main_junctions

September 8, 2021

1 eQTL boxplot: Enrichment and Overlap of PGC2+CLOZUK

This is script ported from python to fix unknown plotting error.

```
[1]: suppressPackageStartupMessages({
    library(tidyverse)
    library(ggpubr)
})
```

1.1 Functions

```
[2]: feature = "junctions"
```

1.1.1 Cached functions

```
[3]: get_de_df <- function(){
         de_file = paste0("../../differential_expression/_m/", feature,
                           "/diffExpr_szVctl_full.txt")
         return(data.table::fread(de_file))
     memDE <- memoise::memoise(get_de_df)</pre>
     get_eqtl_df <- function(){</pre>
         eGenes_file = paste0('../../eqtl/caudate/summary_table/_m/',
                              'Brainseq_LIBD_caudate_4features.signifpairs.txt.gz')
         eGenes = data.table::fread(eGenes_file) %>%
             filter(Type == feature_map(feature)) %>%
             arrange(pval_nominal)
         return(eGenes)
     memEQTL <- memoise::memoise(get_eqtl_df)</pre>
     get_pheno_df <- function(){</pre>
         phenotype_file = paste0('/ceph/projects/v4_phase3_paper/inputs/',
                                   'phenotypes/_m/merged_phenotypes.csv')
         return(data.table::fread(phenotype_file))
     memPHENO <- memoise::memoise(get_pheno_df)</pre>
```

```
get residualized df <- function(){</pre>
    expr_file = paste0("../../differential_expression/_m/", feature,
                        "/residualized_expression.tsv")
    return(data.table::fread(expr_file) %>% column_to_rownames("V1"))
}
memRES <- memoise::memoise(get_residualized_df)</pre>
get genotypes <- function(){</pre>
    traw_file = paste0("/ceph/projects/brainseq/genotype/download/topmed/
"filter_maf_01/a_transpose/_m/LIBD_Brain_TopMed.traw")
    traw = data.table::fread(traw_file) %>% rename_with(~ gsub('\\_.*', '', .x))
    return(traw)
memSNPs <- memoise::memoise(get_genotypes)</pre>
get_gwas_snps <- function(){</pre>
    gwas_snp_file = paste0('/ceph/projects/v4_phase3_paper/inputs/sz_gwas/',
                           'pgc2_clozuk/map_phase3/_m/libd_hg38_pgc2sz_snps.tsv')
    gwas df = data.table::fread(gwas snp file) %>% arrange(P)
    return(gwas df)
memGWAS <- memoise::memoise(get_gwas_snps)</pre>
get_integration_df <- function(){</pre>
    return(inner_join(memGWAS(), memEQTL(),
                      by=c("our_snp_id"="variant_id"),
                      suffix=c("_PGC2", "_eQTL")) %>%
            inner_join(memDE(), by=c("gene_id"="V1")) %>%
            mutate(agree_direction=sign(OR -1) * sign(slope) * sign(t) *_
\rightarrowifelse(pgc2 a1 same as our counted, 1, -1)))
memMERGE <- memoise::memoise(get integration df)</pre>
get_snp_df <- function(variant_id, gene_id){</pre>
    zz = get_geno_annot() %>% filter(SNP == variant_id)
    xx = get_snps_df() %>% filter(SNP == variant_id) %>%
        column_to_rownames("SNP") %>% t %>% as.data.frame %>%
        rownames to column("BrNum") %>% mutate(COUNTED=zz$COUNTED, ALT=zz$ALT)_
 ,>%
        rename("SNP"=all of(variant id))
    yy = memRES()[gene_id, ] %>% t %>% as.data.frame %>%
        rownames_to_column("RNum") %>% inner_join(memPHENO(), by="RNum")
    ## Annotated SNPs
    letters = c()
    for(ii in seq_along(xx$COUNTED)){
```

```
a0 = xx$COUNTED[ii]; a1 = xx$ALT[ii]; number = xx$SNP[ii]
    letters <- append(letters, letter_snp(number, a0, a1))
}
xx = xx %>% mutate(LETTER=letters, ID=paste(SNP, LETTER, sep="\n"))
df = inner_join(xx, yy, by="BrNum") %>% mutate_if(is.character, as.factor)
    return(df)
}
memDF <- memoise::memoise(get_snp_df)</pre>
```

