

Pharmacological and genetic induction of fetal haemoglobin converge on a shared transcriptional signature

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Abstract

Reactivating fetal haemoglobin ameliorates sickle cell disease, but existing inducers cause dose-limiting myelosuppression and repurposing has proceeded one compound at a time. Transcriptomic signature matching, routine in other indications, has not been applied to fetal haemoglobin. It is unclear whether it can be applied because drug and genetic induction have never produced comparable transcriptional output in erythroid cells. We derived ten differential-expression contrasts from five public human erythroid datasets and grouped them into five mechanistic classes. In the single dataset perturbing a repressor both pharmacologically and genetically, every gene significantly changed by both the degrader and the knockout moved in the same direction, for WIZ and EHMT2 alike. A consensus signature requiring concordance across three mechanism classes comprised 139 induced and 28 repressed genes, led by HBG1, HBG2 and BGLT3, and recovered decitabine as the top-ranked mimicking compound of 2,099 tested. Three widely used computational tools failed under control experiments, and each failure was invisible without the control.

SIGNIFICANCE

Drug and CRISPR perturbation of the same fetal haemoglobin repressor change gene expression in the same direction, establishing the basis for signature-based repurposing in sickle cell disease.

INTRODUCTION

Fetal haemoglobin is the most powerful known modifier of sickle cell disease severity, and raising it is an established therapeutic strategy. *BCL11A* is a validated target: shmiR knockdown and CRISPR editing of its erythroid enhancer both produce durable induction in patients, and base editing of specific *BCL11A* zinc-finger residues derepresses fetal globin while sparing erythroid maturation (Rajendiran et al., 2024). The pharmacological options are older and less selective. Hydroxyurea, decitabine and the histone deacetylase inhibitors all carry myelosuppression as a dose-limiting toxicity.

Repurposing has so far proceeded one compound at a time, each identified by starting from a single drug and inferring its targets. Single-target virtual screens exist in parallel. What has not been attempted is the inverse: starting from a transcriptional signature of reactivation and screening the approved pharmacopoeia for compounds that reproduce it.

A negative result shapes the design. Khandros et al. (2020) purified differentiation-stage-matched F cells and A cells from HUDEP-2 and primary CD34-positive erythroid cultures and found very few RNA-level differences between them, at baseline or after hydroxyurea or pomalidomide treatment, and no difference in *BCL11A*, *ZBTB7A* or any other known regulator. They concluded that the determining difference is transcriptional and local to the beta-globin locus. The practical consequence is that an HbF-high versus HbF-low cell-state contrast cannot serve as a signature anchor; the signature must instead be built from perturbations that actively induce gamma-globin.

That constraint raises a prior question the field has not tested. Signature-based repurposing assumes that a drug and a genetic perturbation acting on the same target produce comparable transcriptional output. For fetal haemoglobin, this has never been measured, and the findings of Khandros et al. (2020) give reason for doubt. Our first objective was therefore to test that assumption directly, using a dataset in which one repressor is perturbed both pharmacologically and genetically in a single experimental system.

RESULTS

Ten contrasts across five datasets, with gamma-globin induced in every one

All results reported here derive from independently generated public datasets analysed under a single fixed pipeline; every contrast, threshold and control is specified in Materials and Methods, and the complete analysis code is provided, so each number is reproducible from the deposited data.

HBG1 and *HBG2* were significantly induced in all ten contrasts, spanning four pharmacological and six genetic perturbations across five mechanism classes (Table 1). This is the primary internal validity check: every contrast entering the consensus demonstrably induces the phenotype under study.

Table 1
The ten differential expression contrasts. DE counts are at adjusted $P < 0.05$ and absolute $\log_2$ fold change ≥ 0.58 . All ten contrasts induce *HBG1* and *HBG2*.

