

Nature Communications Revision

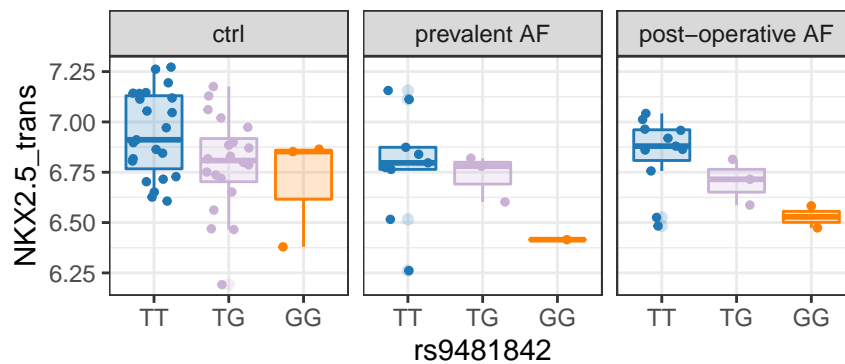
Ines Assum

July 12, 2021

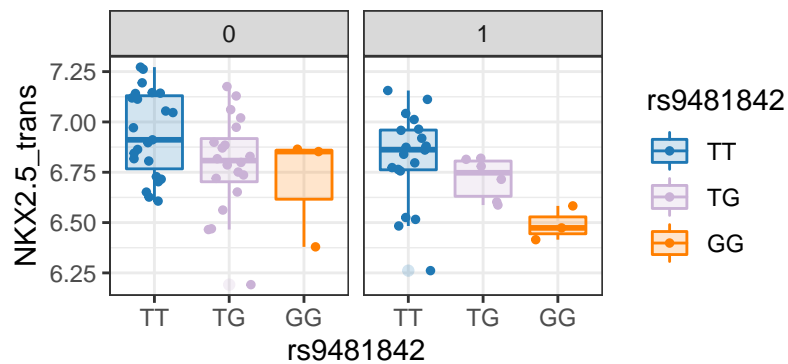
```
## [1] "eQTL genes:"
## [1] "NKX2-5" "TNNT2"
## [1] "pQTL genes:"
## [1] "CYB5R3" "NDUFA9" "DLAT" "NDUFB3" "HIBADH"
## [1] "NKX2-5 targets:"
## [1] "PPIF" "MYL4" "CKM" "MYL7" "PGAM2" "TNNC1" "CYC1" "ETFB" "PRDX5"
## [10] "AK1" "ALDOA" "TCAP" "TOM1L2"
## [1] "Genes in fibrosis score: "
## [1] "ELN" "FGF10" "JAG1" "KIAA1199" "CPXM2" "FOSB" "FCRL2"
## [8] "SCN7A" "NOV" "ARHGAP20" "CILP" "FRAS1" "DCDC2" "NRG1"
## [15] "CLEC3B" "AFAP1L2" "COL14A1" "ITGBL1"
```