1.1.2 Simple functions

```
[4]: feature_map <- function(feature){
         return(list("genes"="Gene", "transcripts"= "Transcript",
                      "exons"= "Exon", "junctions"= "Junction")[[feature]])
     }
     get_geno_annot <- function(){</pre>
         return(memSNPs() %>% select(CHR, SNP, POS, COUNTED, ALT))
     }
     get_snps_df <- function(){</pre>
         return(memSNPs() %>% select("SNP", starts_with("Br")))
     }
     letter_snp <- function(number, a0, a1){</pre>
         if(is.na(number)){ return(NA) }
         if( length(a0) == 1 & length(a1) == 1){
             seps = ""; collapse=""
         } else {
             seps = " "; collapse=NULL
         return(paste(paste0(rep(a0, number), collapse = collapse),
                       pasteO(rep(a1, (2-number)), collapse = collapse), sep=seps))
     }
     save_ggplots <- function(fn, p, w, h){</pre>
         for(ext in c('.pdf', '.png', '.svg')){
             ggsave(pasteO(fn, ext), plot=p, width=w, height=h)
         }
     }
     get_biomart_df <- function(){</pre>
         biomart = data.table::fread("../_h/biomart.csv")
     memMART <- memoise::memoise(get biomart df)</pre>
     get_gene_symbol <- function(gene_id){</pre>
```

```
ensemblID = gsub("\\..*", "", gene_id)
    geneid = memMART() %>% filter(ensembl_gene_id == gsub("\\..*", "", gene_id))
    if(dim(geneid)[1] == 0){
        return("")
    } else {
        return(geneid$external_gene_name)
    }
}
plot_simple_eqtl <- function(fn, gene_id, variant_id, eqtl_annot){</pre>
    bxp = memDF(variant_id, gene_id) %>%
        ggboxplot(x="ID", y=gene_id, fill="red", add="jitter", xlab="",
                  ylab="Residualized Expression", outlier.shape=NA,
                  add.params=list(alpha=0.5), alpha=0.4,
                  ggtheme=theme_pubr(base_size=20, border=TRUE)) +
        font("xy.title", face="bold") +
        ggtitle(paste(get_gene_symbol(gene_id), gene_id, eqtl_annot, sep='\n'))_u
        theme(plot.title = element text(hjust = 0.5, face="bold"))
    print(bxp)
    save ggplots(fn, bxp, 7, 7)
}
```

1.1.3 GWAS plots

```
[5]: get_risk_allele <- function(OR, A1, A2){</pre>
         ra = ifelse(OR > 1, A1, A2)
         return(ra)
     }
     get_df <- function(){</pre>
         return(memEQTL() %>% inner join(memGWAS(), by="variant id"))
     }
     get_gwas_ordered_snp_df <- function(variant_id, gene_id,_
      →pgc2_a1_same_as_our_counted, OR){
         df = memDF(variant_id, gene_id)
         if(!pgc2_a1_same_as_our_counted){ # Fix bug with matching alleles!
             if(OR < 1){ df = df %>% mutate(SNP = 2-SNP, ID=paste(SNP, LETTER, _
      →sep="\n")) }
         } else {
             if(OR > 1){ df = df %>% mutate(SNP = 2-SNP, ID=paste(SNP, LETTER, __
      →sep="\n")) }
         return(df)
     }
```

```
plot_gwas_eqtl_pheno <- function(fn, gene_id, variant_id,__
 →pgc2_a1_same_as_our_counted, OR, title){
   bxp = get_gwas_ordered_snp_df(variant_id, gene_id,__
⇒pgc2 a1 same as our counted, OR) %>%
        mutate_if(is.character, as.factor) %>% filter(Dx %in% c("CTL", "SZ"),_
 →Age > 17) %>%
        ggboxplot(x="ID", y=gene_id, fill="Dx", color="Dx", add="jitter", u
⇒xlab=variant id,
                  ylab="Residualized Expression", outlier.shape=NA,
                  add.params=list(alpha=0.5), alpha=0.4, legend="bottom",
                  ggtheme=theme_pubr(base_size=20, border=TRUE)) +
        font("xy.title", face="bold") + ggtitle(title) +
        theme(plot.title = element_text(hjust = 0.5, face="bold"))
   print(bxp)
    save_ggplots(fn, bxp, 7, 9)
}
```