Pociredir vs DMSO	GSE309131	PRC2	3 donors, 4 doses	6619	4709
AMPK activator vs DMSO	GSE223925	AMPK	3 donors, 2 batches	625	237
dWIZ-2 degrader vs DMSO	GSE247096	H3K9	3 vs 3	266	168
UNC0642 vs DMSO	GSE247096	H3K9	3 vs 3	299	211
WIZ CRISPR vs control	GSE247096	H3K9	6 vs 6	190	210
EHMT2 CRISPR vs control	GSE247096	H3K9	6 vs 6	106	18
BCL11A enhancer edit	GSE264491	Locus	3 vs 3	246	128
HBG1/2 promoter edit	GSE264491	Locus	3 vs 3	72	15
TET editing at HBG	GSE284289	Locus	3 vs 3	585	213
MBD2 Y178F vs WT	GSE284289	MBD2	5 vs 5	235	65

The pociredir contrast behaves unlike the others, with 61.5% of tested genes reaching significance. A dose-matched re-analysis restricted to 100 nM, the only dose present in all three donors, gives 64.5%, so this is not an artefact of pooling doses. Polycomb repressive complex 2 inhibition removes H3K27me3 genome-wide, and the transcriptional footprint is correspondingly broad. The other contrasts range from

0.8% to 17%. This asymmetry is why a consensus rule that allows any single contrast to carry a gene is inadequate here.

Pharmacological and genetic perturbation of the same repressor converge completely in direction.

GSE247096 perturbs two repressors, *WIZ* and *EHMT2*, both with a small molecule and by CRISPR knockout, in one experimental system at one time point. This permits a direct test of the assumption underlying signature-based repurposing (Fig. 1).

For *WIZ*, 434 genes were differentially expressed under the dWIZ-2 degrader and 400 under CRISPR knockout, with 70 shared; all 70 moved in the same direction. For *EHMT2*, 510 genes responded to UNC0642 and 124 to knockout, with 92 shared; all 92 agreed in direction. Genome-wide Spearman correlations were 0.39 and 0.37, respectively. Convergence is therefore complete in direction but partial in extent, which is the regime in which signature matching is informative rather than trivial.

An internal control supports this interpretation. *EHMT2* transcript falls only in the CRISPR arm ($\log_2$ fold change -0.58 , adjusted $P = 1.1 \times 10^{-6}$) and not under UNC0642 (-0.04), as expected for an inhibitor that blocks the protein without reducing its mRNA. The convergence is therefore in downstream consequence rather than in a shared artefact of target abundance.

Mechanism class, not perturbation arm, is the unit of independence.

The conventional construction for a consensus signature requires support from both a pharmacological and a genetic contrast. That rule fails here. GSE247096 supplies a drug contrast and a CRISPR contrast against the same target, so a gene hit by both satisfies the rule while resting on a single mechanism. *WIZ* is also a component of the G9a-GLP complex, so the *WIZ* and *EHMT2* contrasts are not independent of one another either; four of the ten contrasts are mechanistically close to one experiment.

The consequence was concrete. Under the arm-based rule, the repressed signature was dominated by chromosome 19 KRAB zinc-finger genes: 11 of 15 genes against 0.22 expected from the matched-opportunity background of 17,566 genes (one-sided Fisher exact test, odds ratio 196, $P = 6.0 \times 10^{-18}$), distributed across both major cluster regions rather than one locus.

Two tests refuted that reading. First, the six individual-guide TET editing arms of GSE284289, held out of the consensus, induce *HBG1* and *HBG2* by $\log_2$ fold changes of 5.0 to 6.7, more strongly than any contrast used, with no KRAB zinc-finger gene significantly changed in any of the six, and *TRIM28*, *SETDB1*, *ATRX* and *DAXX* unchanged. Second, attributing the signal by contrast gives a clean split: 11 of 11 pass the threshold in pociredir, UNC0642, *WIZ* knockout and *EHMT2* knockout, and 0 of 11 in all four locus-editing and *MBD2* contrasts (Fig. 2).

KRAB zinc-finger depletion is therefore a marker of trans-acting chromatin perturbation, not of gamma-globin reactivation. It is absent from cis locus editing, which induces fetal haemoglobin more strongly. Reported as a fetal haemoglobin signature, it would have been incorrect.