1 Trans QTLs may be disease-specific

Disease-specific trans eQTL rs9481842 and NKX2-5



Disease-specific trans eQTL rs9481842 and NKX2-5



2 PRS missingness

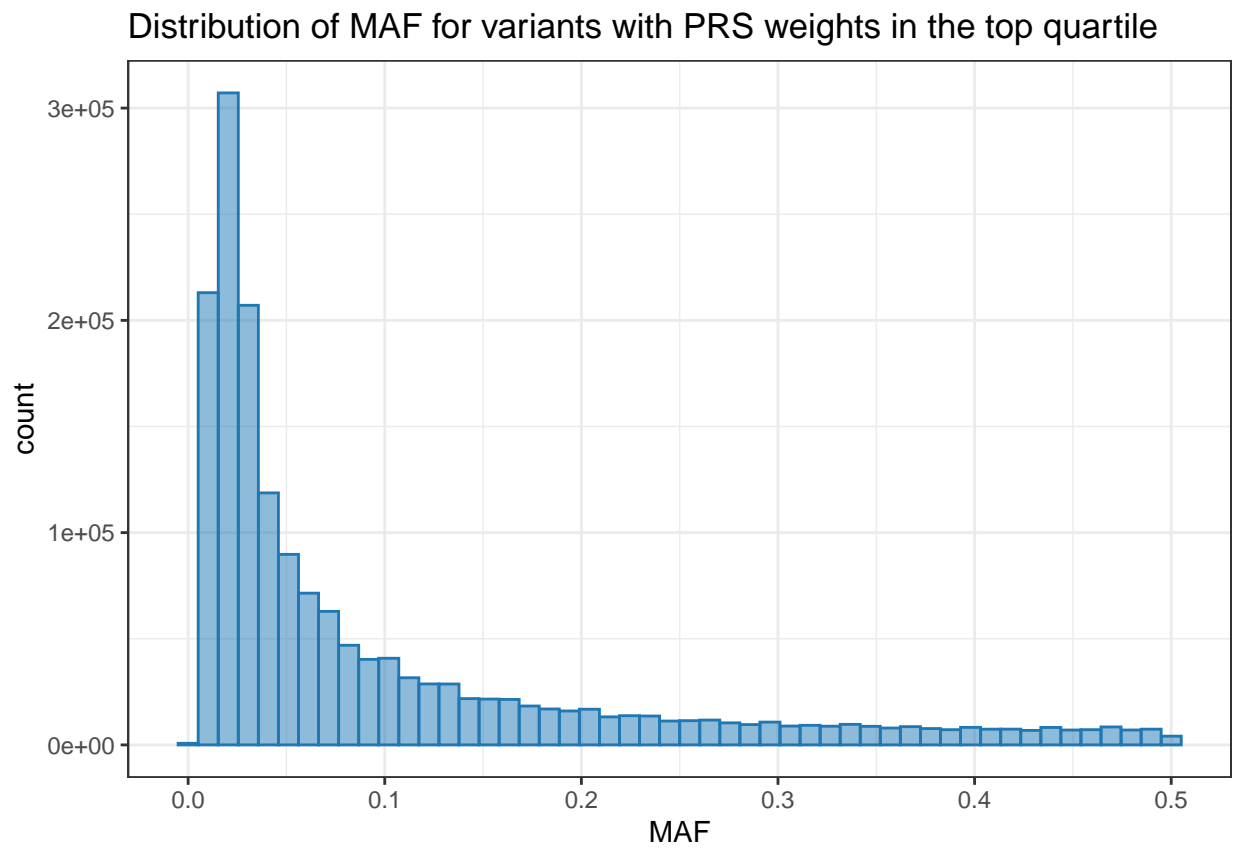
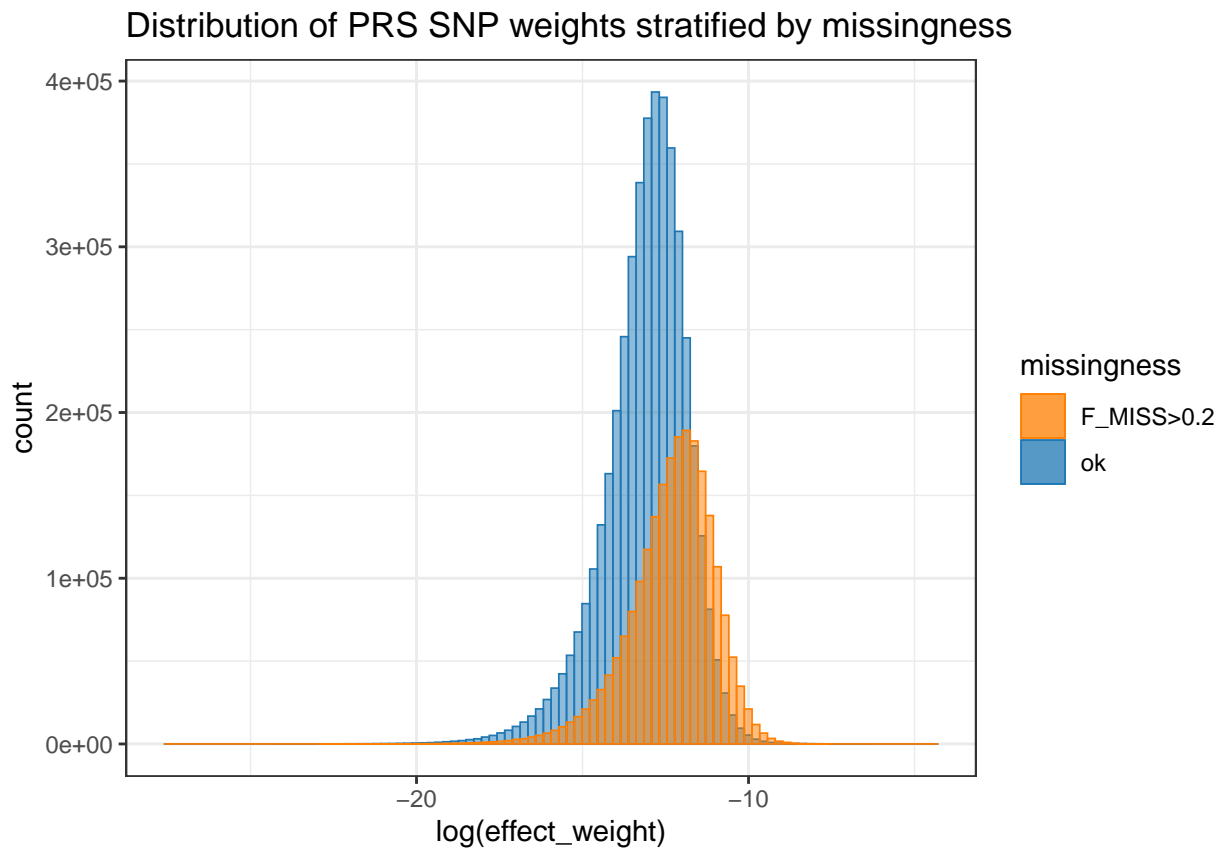
```
## [1] "Missing (>20%) vs. higher weight (top quartile) SNPs:"
```

```
##
```

```
##           0           1
```

```
##    0 3757677 715315
```

```
##    1 1290256 967292
```

