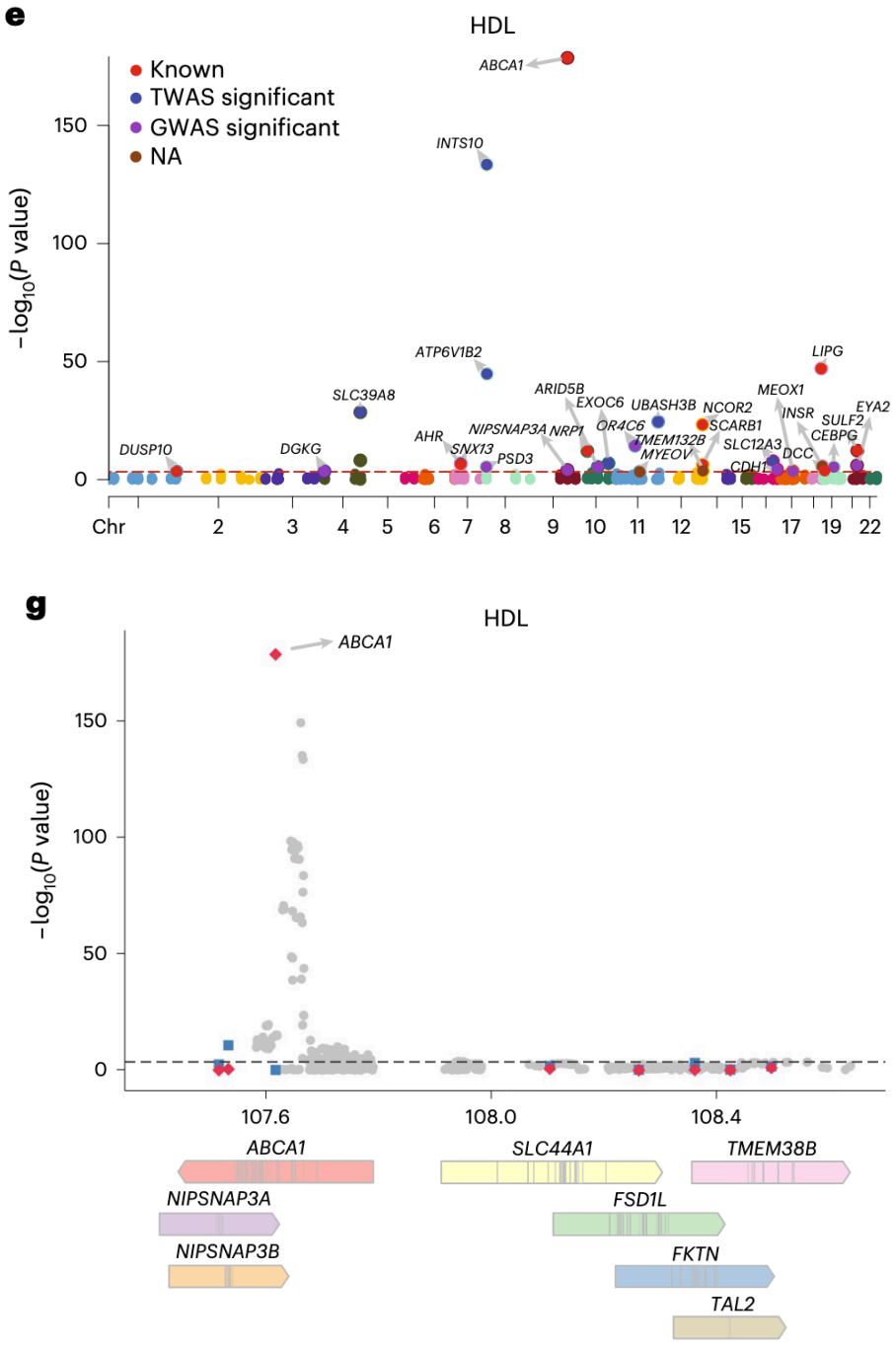
GIFT simulation

Simulation setup

We selected the region (chr9, 107581749-109298754) corresponding to Fig. 4g for simulation, which includes $m = 8$ genes. Among them, ABCA1 is considered by GIFT to be the gene most closely related to HDL in real data analysis:



We obtained the .bed data from GEUVADIS and UK Biobank, and extracted the corresponding 8 gene regions based on https://github.com/yuanzhongshang/GIFT/blob/main/reproduce/gencodev12.tsv. Then, we took the intersection of SNPs from the GEUVADIS and UK Biobank data. Now, the number of eQTL SNPs corresponding to each gene is as follows:

Gene ID	Number of SNPs
ABCA1	141
FKTN	63
FSD1L	51
NIPSNAP3A	79
NIPSNAP3B	75
SLC44A1	61
TAL2	37
TMEM38B	48
total	$p = 555$

We used the GIFT function pre_process_individual to read the .bed files. This function removes samples with missing values. For the GEUVADIS data, the final sample size was $n_1 = 379$. For the UK Biobank data, about 50% of the rows had missing values. Therefore, we used plink to retain 10,000 samples, and after reading with pre_process_individual, $n_2 = 5446$ samples remained.