Rebuilt on mechanism classes, the consensus comprises 139 induced and 28 repressed genes. *HBG1*, *HBG2* and *GPNUMB* are supported by all five classes, and *BGLT3*, the long non-coding RNA transcribed between *HBG1* and *HBG2*, by four. Seventeen of the 28 repressed genes remain KRAB zinc-finger genes, but only one has any support from the locus-editing class, as the corrected interpretation predicts. Neither *ZNF410* (Vinjamur et al., 2021) nor *JAZF1* (Wongborisuth et al., 2022), the two zinc-finger proteins with established gamma-globin repressor roles, change at the transcript level in any contrast, consistent with both acting without altering their own mRNA.

The signature recovers decitabine first of 2,099 compounds.

Against 2,099 drug terms, the pre-specified positive-control checkpoint was satisfied: decitabine ranked 1st ($q = 6.2 \times 10^{-4}$) and vorinostat 27th ($q = 1.4 \times 10^{-2}$). Pomalidomide, thalidomide and hydroxyurea were not recovered, ranking 1007th, 1311th and 1576th, respectively.

Hydroxyurea's absence is expected and self-consistent. Khandros et al. (2020) showed that it produces very few RNA-level changes in erythroid cells, and a transcriptional matching method should not recover a drug with a weak transcriptional footprint. Beyond the controls, three mechanisms appeared with independent replication rather than as single terms: retinoic acid (ranks 2 and 16), peroxisome proliferator-activated receptor gamma agonism (rosiglitazone rank 5, troglitazone rank 12), and cyclic AMP signalling through colforsin (rank 4).

Three control experiments expose three tool failures.

The same signature queried against the L1000 platform returned no positive control in the top 50. The reason is coverage, not signature quality: L1000 measures 45 of the 139 induced genes, 4 of the 28 repressed genes, and none of *HBG1*, *HBG2*, *BGLT3*, *HBZ* or the 17 KRAB zinc-finger genes (Fig. 3A). L1000 profiles approximately 978 landmark genes plus inference, and the beta-globin locus falls outside that space.

Docking against *EHMT2*, *EED* and *LSD1* reproduced crystallographic poses at root mean square deviations of 0.24 to 0.45 Å, so pose placement is accurate. Scoring is not. Rebuilding each co-crystal ligand by the flexible route used for the candidates shifted its score by a mean of 2.67 kcal/mol (Fig. 3B), exceeding most differences the analysis would otherwise interpret; under matched preparation, the candidates outscore the crystallographic inhibitors. Of three drugs with a co-crystallised receptor in the panel, only tretinoin scored best on its own receptor, while rosiglitazone and troglitazone each ranked theirs fourth of five (Fig. 3C). Rosiglitazone scored more favourably against *EED*, an unrelated chromatin pocket, than against its own receptor. No structural claim is therefore made in either direction.

DISCUSSION

The central result is that pharmacological and genetic perturbation of the same gamma-globin repressor converge completely in direction and partially in extent. This is the assumption on which signature-based

repurposing rests, and for fetal haemoglobin it had not been tested. Khandros et al. (2020) gave a specific reason to doubt it: if F cells and A cells differ so little transcriptionally, it was not obvious that drug and genetic induction would share a readable signature. They do, but only when the comparison is made between perturbations that actively induce rather than between cell states.

The consensus signature is small and interpretable. *HBG1*, *HBG2* and *GPNMB* at maximal support, with *BGLT3* close behind, means the method recovers the beta-globin locus and its known regulatory long non-coding RNA without being directed to. *HBD* falling as gamma-globin rises is the expected displacement.

What distinguishes this study is less the candidates it produced than what went wrong on the way, three times, in three different tools. The pharmacological-genetic axis did not measure mechanistic independence, because one dataset supplied both arms against the same target, and it admitted a KRAB zinc-finger block that a held-out replication showed was unrelated to fetal haemoglobin. The L1000 platform does not measure the genes that define the phenotype, so connectivity mapping returned noise that could readily have been read as a failed signature. Rigid-receptor docking recovered only one of three cognate drug-receptor pairs, so an apparent negative structural result was no result at all.