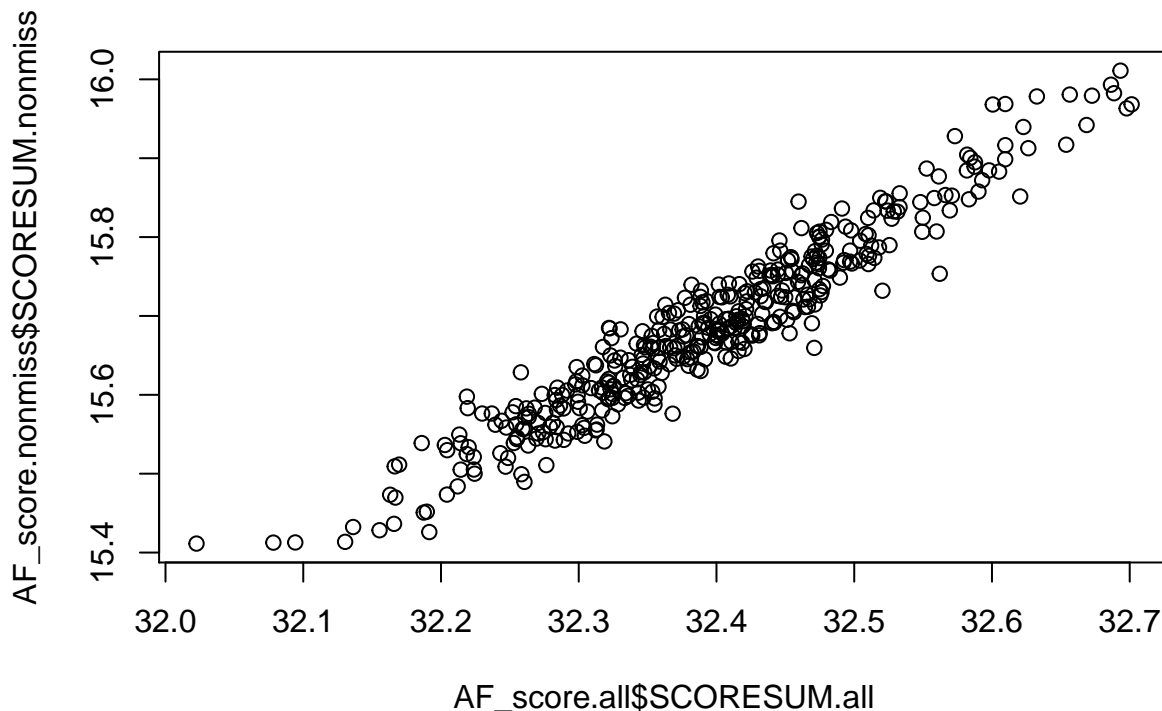


```
## [1] "Fraction of missing SNPs: 0.33541855482621"
```

```
## [1] "Fraction of higher weight SNPs that are missing: 0.574876961762313"
```

