistatic to the *17 promoter up-regulation, the cis-haplotype behaves functionally as a no-function allele. Paired with a normal-function* [2]1 on the other chromosome, the predicted phenotype is **intermediate metabolizer** (reduced clopidogrel response); paired with a second no-function allele it becomes a **poor metabolizer.**[3] This differs from the trans configuration, where a genuine increased-function *17 allele sits opposite the LOF allele and still yields an intermediate-metabolizer call. Confirming phase (allele-specific PCR) and the identity of the second allele is essential before finalizing the interpretation.*[3][5][1]

References

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5. Genotype-Guided Antiplatelet Therapy: JACC Review Topic of the Week. van den Broek WWA, Ingraham BS, Pereira NL, et al. Journal of the American College of

A shortcoming of WGS is the inability to determine "phase" when 2 variants are present in the same gene.

Allele phase describes **which chromosome each variant sits on** when a person carries two or more variants at a single gene locus — and "cis" versus "trans" are the two possible orientations arrangements.

The core concept

Humans are diploid: every autosomal gene exists as two copies (alleles), one inherited from each parent, on two homologous chromosomes. When genotyping detects two different variants in the same gene, the raw genotype tells you *that* both variants are present but not *how they are distributed* across the two chromosomes. **Phase is the resolution of that distribution — assigning each variant to a specific one of the two homologs.**

Standard genotyping assays (SNP arrays, most targeted panels, even much of short-read sequencing) are typically **unphased**: they report the variants present at each position independently, without linking them along a single strand. Determining phase generally requires additional methods such as allele-specific/long-range PCR, long-read sequencing, or inference from parental/trio genotypes.

Cis vs. trans

Configuration	Physical arrangement	Meaning
Cis (coupling)	Both variants are on the **same** chromosome	The other homolog carries neither variant (is "wild-type" at both positions)
Trans (repulsion)	The two variants are on **opposite** chromosomes	Each homolog carries one of the two variants

[1]

A worked example with two variants, A and B:

- **Cis:** Chromosome 1 = A + B; Chromosome 2 = wild-type / wild-type. One chromosome carries both changes; the other is unaffected.
- **Trans:** Chromosome 1 = A + wild-type; Chromosome 2 = wild-type + B. Each chromosome carries exactly one change.

Both produce the *identical* unphased genotype ("heterozygous for A, heterozygous for B"), which is exactly why phase must be determined separately — the genotype call alone cannot distinguish them.

Why phase is clinically decisive

Phase changes functional interpretation whenever two variants interact within the same gene product. Two illustrative situations:

1. Two loss-of-function variants (recessive-disease logic). If both LOF variants are in **trans**, *both* copies of the gene are disrupted → no functional protein → affected/compound-heterozygous phenotype. If the same two LOF variants are in **cis**, one chromosome carries both hits but the other homolog remains fully intact → a normal protein is still produced from the wild-type allele → typically unaffected (carrier). This cis/trans distinction is the basis for compound-heterozygosity analysis in autosomal recessive disease.

2. A gain-of-function variant paired with a loss-of-function variant (the CYP2C19 case discussed earlier). In **trans**, the two variants define two separate star alleles — e.g., an increased-function *17 on one chromosome opposite a no-function allele on the other. In cis, both variants sit on one chromosome, describing a* single *compound haplotype (whose net function is dictated by the dominant/epistatic variant), while the* other *chromosome's identity — not captured by those two SNPs — then determines the diplotype and phenotype.* ***This is why, for Pharmacogenes, resolving phase in compound heterozygotes is required before a definitive metabolizer phenotype can be assigned.***

Bottom line

Phase = which homolog each variant resides on. Cis means both variants are on the same chromosome (leaving the other homolog unaffected at those positions); trans means they are on opposite chromosomes (each homolog carrying one). The two arrangements yield the same unphased genotype but often opposite functional consequences — trans typically disrupts both gene copies while cis spares one — so phase must be resolved (allele-specific PCR, long-read sequencing, or trio data) whenever two intragenic variants could interact