Genetic Evidence for Repurposing in Giant Cell Arteritis

A brief to the candidate table

Zatoona Labs · October 2026

Summary

Giant cell arteritis resolves to one Open Targets node, MONDO:0008538 (temporal arteritis), with no ontology children. Fifteen targets carry genetic association evidence in release 26.09, all of it from GWAS credible sets, and they occupy 6 loci. Two of the fifteen are targets of a known drug; one, plasminogen (PLG), is the target of approved medicines. The accompanying table lists the six approved drugs that act on a genetically supported target, sorted by genetic score; a companion table adds the eight clinical-stage pairs. None of the fourteen is a candidate. Open Targets records no direction of effect for any GCA genetic association, so every pair is flagged as directionally unassessed. The table is therefore a set of leads with an unresolved mechanistic sign, not a ranked shortlist, and the genetics for this disease are sparse.

1 Findings

Figure 1A shows where the evidence narrows. Open Targets associates 1268 targets with GCA on some evidence type, but only 15 on genetic association alone. The difference is not noise: the overall score is dominated by literature mining, and its top-ranked target, IL6R at 0.578, has no genetic score at all. Ranking on that score and calling the result genetics-driven would be circular, so the analysis isolates the genetic association datatype. Genetic support is among the strongest predictors of clinical success in target selection [5], which is what makes the fifteen worth examining despite their number.

The fifteen targets are not fifteen independent signals. They take their evidence from 8 credible sets in 6 loci, 5 of those sets are assigned to more than one gene, and 13 of the fifteen share a locus with another target (Figure 1B). Loci, not genes, are the unit of evidence here.

The two strongest targets are VTN (0.55, locus-to-gene 0.91) and PLG (0.53, 0.70). Both belong to the plasminogen activation and extracellular matrix axis, and they come from different loci and different studies: PLG and P4HA2 were the two signals of the 2017 GCA genome-wide association study [3], and VTN came from the 2024 study [4]. VTN has no known drug. PLG has eight, six of them approved.

CSF2 (0.14) is the only other drugged target, with 6 clinical-stage agents, five of them antibodies, and no approved agent. It sits in a shared chromosome 5 credible set in which P4HA2 carries the higher locus-to-gene score (0.43 against 0.24), so assigning that signal to CSF2 is a prediction rather than a finding.

The two drugs Open Targets lists as approved for GCA, tocilizumab on IL6R [6] and upadacitinib on the JAK kinases, act on targets with no genetic association evidence for the disease. The genetics and the marketed drugs point at different biology. None of the fourteen drugs appears in any of the 208 GCA trials registered on ClinicalTrials.gov or the EU CTIS; that landscape is