For the 1000 Genomes individuals, almost all of the 6 730 540 SNPs with weights in the PRS were measured with an overall genotyping rate of 99.9%. For the AFHRI-B cohort, 33.5% had a genotyping rate per SNP lower than 80%. If we consider “higher weight SNPs” as the top quartile of SNPs ranked by their risk score weight, 57.5% of higher weight SNPs have a genotyping rate per SNP of less than 80.0%.

2.1 Estimate PRS variance from 1000 genomes data only



```
## [1] 0.9598741
```

```
## [1] TRUE
```

```
##
```

```
## Call:
```

```
## lm(formula = SCORESUM.all ~ SCORESUM.nonmiss, data = score1k)
```

```
##
```

```
## Residuals:
```

```
##      Min       1Q   Median       3Q      Max
## -0.11051 -0.02196  0.00119  0.02063  0.10412
```

```
##
```

```
## Coefficients:
```

```
##              Estimate Std. Error t value Pr(>|t|)
## (Intercept)    17.49360    0.21630   80.88  <2e-16 ***
## SCORESUM.nonmiss 0.94991    0.01379   68.88  <2e-16 ***
```

```
## ---
```

```
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
##
```

```
## Residual standard error: 0.03185 on 405 degrees of freedom
```

```
## Multiple R-squared:  0.9214, Adjusted R-squared:  0.9212
```

```
## F-statistic: 4745 on 1 and 405 DF, p-value: < 2.2e-16
```

```
##
## Call:
## lm(formula = SCORESUM.all ~ SCORESUM.topquar, data = score1k)
##
## Residuals:
##      Min       1Q   Median       3Q      Max
## -0.084372 -0.021344 -0.000491  0.022392  0.091115
##
## Coefficients:
##              Estimate Std. Error t value Pr(>|t|)
## (Intercept)    9.61489    0.31818   30.22  <2e-16 ***
## SCORESUM.topquar 1.09576    0.01531   71.59  <2e-16 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 0.03073 on 405 degrees of freedom
## Multiple R-squared:  0.9268, Adjusted R-squared:  0.9266
## F-statistic: 5125 on 1 and 405 DF, p-value: < 2.2e-16
```

