Biologically informed Polygenic Risk Score (ePRS) calculation for

Peripheral Leptin Receptor Gene Network Modulates the Impact of Childhood Adversity on Mental Health Disorders

This repository contains a tool developed to facilitate the calculation of biologically informed Polygenic Risk Score (ePRS).

The original method for ePRS calculation was published by Silveira Lab in 2017[1]. The details of the method provided below are based on one of the ePRS, specifically the Liver Leptin Receptor ePRS, described in de Lima et al 2025.

Generation of any ePRS starts from defining the critical determinant of the biological functionality that represents the research question. In this example we were interested in genes that were co-expressed with the leptin receptor gene (LEPR, ENSG00000116678) in the liver.

The Liver Leptin Receptor ePRS

The expression-based polygenic risk score was created considering genes co-expressed with the leptin receptor gene (LepR-ePRS) in the liver, according to the protocol previously described by Silveira et al (2017)[1], de Lima et al (2020)[2,] and Miguel et al (2019)[3].

Online resources/databases used for expression-based polygenic risk score:

(A) GeneNetwork: http://genenetwork.org;
(B) NCBI Variation Viewer: https://www.ncbi.nlm.nih.gov/variation/view;
(C) The Genotype-Tissue Expression (GTEx): https://gtexportal.org/home/.

GeneNetwork (A) was used to generate a list of genes co-expressed with the leptin receptor gene in the liver of mice (Mulligan et al., 2016)[4], retaining only the genes with absolute value of co-expression correlation higher or equal to 0.5 (49 genes). The list of mouse genes was converted to orthologous human genes (37 genes).

Based on their functional annotation in the National Center for Biotechnology Information, U.S. National Library of Medicine, **NCBI Variation Viewer** (B), using GRCh37.p13, we gathered all the SNPs from these genes and merged this list with the SNPs from the **GTEx data** (C) in human liver to form a list of common SNPs reqired for the ePRS calculation.

In ePRS calculation, alleles at a given cis-SNP were weighed by the estimated effect of the genotype on gene expression. Final ePRS was obtained by summation over all SNPs accounting for the sign of correlation coefficient between the genes and LepR gene expression. For more information on ePRS calculation. The summation of these values across all SNPs provides the LepR- ePRS score.

Necessary tools and resources

PRSice[5]: https://choishingwan.github.io/PRSice/step_by_step/

The script could be run using R or command prompt. Please specify the names and locations for the following files:

SNPLIST_LepR_ePRS.txt – list of SNPs selected from the GTEx for the LepR-ePRS calculation; to be downloaded from the LepR-ePRS repository

GENODATA – genodata file

OUTPUT – name of the output file

Rscript **PRSice.R** --prsice **PRSice_linux** –base **Sumstats_LepR-ePRS_LIVER.txt** --snp **rsid** --pvalue **p-value** --stat **beta** --A1 **effect_allele** --A2 **non-effect_allele** --target **GENODATA** --no-regress --clump-kb **500** —clump-r2 **0.2** --clump-p **1** --print-snp --bar-levels **1.0** --fastscore --model **add** --score **sum** --missing **SET_ZERO** --thread **max** --out **OUTPUT**

Output files are the following:

- *.snp – list of SNPs included in the calculated score,
- *.all.score – contains calculated score for each subject

References

1. Silveira PP, Pokhvisneva I, Parent C, et al. Cumulative prenatal exposure to adversity reveals associations with a broad range of neurodevelopmental outcomes that are moderated by a novel, biologically informed polygenetic score based on the serotonin transporter solute carrier family C6, member 4 (SLC6A4) gene expression. Dev Psychopathol. 2017;29(5):1601-1617.
2. de Lima RMS, Barth B, Arcego DM, et al. Amygdala 5-HTT Gene Network Moderates the Effects of Postnatal Adversity on Attention Problems: Anatomo-Functional Correlation and Epigenetic Changes. Frontiers in neuroscience. 2020;14(198).
3. Miguel PM, Deniz BF, Deckmann I, et al. Prefrontal cortex dysfunction in hypoxic-ischaemic encephalopathy contributes to executive function impairments in rats: Potential contribution for attention-deficit/hyperactivity disorder. The world journal of biological psychiatry : the official journal of the World Federation of Societies of Biological Psychiatry. 2017:1-14.
4. Mulligan MK, Mozhui K, Prins P, Williams RW. GeneNetwork: a toolbox for systems genetics. In: Systems Genetics. Springer; 2017:75-120.
5. Choi SW, and O'Reilly PF. "PRSice-2: Polygenic Risk Score Software for Biobank-Scale Data." GigaScience 8, no. 7 (July 1, 2019). https://doi.org/10.1093/gigascience/giz082.