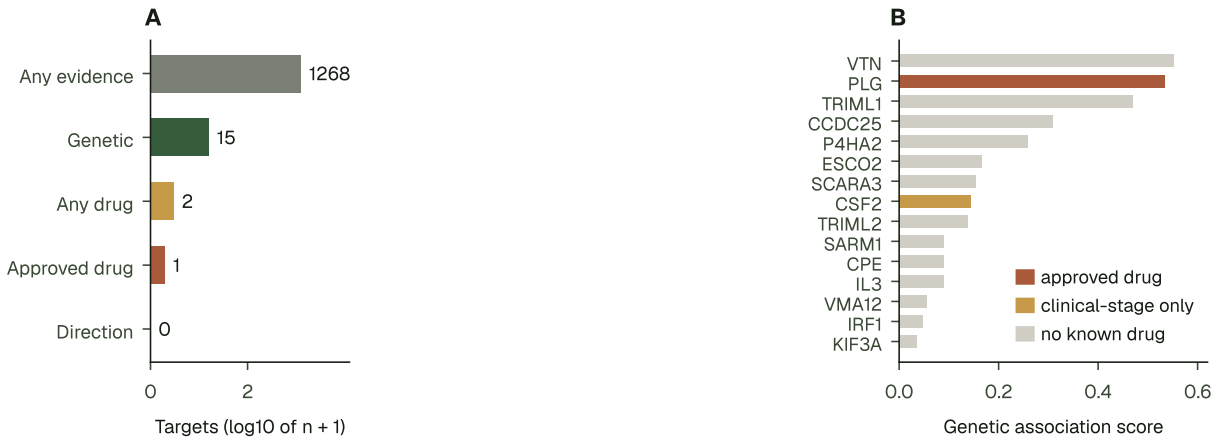


Figure 1. Evidence attrition and the genetically supported targets. **A**, targets associated with GCA at each step, on a log scale: 1268 on any evidence type, 15 on genetic association, 2 with a known drug, 1 with an approved drug, and none with a recorded direction of effect. **B**, the fifteen targets ranked by genetic association score and colored by whether a known drug acts on them. The strongest signal, VTN, has no known drug; the only approved-drug target is PLG.

dominated by IL-6 receptor blockade (34 trials) and glucocorticoids, and the single GM-CSF trial tested mavrilimumab against the receptor rather than CSF2 itself (NCT03827018).

Table 1. Approved drugs acting on a genetically supported target. All six act on plasminogen and all six are flagged: no direction of effect is recorded for the association, so concordance cannot be assessed.

Drug	ChEMBL	Target	Genetic score	Action on target
Aminocaproic Acid	CHEMBL1046	PLG	0.53	inhibits
Anistreplase	CHEMBL2108250	PLG	0.53	activates
Aprotinin	CHEMBL1201619	PLG	0.53	inhibits
Defibrotide	CHEMBL2108396	PLG	0.53	activates
Streptokinase	CHEMBL2108147	PLG	0.53	activates
Tranexamic Acid	CHEMBL877	PLG	0.53	inhibits

2 Flags

All 14 pairs are flagged, and none is discordant. Discordance requires a known direction, and there is none to have: every GCA genetic association row in the release has an empty direction on target and direction on trait. Unknown is not concordant, so no pair is promoted to a candidate.

The PLG set is internally contradictory in a way that makes the missing direction decisive. 5 of its drugs activate plasminogen (streptokinase, anistreplase, defibrotide, amediplase, desmoteplase) and 3 inhibit it (tranexamic acid, aminocaproic acid, aprotinin). At most one class can run with the genetics; without a direction neither can be preferred, and the two classes are therapeutic opposites. For CSF2 the flag has a second layer: the target's own assignment to its credible set is uncertain, so even a recorded direction would need the locus resolved first.

3 Methods

Targets were read from the Open Targets Platform, release 26.09, on 24 October 2026, restricted to the genetic association datatype and to direct associations, since the disease node has no children [1]. Drugs and their ChEMBL action types came from the same release [2]; a molecule counted as approved when its maximum clinical phase was approval, phase 4, or withdrawal after marketing. Direction of effect was taken from genetic evidence only, over the GWAS credible set, gene burden, EVA, UniProt variant, Orphanet, Gene2Phenotype, Genomics England and ClinGen sources, and a pair was called concordant only when the drug's action matched the direction the genetics favors. ClinicalTrials.gov and the EU CTIS were searched for prior art on the same date.

4 Limitations

Fifteen targets is a thin base, and the scores are uncalibrated heuristics that rank targets within this analysis only. No target has rare-variant or burden evidence, and no direction is recorded, so the table cannot separate a drug that would help from one that would harm. Drug-target annotation is incomplete: alteplase, tenecteplase and reteplase act through plasminogen but are annotated to PLAT, so the PLG list understates the fibrinolytic class. Locus-to-gene scores are predictions and four of six loci are shared. Approval status comes from ChEMBL and can lag a label. The trial search was keyword-based over titles and interventions, so a trial naming a drug only in its full protocol would be missed. The GWAS Catalog lists 8 GCA studies, 2 of them absent from this release, and 3 regions where the release assigns no target.

References

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