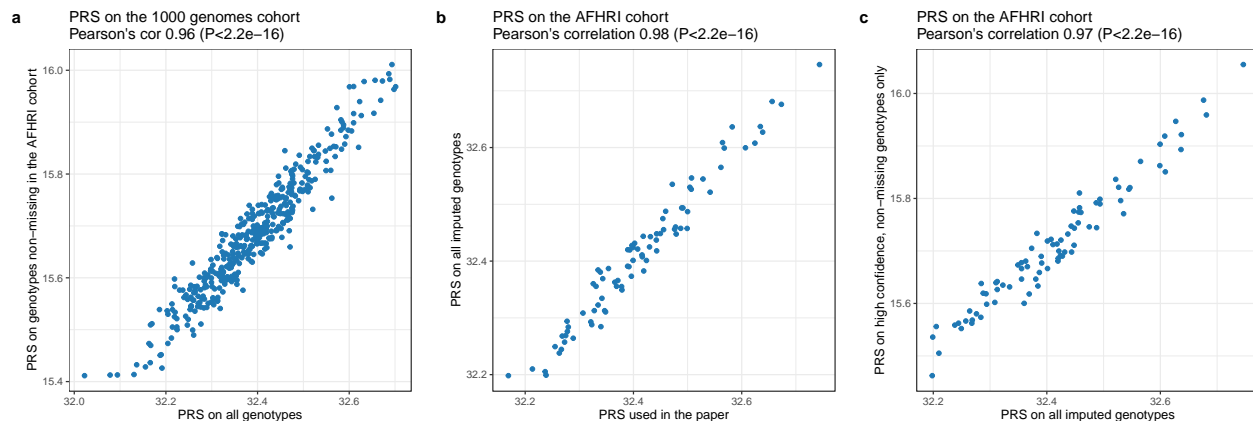
2.2 PRS incl low-confidence imputed genotypes

Calculate PRS based on the unfiltered dosages of the imputed genotypes using `scripts/PRS_trans_analyses/impute_to_prs.py`.

```
##
## Pearson's product-moment correlation
##
## data: df$AF.GPS and df$PRS
## t = 43.87, df = 81, p-value < 2.2e-16
## alternative hypothesis: true correlation is not equal to 0
## 95 percent confidence interval:
##  0.968554 0.986790
## sample estimates:
##      cor
## 0.9795985
##
## Pearson's product-moment correlation
##
## data: df$PRS and df$SCORESUM
## t = 38.846, df = 81, p-value < 2.2e-16
## alternative hypothesis: true correlation is not equal to 0
## 95 percent confidence interval:
##  0.9602857 0.9832759
## sample estimates:
##      cor
## 0.9741962
##
## Pearson's product-moment correlation
##
## data: df$AF.GPS and df$SCORESUM
## t = 97.877, df = 81, p-value < 2.2e-16
## alternative hypothesis: true correlation is not equal to 0
## 95 percent confidence interval:
##  0.9934960 0.9972877
## sample estimates:
```

```
##      cor
## 0.995799

##
## Pearson's product-moment correlation
##
## data: AF_score.all$SCORESUM.all and AF_score.nonmiss$SCORESUM.nonmiss
## t = 68.884, df = 405, p-value < 2.2e-16
## alternative hypothesis: true correlation is not equal to 0
## 95 percent confidence interval:
##  0.9514432 0.9668660
## sample estimates:
##      cor
## 0.9598741
```



```
##
## Welch Two Sample t-test
##
## data: AF.GPS by preOP_AF
## t = -1.5507, df = 24.19, p-value = 0.06698
## alternative hypothesis: true difference in means is less than 0
## 95 percent confidence interval:
##      -Inf 0.004718019
## sample estimates:
## mean in group 0 mean in group 1
##      32.39808      32.44390

##
## Welch Two Sample t-test
##
## data: PRS by preOP_AF
## t = -1.3044, df = 22.764, p-value = 0.1026
## alternative hypothesis: true difference in means is less than 0
## 95 percent confidence interval:
##      -Inf 0.01317319
## sample estimates:
## mean in group 0 mean in group 1
##      32.39839      32.44028

##
## Welch Two Sample t-test
##
```

a PRS used in the paper
 $t = -1.5$, $P = 0.067$ (one-sided t -test)

b Dosages for all imputed genotypes
 $t = -1.3$, $P = 0.10$ (one-sided t -test)

c Non-missing genotypes only
 $t = -1.7$, $P = 0.053$ (one-sided t -test)