1.2 Integration analysis

```
[6]: dir.create(feature)
```

1.2.1 Enrichment

Integrate DEG with PGC2+CLOZUK SNPs

```
[7]: dft = memMERGE() %>% mutate(agree_direction=ifelse(agree_direction == 1, "Yes", 

→ifelse(agree_direction == -1, "No", 0)))
dim(dft)
```

1. 3190613 2. 58

```
[8]: table(dft$agree_direction)
```

0 No Yes 3267 1557478 1629868

```
[,1] [,2]
[1,] 5196 74475
[2,] 122145 2988797
```

Fisher's Exact Test for Count Data

data: table

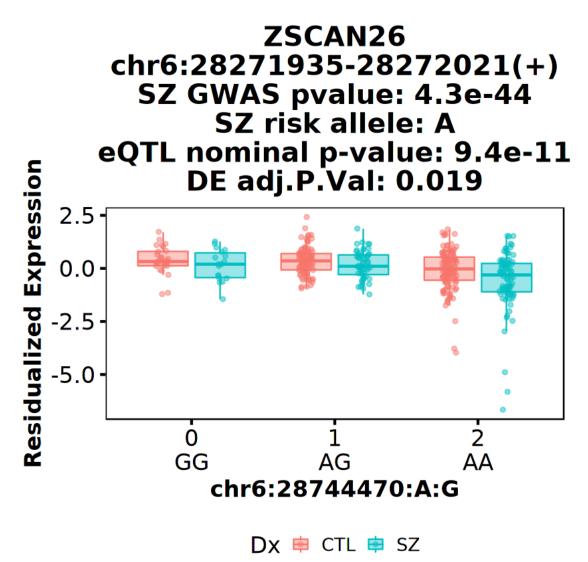
```
p-value < 2.2e-16
     alternative hypothesis: true odds ratio is not equal to 1
     95 percent confidence interval:
      1.658580 1.756912
     sample estimates:
     odds ratio
       1.707175
[10]: dft2 = dft %>% filter(P <= 5e-8, `adj.P.Val` < 0.05) %>%
          mutate(eqtl_gwas_dir=sign(OR -1) * sign(slope) *__
       →ifelse(pgc2_a1_same_as_our_counted, 1, -1),
                 de_dir=sign(t), eqtl_slope=sign(OR_
       \rightarrow-1)*sign(slope)*ifelse(pgc2_a1_same_as_our_counted, 1, -1)) %>%
          #rowwise() %>% mutate(risk allele=qet risk allele(our snp id)) %>%
          select(gene_id, newGeneSymbol, our_snp_id, rsid, A1, A2, OR, P,__
       →pval_nominal, adj.P.Val, logFC,
                 t, eqtl_slope, de_dir, eqtl_gwas_dir, agree_direction,__
       →pgc2_a1_same_as_our_counted) %>%
          rename("variant_id"="our_snp_id", "Symbol"="newGeneSymbol") %>%__
       →mutate_all(list(~na_if(.,""))) %>%
          mutate(Symbol = coalesce(Symbol,gene_id))
      dft2 %>% data.table::fwrite(paste0(feature, "/integration_by_symbol.txt"),__
       →sep='\t')
      dim(dft2)
     1. 5196 2. 17
[11]: df = dft2 %>% group_by(Symbol) %>% slice(1) %>% arrange(P)
      table(df$agree_direction)
      No Yes
       9 12
[12]: df
```

