r2redux

Hong Lee and Moksedul Momin

20/07/2022

# r2redux\_version4

The ‘r2redux’ package can be used to derive test statistics for R2 values from polygenic score (PGS) models (variance and covariance of R2 values, p-value and 95% confidence intervals (CI)). For example, it can test if two sets of R2 values from two different PGS models are significantly different to each other whether the two sets of PGS are independent or dependent. Because R2 value is often regarded as the predictive ability of PGS, r2redux package can be useful to assess the performances of PGS methods or multiple sets of PGS based on different information sources. Furthermore, the package can derive the information matrix of beta1^2 and beta2^2 from a multiple regression (see olkin\_beta1\_2 or olkin\_beta\_info function in the manual), which is a basis of a novel PGS-based genomic partitioning method (see r2\_enrich or r2\_enrich\_beta function in the manual). It is recommended that the target sample size in the PGS study should be more than 2,000 for quantitative traits (Supplementary Figure 27) and more than 5,000 for binary responses or case-control studies (Supplementary Figures 28 and 29). The p-value generated from r2redux is a two-tail test. Depending on hypothesis, one-tail p-value can be obtained as the two-tail p-value divided by 2

# INSTALLATION

To use r2redux: - install.packages(“devtools”) - library(devtools) - devtools::install\_github(“mommy003/r2redux\_version4”) or - install.packages(“r2redux”) - library(r2redux)

# QUICK START

We illustrate the usage of r2redux using multiple sets of PGS estimated based on GWAS summary statistics from UK Biobank or Biobank Japan (reference datasets). In a target dataset, the phenotypes of target samples (y) can be predicted with PGS (a PGS model, e.g. y = PGS + e where y and PGS are column-standardised (Olkin and Finn 1995)). Note that the target individuals should be independent from reference individuals. We can test the significant differences of the predictive ability (R2) between a pair of PGS (see r2\_diff function and example in the manual).

# DATA PREPARATION

**a. Statistical testing of significant difference between R2 values for p-value thresholds:** r2redux requires only phenotype and estimated PGS (from PLINK or any other software). Note that any missing value in the phenotypes and PGS tested in the model should be removed. If we want to test the significant difference of R^2 values for p-value thresholds, r2\_diff function can be used with an input file that includes the following fields (also see test\_ukbb\_thresholds\_scaled in the example directory or read dat1 file embedded within the package and r2\_diff function in the manual).

* Phenotype (y)
* PGS for p value 1 (x1)
* PGS for p value 0.5 (x2)
* PGS for p value 0.4 (x3)
* PGS for p value 0.3 (x4)
* PGS for p value 0.2 (x5)
* PGS for p value 0.1 (x6)
* PGS for p value 0.05 (x7)
* PGS for p value 0.01 (x8)
* PGS for p value 0.001 (x9)
* PGS for p value 0.0001 (x10)

To get the test statistics for the difference between R2(y=x[,v1]) and R2(yx[,v2]). (here we define R\_1^2= R^2(y=x[,v1])) and R\_22=R2(y=x[,v2]))) - dat=read.table(“test\_ukbb\_thresholds\_scaled”) (see example files) or - dat=dat1 (this example embedded within the package) - nv=length(dat$V1) - v1=c(1) - v2=c(2) - output=r2\_diff(dat,v1,v2,nv)

* r2redux output
* output$var1 (variance of R\_1^2)
* 0.0001437583
* output$var2 (variance of R\_2^2)
* 0.0001452828
* output$var\_diff (variance of difference between R\_1^2and R\_2^2)
* 5.678517e-07
* output$r2\_based\_p (p-value for significant difference between R\_1^2 and R\_2^2)
* 0.5514562
* output$mean\_diff (differences between R\_1^2 and R\_2^2)
* -0.0004488044
* output$upper\_diff (upper limit of 95% CI for the difference)
* 0.001028172
* output$lower\_diff (lower limit of 95% CI for the difference)
* -0.001925781

**b. PGS-based genomic enrichment analysis:** If we want to perform some enrichment analysis (e.g., regulatory vs non\_regulatory) in the PGS context to test significantly different from the expectation (4% = # SNPs in the regulatory / total # SNPs). We simultaneously fit two sets of PGS from regulatory and non-regulatory to get Î²\_regu^2 and Î²\_non\_regu^2, using a multiple regression, and assess if the differences, (Î²\_regu^2/expectation) - (Î²\_non\_regu^2/(1-expectation)), is significantly different from the null hypothesis. To test this, we need to prepare input file for r2redux that includes the following fields (e.g. test\_ukbb\_enrichment\_choles in example directory or read dat2 file embedded within the package and r2\_enrich\_beta function in the manual). - Phenotype (y) - PGS for regulatory region (x1) - PGS for non-regulatory region (x2)

To get the test statistic for the ratio which is significantly different from the expectation. var(t\_1/p\_exp -t\_2/(1-p\_exp )), where t\_1 = β ̂\_1^2 and t\_2 = β ̂\_2^2. β\_1 and β\_2 are regression coefficients from a multiple regression model, i.e. y=x\_1.β\_1+ x\_2.β\_2+e, where y, x\_1 and x\_2 are column standardised.

* dat=read.table(“test\_ukbb\_enrichment\_choles”) (see example file) or
* dat=dat2 (this example embedded within the package)
* nv=length(dat$V1)
* v1=c(1)
* v2=c(2)
* expected\_ratio=0.04
* output=r2\_enrich\_beta(dat,v1,v2,nv,expected\_ratio)
* output
* r2redux output
* output$beta1\_sq (t\_1)
* 0.01118301
* output$beta2\_sq (t\_2)
* 0.004980285
* output$var1 (variance of t\_1)
* 7.072931e-05
* output$var2 (variance of t\_2)
* 3.161929e-05
* output$var1\_2 (variance of difference between t\_1 and t\_2)
* 0.000162113
* output$cov (covariance between t\_1 and t\_2)
* -2.988221e-05
* output$enrich\_p2 (p-value for testing the difference between t\_1/p\_exp and t\_2/(1-p\_exp ))
* 0.1997805
* output$mean\_diff (difference between t\_1/p\_exp and t\_2/(1-p\_exp ))
* 0.2743874
* output$var\_diff (variance of difference, t\_1/p\_exp -t\_2/(1-p\_exp ))
* 0.04579649
* output$upper\_diff (upper limit of 95% CI for the mean difference)
* 0.6938296
* output$lower\_diff (lower limit of 95% CI for the mean difference)
* -0.1450549

# References

1. Olkin, I. and J.D. Finn, Correlations redux. Psychological Bulletin, 1995. 118(1): p. 155.
2. Momin, M.M., Lee, S., Wray, N.R. and Lee S.h. 2022. Significance tests for R2 of out-of-sample prediction using polygenic scores. bioRxiv.

# Contact information

Please contact Hong Lee ([hong.lee@unisa.edu.au](mailto:hong.lee@unisa.edu.au)) or Moksedul Momin ([cvasu.momin@gmail.com](mailto:cvasu.momin@gmail.com)) if you have any queries.