PRS on high confidence genotypes estimated together with 1000 genome individuals

PRS on all imputed genotypes

PRS on high confidence/non-missing genotypes only

Disease status: Ctrl, Prevalent AF

```
## [1] "expr"      "heat.AF"   "heat.cor"
## [1] "expr"      "heat.AF"   "GSEA.AF"   "stats.AF"  "heat.cor"
## [1] "heat.cor"
## [1] "expr"      "heat.AF"   "heat.cor"
```

a AF differential expression
(mean centered and scaled values per group)

b Coexpression of NKX2-5 and its targets (Pearson's correlation)

Legend:

- Omic Region:** mRNA (blue), Protein (purple), Region (green)
- Region:** Right atrium (light green), Left atrium (pink)
- Type:** Trans eQTL (dark blue), Trans pQTL (light blue), NKX2-5 targets (light purple)

Table 1: AF differential expression (mean centered and scaled values per group)

Gene	AFHRI	AFHRI	GSE128188	GSE128188	PXD006675
TNNI2 ² ,++	0.15	0.15	0.15	0.15	0.15
NKX2-5 ²	0.15	0.15	0.15	0.15	0.15
CYB5R3	0.15	0.15	0.15	0.15	0.15
NDUFB3+	0.15	0.15	0.15	0.15	0.15
HIBADH	0.15	0.15	0.15	0.15	0.15
NDUFA9++	0.15	0.15	0.15	0.15	0.15
DLAT	0.15	0.15	0.15	0.15	0.15
PPIF	0.15	0.15	0.15	0.15	0.15
MYL4 ² ,++	0.15	0.15	0.15	0.15	0.15
CKM++	0.15	0.15	0.15	0.15	0.15
MYL7	0.15	0.15	0.15	0.15	0.15
PGAM2++	0.15	0.15	0.15	0.15	0.15
TNNC1*	0.15	0.15	0.15	0.15	0.15
CYC1	0.15	0.15	0.15	0.15	0.15
ETFB ² ,++	0.15	0.15	0.15	0.15	0.15
PRDX5	0.15	0.15	0.15	0.15	0.15
AK1	0.15	0.15	0.15	0.15	0.15
ALDOA++	0.15	0.15	0.15	0.15	0.15
TCAP*	0.15	0.15	0.15	0.15	0.15
TOM1L2	0.15	0.15	0.15	0.15	0.15

Table 2: Coexpression of NKX2-5 and its targets (Pearson's correlation)

Gene	AFHRI	AFHRI	GSE128188	GSE128188
NKX2-5 ²	1	1	1	1
PPIF	0.53	0.48	0.47	0.16
MYL4 ² ,++	0.50	0.43	0.43	0.46
CKM++	0.54	0.48	0.55	0.38
MYL7	0.45	0.45	0.44	0.70
PGAM2++	0.60	0.46		0.66
TNNC1*	0.39	0.41	0.49	0.70
CYC1	0.63	0.37	0.63	0.58
ETFB ² ,++	0.59	0.39	0.57	0.53
PRDX5	0.57	0.38	0.70	0.26
AK1	0.53	0.39	0.60	0.66
ALDOA++	0.51	0.35	0.52	0.56
TCAP*	0.51	0.37	0.53	0.66
TOM1L2	0.49	0.33	0.60	0.81

Table 3: AF differential expression (mean centered and scaled values per group)