	gene_id	Symbol	variant_id	rsid
	<chr></chr>	<chr $>$	<chr></chr>	<chr $>$
A grouped_df: 21×17	chr6:28271935-28272021(+)	ZSCAN26	chr6:28744470:A:G	rs1233578
	chr6:31270086-31270209(-)	HLA-C	chr6:31348749:T:C	rs9265994
	chr6:31651777-31652399(-)	BAG6	chr6:31793436:G:A	rs2607014
	chr6:31996112-31996206(+)	C4A	chr6:31793436:G:A	rs2607014
	chr6:32024325-32024469(+)	C4B	chr6:31793436:G:A	rs2607014
	chr14:103729183-103729792(+)	ZFYVE21	chr14:103762504:C:T	rs7142769
	chr14:103520312-103520468(-)	CKB	chr14:103710761:G:T	rs4900592
	chr2:232888108-232891357(-)	NGEF	chr2:232926898:C:G	rs1878289
	chr11:113412884-113415420(-)	DRD2	chr11:113522272:C:T	rs2514218
	chr3:136262066-136283836(+)	PCCB	chr3:136569563:G:A	rs7432375
	chr6:83346335-83352063(-)	ME1	chr6:83668266:G:A	rs217300
	chr1:2497011-2497501(+)	PLCH2	chr1:2441515:A:G	rs6673661
	chr6:33080535-33080671(+)	HLA-DPB1	chr6:33020111:A:G	rs17214290
	chr16:58510684-58511421(+)	NDRG4	chr16:58511522:A:G	rs42945
	chr6:33728301-33735277(-)	IP6K3	chr6:33773939:A:G	rs4711350
	chr2:58048968-58084088(+)	VRK2	chr2:57939634:T:C	rs28718871
	chr1:8359987-8360111(-)	RERE	chr1:8443182:G:A	rs301818
	chr11:47180691-47182402(-)	PACSIN3	chr11:46729945:T:TAGG	rs3136476
	chr5:138445599-138445682(+)	REEP2	chr5:138439892:C:G	rs982085
	chr13:79551123-79552515(+)	NDFIP2	chr13:79285321:A:C	rs9545047
	chr7:24641869-24649611(+)	MPP6	chr7:24737470:CA:C	rs146678232

1.2.2 Plot with PGC2 risk allele

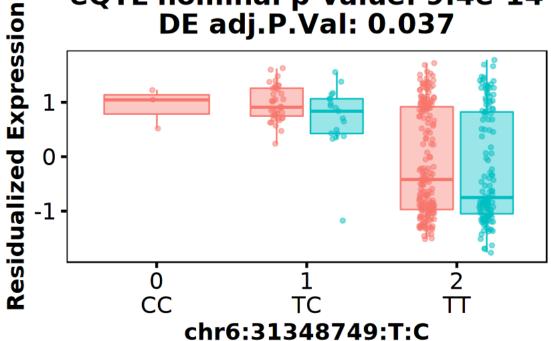
```
[13]: for(num in seq_along(df$gene_id)){
          variant_id = df$variant_id[num]
          gene_id = df$gene_id[num]
          gene_name = df$Symbol[num]
          pgc2_a1_same_as_our_counted = df$pgc2_a1_same_as_our_counted[num]
          OR = df\$OR[num]; A1 = df\$A1[num]; A2 = df\$A2[num]
          fn = paste0(feature, "/eqtl_gwas_", gsub("\\.", "_", gene_name))
          de_annot = paste('DE adj.P.Val:', signif(df$adj.P.Val[num], 2))
          eqtl_annot = paste("eQTL nominal p-value:", signif(df$pval_nominal[num], 2))
          gwas_annot = paste("SZ GWAS pvalue:", signif(df$P[num], 2))
          risk_annot = paste("SZ risk allele:", get_risk_allele(OR, A1, A2))
          title = paste(gene_name, gene_id, gwas_annot,
                        risk_annot, eqtl_annot, de_annot, sep='\n')
          plot_gwas_eqtl_pheno(fn, gene_id, variant_id, pgc2_a1_same_as_our_counted,_u
       →OR, title)
          #print(title)
```

Warning message in data.table::fread(expr_file):
"Detected 393 column names but the data has 394 columns (i.e. invalid file).
Added 1 extra default column name for the first column which is guessed to be row names or an index. Use setnames() afterwards if this guess is not correct,



HLA-C chr6:31270086-31270209(-) SZ GWAS pvalue: 1e-32 SZ risk allele: T

eQTL nominal p-value: 9.4e-14 **DE adj.P.Val: 0.037**



Chr6:31651777-31652399(-)
SZ GWAS pvalue: 1.2e-31
SZ risk allele: G
eQTL nominal p-value: 1.7e-05
DE adj.P.Val: 0.019