In each case the failure mode was invisible in the primary output and became obvious only under a control: a held-out arm, a coverage audit, a cognate-ligand test. Each control was inexpensive. None is standard practice in published repurposing pipelines, and the first two failures would have produced a plausible-looking study with an incorrect central claim.

Candidate prioritisation accordingly rests on signature matching and documented safety alone, with no structural support claimed. Rosiglitazone is the leading developable candidate: peroxisome proliferator-activated receptor gamma agonism was recovered twice independently, it has the best drug-likeness in the set, and it carries no myelosuppression signal. Two higher-scoring compounds are not developable on documented grounds. Troglitazone was withdrawn for idiosyncratic drug-induced liver injury and serves as the reference hepatotoxic compound in mechanistic toxicology (Villanueva-Badenas et al., 2023), and thioridazine carries a black-box warning for QTc prolongation (Labellarte et al., 2003). Rosiglitazone's own cardiovascular history is not erased by the 2013 removal of its restrictions (Hickson et al., 2019), and proposing it in a population with existing vascular pathology requires that history to be addressed directly.

This study has clear limits. No experimental validation was performed, and the candidates are predictions. The convergence result rests on a single dataset, GSE247096, the only series available that perturbs a gamma-globin repressor both pharmacologically and genetically in one system, and should be replicated. The repressed signature is weak, returning nothing significant in drug-perturbation space, so all matching signal derives from the induced list. Three of the five mechanism classes perturb chromatin machinery, and both recovered positive controls are chromatin-directed, so the signature may be enriched for that mechanism class by construction.

The highest-value next step is experimental: rosiglitazone in HUDEP-2 or CD34-positive derived erythroid culture, with *HBG1* and *HBG2* quantitative PCR and fetal haemoglobin flow cytometry as readouts, against a vehicle control and a hydroxyurea or decitabine positive control. This would convert the leading prediction into a result.

MATERIALS AND METHODS

Datasets

Five Gene Expression Omnibus series of *Homo sapiens* erythroid cells were used: GSE309131, GSE223925, GSE264491, GSE284289 and GSE247096. Each was verified against its accession record for sample count, platform, library strategy and group structure before inclusion. Datasets were required to provide at least three biological replicates per compared group, an explicit vehicle or non-targeting control within the same series, and raw or estimated counts rather than within-sample normalised values. Deposited matrices do not use GSM identifiers in their column headers; GSE309131 uses internal library names recoverable from the sample description field, and GSE264491 uses sequencing identifiers. Columns that could not be mapped were dropped rather than inferred.

Quantification and differential expression

GSE309131 and GSE264491 supplied gene-level counts directly. GSE223925 supplied per-sample featureCounts output. GSE284289 (kallisto) and GSE247096 (Salmon) supplied transcript-level estimates, summed to gene level over a 670,670-row Ensembl GRCh38 transcript-to-gene map obtained from Ensembl BioMart. GSE309131 counts are fractional estimates and were rounded after confirming that column sums vary 1.3-fold and so retain library-size scaling; the pipeline rejects matrices whose column sums are near-constant. Differential expression used PyDESeq2 0.5.4 (Muzellec et al., 2023) under Python 3.13, with donor as a covariate wherever a series spanned more than one donor and batch additionally for GSE223925. Thresholds were Benjamini-Hochberg adjusted $P < 0.05$ and absolute $\log_2$ fold change ≥ 0.58 .

Mechanism-class consensus

Contrasts were assigned to five classes by the biology perturbed: Polycomb repressive complex 2 inhibition, AMP-activated protein kinase activation, H3K9 methylation machinery (G9a-GLP-WIZ), direct locus editing, and MBD2-NuRD. A gene entered the consensus only if it moved concordantly in at least three distinct classes, including at least one pharmacological and one genetic contrast.