Gene	AFHRI	AFHRI	GSE128188	GSE128188	PXD006675
TNNI2 ² ,++	0.15	0.15	0.15	0.15	0.15
NKX2-5 ²	0.15	0.15	0.15	0.15	0.15
CYB5R3	0.15	0.15	0.15	0.15	0.15
NDUFB3+	0.15	0.15	0.15	0.15	0.15
HIBADH	0.15	0.15	0.15	0.15	0.15
NDUFA9++	0.15	0.15	0.15	0.15	0.15
DLAT	0.15	0.15	0.15	0.15	0.15
PPIF	0.15	0.15	0.15	0.15	0.15
MYL4 ² ,++	0.15	0.15	0.15	0.15	0.15
CKM++	0.15	0.15	0.15	0.15	0.15
MYL7	0.15	0.15	0.15	0.15	0.15
PGAM2++	0.15	0.15	0.15	0.15	0.15
TNNC1*	0.15	0.15	0.15	0.15	0.15
CYC1	0.15	0.15	0.15	0.15	0.15
ETFB ² ,++	0.15	0.15	0.15	0.15	0.15
PRDX5	0.15	0.15	0.15	0.15	0.15
AK1	0.15	0.15	0.15	0.15	0.15
ALDOA++	0.15	0.15	0.15	0.15	0.15
TCAP*	0.15	0.15	0.15	0.15	0.15

3.2 Differential expression

3.2.1 PXD006675

##	symbol	Gene.names	Difference2	P.value2	Significant	FDR
##	TNNT2	TNNT2;HNTN1	-1.30454890	0.0009732051	+	0.01849090
##	<NA>	<NA>	NA	NA	<NA>	NA
##	CYB5R3	CYB5R3	0.26043574	0.1127526425		0.19475456
##	NDUFB3	NDUFB3	-0.19542440	0.6109977515		0.72555983
##	HIBADH	HIBADH	-0.19658025	0.5037439323		0.63807565
##	NDUFA9	NDUFA9	-0.07503382	0.7270170332		0.72701703
##	DLAT	DLAT	-0.40919495	0.0283988007		0.06744715
##	PPIF	PPIF	-0.12356631	0.7114231071		0.72701703
##	MYL4	MYL4	-1.47692871	0.0059350682	+	0.03758877
##	CKM	CKM	-0.95478821	0.0049934778	+	0.03758877
##	MYL7	MYL7	-0.77145386	0.0187746468		0.05621817
##	PGAM2	PGAM2	-0.77551651	0.0207119576		0.05621817
##	TNNC1	TNNC1	0.29302724	0.6922828358		0.72701703
##	CYC1	CYC1	-0.72316996	0.0186895464		0.05621817
##	ETFB	ETFB	0.56162262	0.1266605376		0.20054585
##	PRDX5	PRDX5	-0.64683660	0.0142015854		0.05621817
##	AK1	AK1	-0.60873032	0.0561397280		0.10666548
##	ALDOA	ALDOA	-0.64443715	0.0391012845		0.08254716
##	TCAP	TCAP	0.53084183	0.3603888218		0.48909912
##	TOM1L2	TOM1L2	0.28782463	0.1831180091		0.26763401

3.2.2 GSE128188

[1] "Right atrial appendage tissue:"