Dx 😑 CTL 😑 SZ

chr6:31793436:G:A

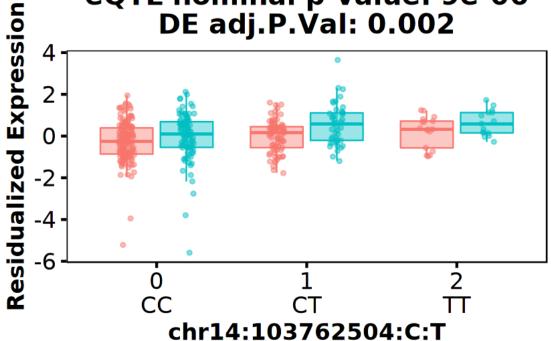
C4A chr6:31996112-31996206(+) SZ GWAS pvalue: 1.2e-31 SZ risk allele: G eQTL nominal p-value: 4.1e-36 Residualized Expression DE adj.P.Val: 0.0068 2 0 -2 -4 -6 Ö ż AA GA GG chr6:31793436:G:A

C₄B chr6:32024325-32024469(+) SZ GWAS pvalue: 1.2e-31
SZ risk allele: G eQTL nominal p-value: 1.6e-06 Residualized Expression DE adj.P.Val: 0.046 2 0 -2 4 ò ż AA GA GG chr6:31793436:G:A

ZFYVE21 chr14:103729183-103729792(+) SZ GWAS pvalue: 4.5e-14

SZ risk allele: T

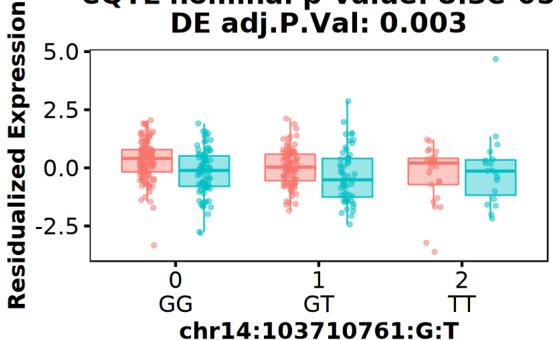
eQTL nominal p-value: 9e-06



CKB chr14:103520312-103520468(-) SZ GWAS pvalue: 3.3e-13

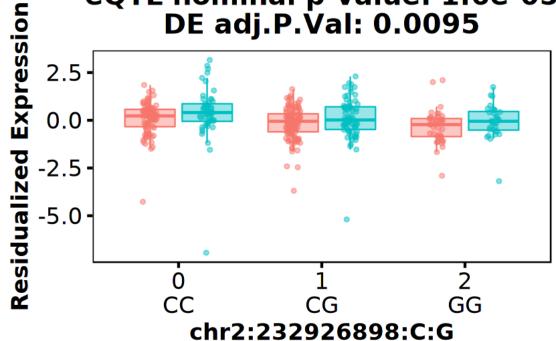
SZ risk allele: T

eQTL nominal p-value: 8.3e-05



NGEF chr2:232888108-232891357(-) SZ GWAS pvalue: 1.3e-12 SZ risk allele: G

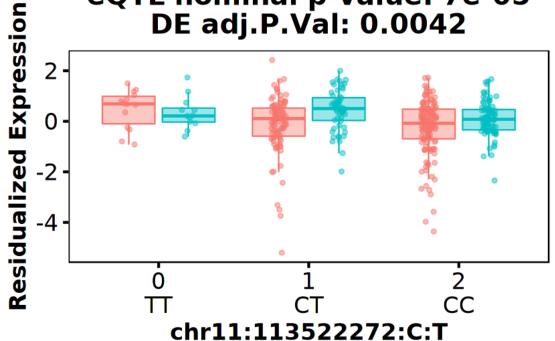
eQTL nominal p-value: 1.6e-05 DE adj.P.Val: 0.0095



Dx 🖶 CTL 🖶 SZ

DRD2 chr11:113412884-113415420(-) SZ GWAS pvalue: 2.4e-12 SZ risk allele: C

eQTL nominal p-value: 7e-05 DE adj.P.Val: 0.0042



chr3:136262066-136283836(+)
SZ GWAS pvalue: 4.1e-12
SZ risk allele: G
eQTL nominal p-value: 4.5e-06
DE adj.P.Val: 0.021