Signature matching

Induced and repressed gene lists were queried against L1000CDS2 and, through Enrichr (Kuleshov et al., 2016), against DSigDB (Yoo et al., 2015) and Drug Perturbations from GEO. A positive-control checkpoint was specified in advance: hydroxyurea, decitabine, mithramycin or pomalidomide had to appear among the top mimicking compounds, failing which the signature would be rebuilt before any novel hit was considered. Protein interaction analysis used STRING v12 (Szklarczyk et al., 2023).

Molecular docking

AutoDock Vina 1.2.5 (Eberhardt et al., 2021; Trott and Olson, 2010) was used against EHMT2 (Protein Data Bank 5VSE), EED (6W7G) and LSD1 (5L3E), with PPAR-gamma (4EMA) and RAR-alpha (6FX0) as cognate-receptor controls. Grid boxes were centred on each co-crystal ligand with 5 Å padding and a 20 Å floor. Ligands were built from PubChem SMILES with RDKit 2026.09.1 using ETKDgv3 embedding and MMFF94 optimisation, and written to PDBQT with Meeko 0.8.0. Two controls were applied: redocking each co-crystal ligand, and rebuilding each co-crystal ligand by the same flexible route used for candidates so that reference and candidate scores are comparable. Physicochemical descriptors were computed with RDKit. Regulatory and withdrawal status were taken from indexed literature rather than from prediction servers.

Statistical analysis

Enrichment of chromosome 19 KRAB zinc-finger genes was assessed by one-sided Fisher exact test against the matched-opportunity background, defined as the 17,566 genes tested in at least two pharmacological and two genetic contrasts. Correlations between contrasts are Spearman rank correlations computed on genes tested in both.

Declaration of artificial intelligence use

An artificial intelligence assistant (Claude, Anthropic) was used to execute the computational analysis described here, including dataset retrieval and verification, differential expression, consensus construction, signature matching, docking and the control experiments, and to draft this manuscript. All analysis code is provided in the supplementary archive, and all results are reproducible from the deposited public datasets. The authors verified the analyses and take full responsibility for the content.

Declarations

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This study used only publicly deposited data. The authors thank the laboratories that generated and deposited the datasets analysed here.

COMPETING INTERESTS

No competing interests declared.

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DATA AND CODE AVAILABILITY

All datasets analysed are publicly available in the NCBI Gene Expression Omnibus: GSE309131 (<https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE309131>), GSE223925, GSE264491, GSE284289 and GSE247096, each reachable at the same URL pattern. Protein structures are available in the RCSB Protein Data Bank under accession codes 5VSE, 6W7G, 5L3E, 4EMA and 6FX0 (<https://www.rcsb.org>). Enrichr gene-set identifiers for the consensus induced and repressed lists are 47554c44ca748509d5f9e50eea9d452c and ff76cccf2bbd5d99248e077cff55b353. All analysis code, differential expression tables for the ten contrasts, docking inputs and outputs, and the control experiments are provided in the supplementary archive.

AUTHOR CONTRIBUTIONS

Conceptualization: J.O.O.; Methodology: J.O.O.; Software: J.O.O.; Validation: J.O.O., O.L.K.; Formal analysis: J.O.O.; Investigation: J.O.O., O.L.K.; Data curation: J.O.O.; Writing - original draft: J.O.O.; Writing - review and editing: J.O.O., O.L.K.; Visualization: J.O.O.