##	symbol	logFC	logCPM	PValue	FDR	FDR2	
##	TNNT2	TNNT2	-0.11653678	10.576699	0.3823697568	1.00000000	0.61643729
##	NKX2-5	NKX2-5	-0.12083565	6.893973	0.4309282300	1.00000000	0.61643729
##	CYB5R3	CYB5R3	-0.00111735	8.020750	0.9929176372	1.00000000	0.99291764
##	NDUFB3	NDUFB3	-0.29290140	5.726754	0.0442885310	0.55362105	0.27227924
##	HIBADH	HIBADH	-0.23573597	6.059837	0.0816837728	0.68619551	0.27227924
##	NDUFA9	NDUFA9	-0.13804653	6.521869	0.2852680344	0.97065072	0.57053607
##	DLAT	DLAT	-0.04976546	7.140205	0.7354941667	1.00000000	0.81721574
##	PPIF	PPIF	-0.07457071	6.672741	0.6152418823	1.00000000	0.72381398
##	MYL4	MYL4	-0.54877653	10.508736	0.0006810827	0.05457129	0.01362165
##	CKM	CKM	-0.20800205	11.199817	0.2389393567	0.94110738	0.57053607
##	MYL7	MYL7	-0.35170922	12.340329	0.0730553758	0.65779021	0.27227924
##	PGAM2	PGAM2	-0.52095482	8.508459	0.0029233794	0.12858532	0.02923379
##	TNNC1	TNNC1	-0.03108355	9.051189	0.8333231964	1.00000000	0.87718231
##	CYC1	CYC1	-0.23659353	7.538934	0.1104059337	0.76952662	0.31544552
##	ETFB	ETFB	-0.09987551	6.566480	0.4602519723	1.00000000	0.61643729
##	PRDX5	PRDX5	-0.22579814	6.515512	0.0739769141	0.66018049	0.27227924
##	AK1	AK1	-0.13623868	7.029380	0.3569448794	0.99750456	0.61643729
##	ALDOA	ALDOA	-0.09920934	10.710710	0.4921777069	1.00000000	0.61643729
##	TCAP	TCAP	-0.16364452	9.867318	0.2770849081	0.96690773	0.57053607
##	TOM1L2	TOM1L2	-0.09799518	8.834506	0.4931498320	1.00000000	0.61643729

[1] "Left atrial appendage tissue:"

##	symbol	logFC	logCPM	PValue	FDR	FDR2	
##	TNNT2	TNNT2	-0.19116244	10.576699	0.15196988	0.9830800	0.5216895
##	NKX2-5	NKX2-5	-0.10387860	6.893973	0.49832557	1.0000000	0.7118937

##	CYB5R3	CYB5R3	0.05294066	8.020750	0.67234717	1.0000000	0.8286175
##	NDUFB3	NDUFB3	-0.11250258	5.726754	0.43937307	1.0000000	0.7008306
##	HIBADH	HIBADH	-0.14702979	6.059837	0.27717736	1.0000000	0.5216895
##	NDUFA9	NDUFA9	-0.09637071	6.521869	0.45553987	1.0000000	0.7008306
##	DLAT	DLAT	-0.03726710	7.140205	0.80020535	1.0000000	0.8891171
##	PPIF	PPIF	0.01451649	6.672741	0.92231160	1.0000000	0.9223116
##	MYL4	MYL4	-0.41171128	10.508736	0.01071171	0.3381628	0.2142342
##	CKM	CKM	-0.19433722	11.199817	0.27118284	1.0000000	0.5216895
##	MYL7	MYL7	-0.27127273	12.340329	0.16659110	1.0000000	0.5216895
##	PGAM2	PGAM2	-0.36680728	8.508459	0.03588102	0.5963547	0.3588102
##	TNNC1	TNNC1	0.16665729	9.051189	0.25925345	1.0000000	0.5216895
##	CYC1	CYC1	-0.15774362	7.538934	0.28692925	1.0000000	0.5216895
##	ETFB	ETFB	-0.05129415	6.566480	0.70432490	1.0000000	0.8286175
##	PRDX5	PRDX5	-0.22992992	6.515512	0.06877527	0.7636373	0.4585018
##	AK1	AK1	-0.17956565	7.029380	0.22456629	1.0000000	0.5216895
##	ALDOA	ALDOA	-0.05677004	10.710710	0.69428462	1.0000000	0.8286175
##	TCAP	TCAP	-0.17004265	9.867318	0.25872121	1.0000000	0.5216895
##	TOM1L2	TOM1L2	0.02051197	8.834506	0.88599894	1.0000000	0.9223116

4 GTEx replication: Tissue specific expression of core genes in GTEx

4.1 mRNA

4.2 Protein

4.3 Response figure