The other hyperparameter are shown in the table below:

Parameters	Settings
correlation matrix	exponential covariance structure
number of simulations	100×2
number of casual genes	0 or 1
PVEzx	all SNPs with 0.1
PVEzy	0.01

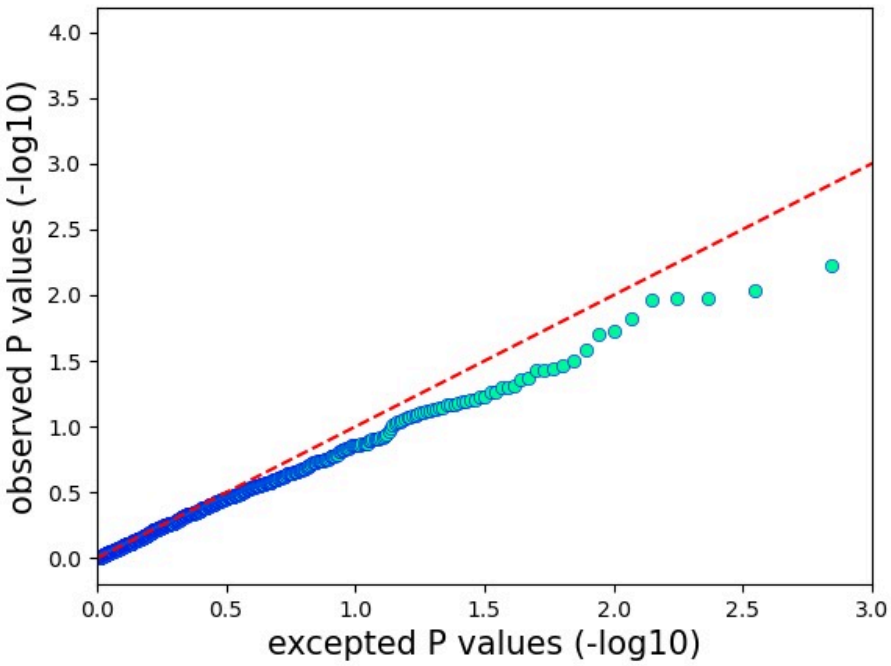
Parameters	Settings
casual effect	sqrt (PVEzy / PVEzx) = sqrt(0.1)
seed	k+500, k+1000, i*k+1
GIFT parameters	default

Under the above data scale and parameter settings, running GIFT once takes approximately 1 minute.

Simulation results

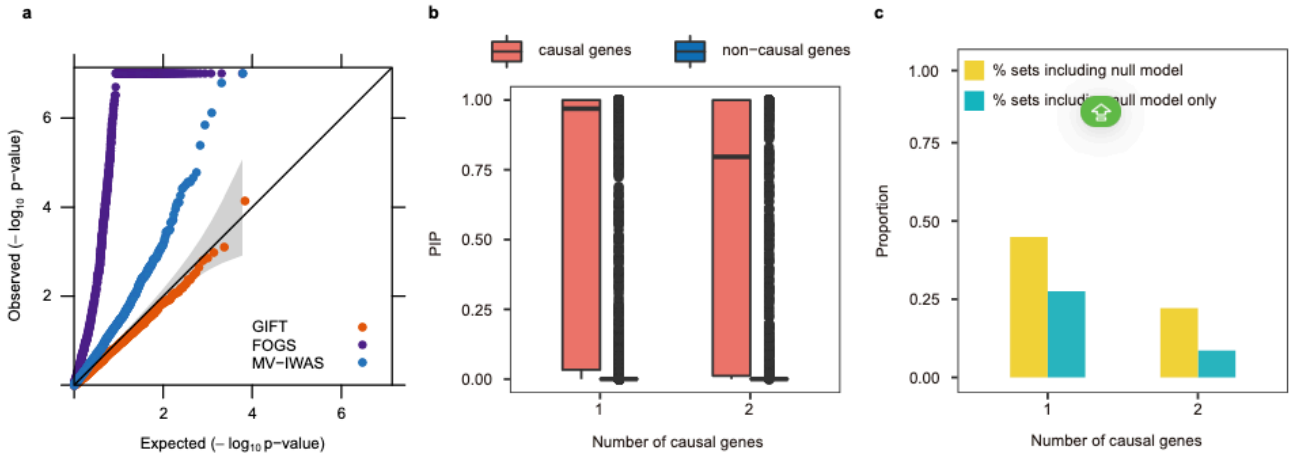
Null simulations

- For the complete null-simulation settings where all genes in the region have zero effects on the outcome trait:

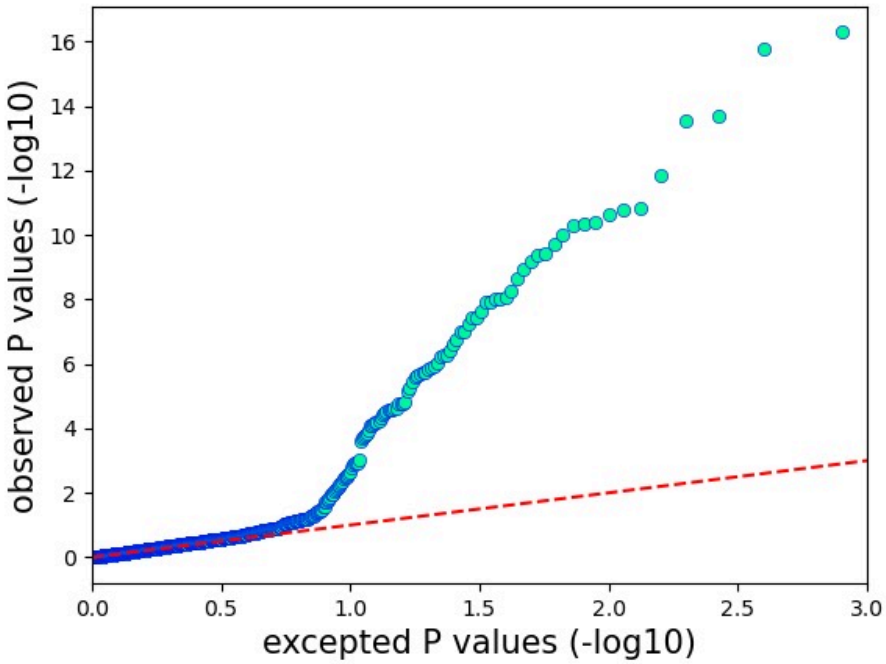


- For null-simulation settings where both the null and causal genes are present in the same region:

> GIFT supplementary Figs show that the q-q plot only includes non-causal gene points:



Supplementary Fig. 3 Comparisons of different methods under different numbers of causal genes in the simulations. The number of causal genes in the region is either one or two. (**a**) Quantile-quantile plot of -log10 *p*-values from the three compared methods, including GIFT (orange), FOGS (purple), and MV-IWAS (blue), is displayed for the non-causal genes where two genes are causal in the region. Two-sided *p*-values are calculated for the three frequentist methods. (**b**) Boxplot displays the PIPs from causal genes and non-causal genes across 1,000 regions. The box is drawn from the first and third quartiles (25^{th} and 75^{th} percentiles) with a horizontal line drawn in the middle to denote the median. The lowest point is the minimum and the highest point is the maximum. (**c**) Bar plot displays the proportion of 90%-credible sets including the null model or including only the null model.



Power and FDR

- For recommended threshold (Bonferroni's adjusted P-value 0.05/m):

Method: GIFT

thresholds	FDR	power
0.05 / 800	0%	63%
0.05 / 5480	0%	49%

> Results in GIFT paper:
> (Bonferroni's adjusted P-value 0.05/5480)
>
> | Methods | FDR | power |
> |---|---|---|
> | GIFT | 0% | 46.8% |
> | FOCUS | 42.1% | 70.6% |
> | FOGS | 39.6% | 49.6% |
> | MV-IWAS | 0.5% | 56.2% |

This indicates that using Bonferroni's adjusted P-value for the GIFT method results is **over-calibrated**.

- For true FDR 0.05:

> For each alternative simulation setting, we first divided 20 simulation replicates into five groups, with four replicates per group. We then calculated power per FDR in each group separately. In each group, we obtained the test statistics from each method for all genes across the four replicates ... Afterwards, we obtained the average power across five groups

In our simulations, we devided 100 simulation replicates into 5 groups, with 20 replicates per groups. That is because the threshold $0.05 = 1/20$.

Across five groups, **The average power is 0.9**, which is close to the results of GIFT.

- For estimated FDR 0.05:

	Predict Positive	Predict Negative
Reference Positive	88	12
Reference Negative	1	699

The result is also close to GIFT paper.

Others

- The impact of sample size on GIFT results:

When $n = 2000$, the power is not high, and false positives may occur:

	gene	causal_effect	p
1	chr9_ABCA1	0.269275526	0.02846179
2	chr9_FKTN	0.022021421	0.80911616
3	chr9_FSD1L	0.024352900	0.92631434
4	chr9_NIPSNAP3A	-0.018265201	0.88104528
5	chr9_NIPSNAP3B	0.172496017	0.15154642
6	chr9_SLC44A1	0.043890436	0.56179384
7	chr9_TAL2	0.006391095	0.90582435
8	chr9_TMEM38B	-0.024847026	0.71445907

Actually, the true casual gene is NIPSNAP3B.