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Figures

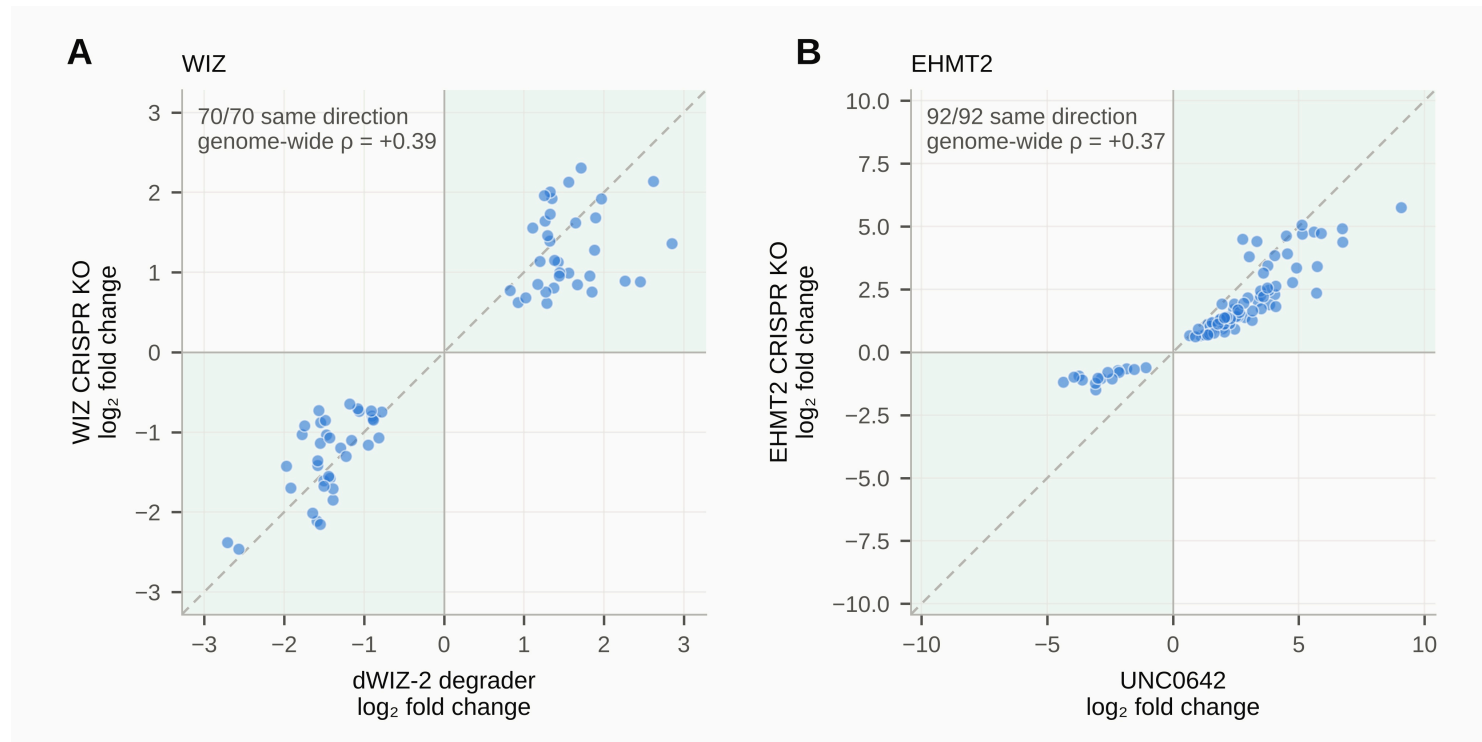


Figure 1

Pharmacological and genetic perturbation of the same repressor agree in direction. Each point is a gene significantly changed (adjusted $P < 0.05$, absolute $\log_2$ fold change at least 0.58) by both the small

molecule and the CRISPR knockout of the same target in GSE247096 at day 7. (A) WIZ, comparing the dWIZ-2 degrader with WIZ knockout. (B) EHMT2, comparing UNC0642 with EHMT2 knockout. Shaded quadrants are concordant, and the dashed line is the identity. No gene falls in a discordant quadrant for either target. Spearman correlations are computed genome-wide on genes tested in both contrasts.

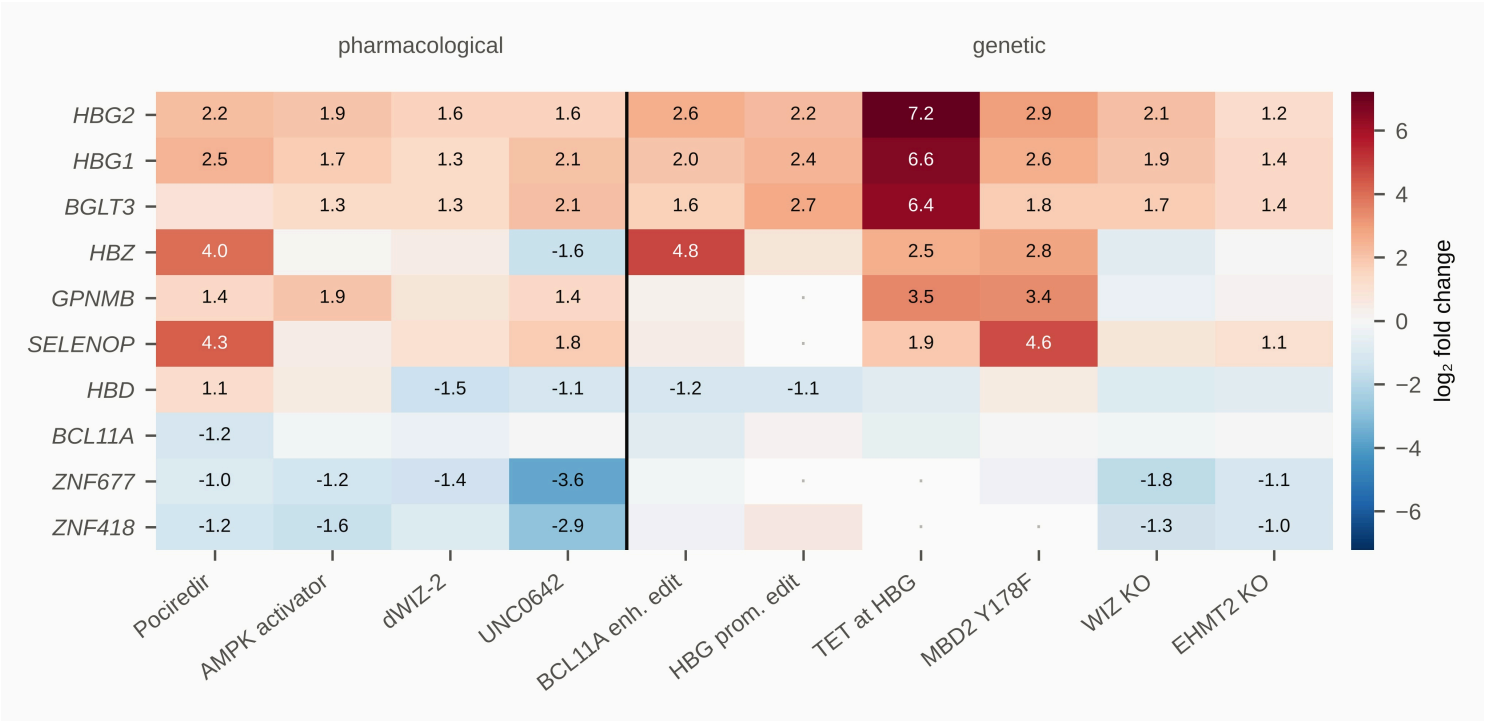


Figure 2

Signature genes across all ten contrasts. Values are log2 fold change; cells are annotated where the absolute value is at least 1. Contrasts are ordered pharmacological then genetic, separated by the vertical rule. *HBG1*, *HBG2* and *BGLT3* are induced throughout. The KRAB zinc-finger rows (*ZNF677*, *ZNF418*) fall only in the four contrasts that perturb chromatin machinery and are near-unchanged under direct locus editing, which is the basis for reclassifying their depletion as a marker of trans-acting perturbation rather than a fetal haemoglobin signature. A centred dot marks a gene not tested in that contrast after independent filtering.

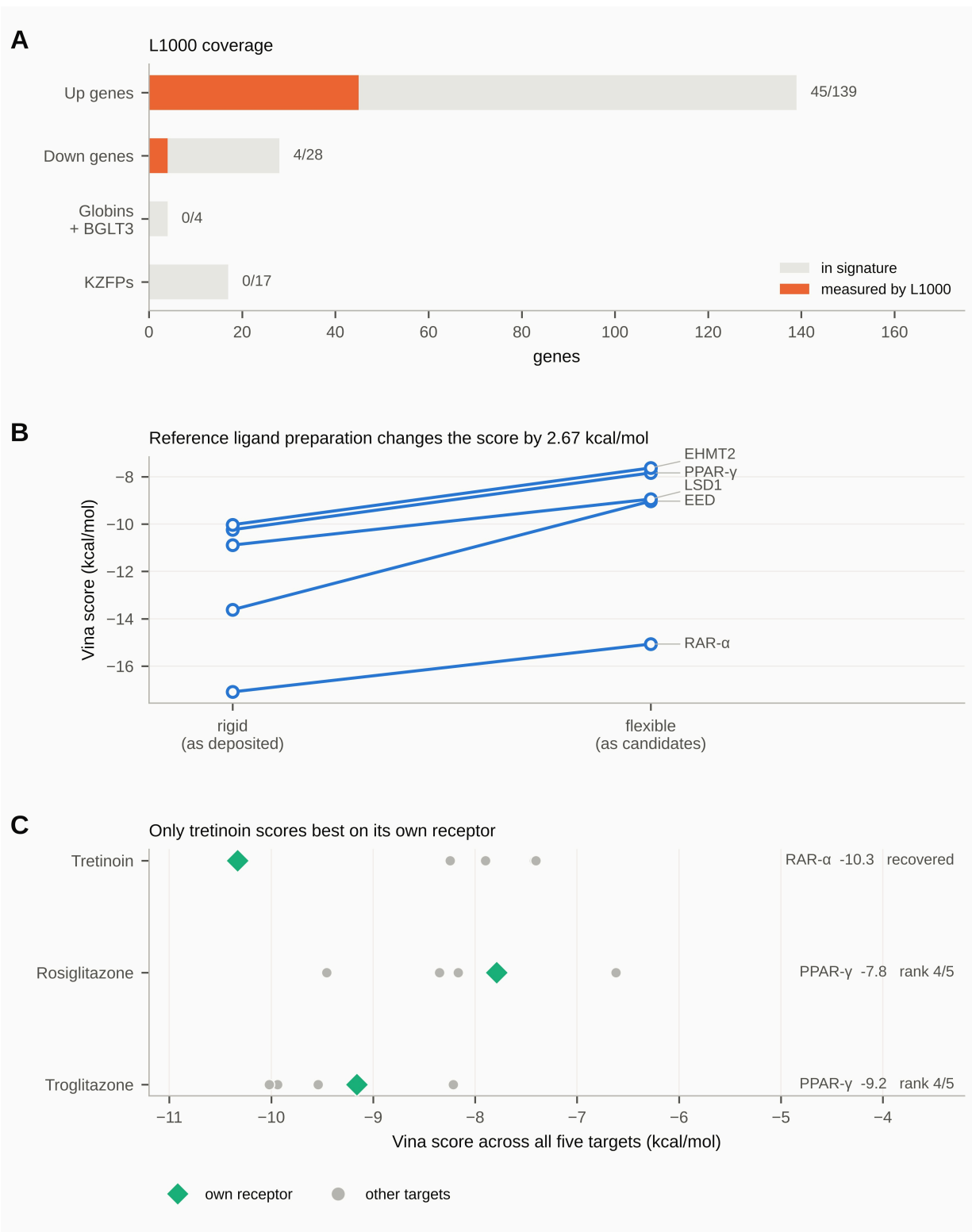


Figure 3

Three control experiments expose three tool failures. (A) The L1000 platform measures 45 of 139 signature-induced genes, 4 of 28 repressed genes, and none of the four beta-globin locus genes or seventeen KRAB zinc-finger genes. (B) Rebuilding each co-crystal ligand by the flexible route used for candidate compounds shifts its docking score by a mean of 2.67 kcal/mol, exceeding most differences the analysis would otherwise interpret as meaningful. (C) Of three drugs with a co-crystallised receptor

in the panel, only tretinoin scores best on its own receptor; rosiglitazone and troglitazone each rank their own receptor fourth of five. Diamonds mark the cognate receptor and circles the other four targets.

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