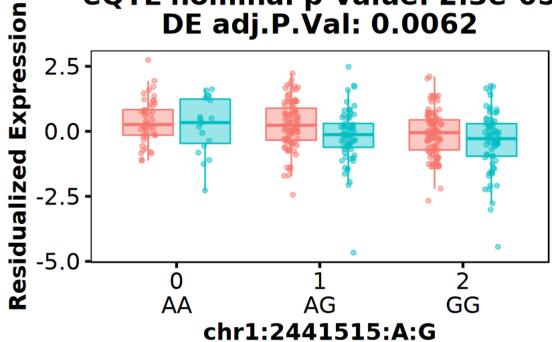
2
AA GA GG
chr3:136569563:G:A

Dx 🖶 CTL 🖶 SZ

ME1 chr6:83346335-83352063(-) SZ GWAS pvalue: 4.2e-12 SZ risk allele: G eQTL nominal p-value: 1e-04 Residualized Expression **DE adj.P.Val: 0.018** 2 0 . -2 ż Ö AA GA GG chr6:83668266:G:A Dx 😑 CTL 😑 SZ

PLCH2 chr1:2497011-2497501(+) SZ GWAS pvalue: 3.7e-11 SZ risk allele: G

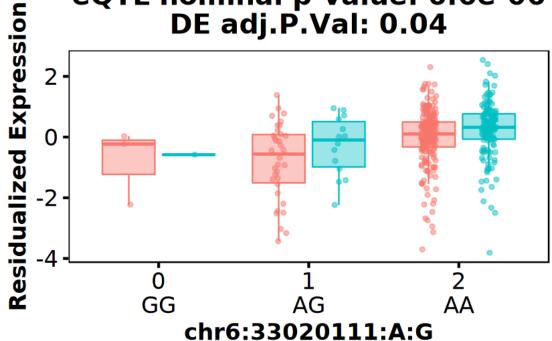
eQTL nominal p-value: 2.3e-05



HLA-DPB1 chr6:33080535-33080671(+) SZ GWAS pvalue: 2.2e-10 SZ risk allele: A

eQTL nominal p-value: 6.6e-06

DE adj.P.Val: 0.04



Dx 🖶 CTL 🖶 SZ

NDRG4 chr16:58510684-58511421(+) SZ GWAS pvalue: 2.2e-10 SZ risk allele: G eQTL nominal p-value: 2.3e-16 Residualized Expression **DE adj.P.Val: 0.028** 0 -5 Ö ż

Dx 🖶 CTL 😑 SZ

AG

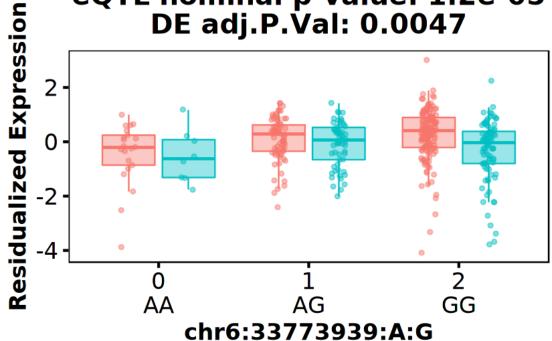
chr16:58511522:A:G

GG

AA

IP6K3 chr6:33728301-33735277(-) SZ GWAS pvalue: 2.3e-10 SZ risk allele: G

eQTL nominal p-value: 1.2e-05 DE adj.P.Val: 0.0047



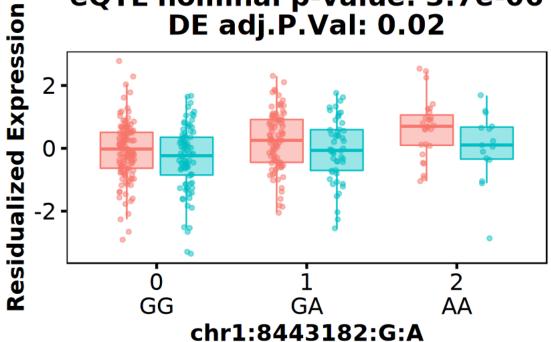
chr2:58048968-58084088(+)
SZ GWAS pvalue: 7.5e-10
SZ risk allele: C
eQTL nominal p-value: 6.4e-05
DE adj.P.Val: 0.042

Dx 🖶 CTL 😑 SZ

chr2:57939634:T:C

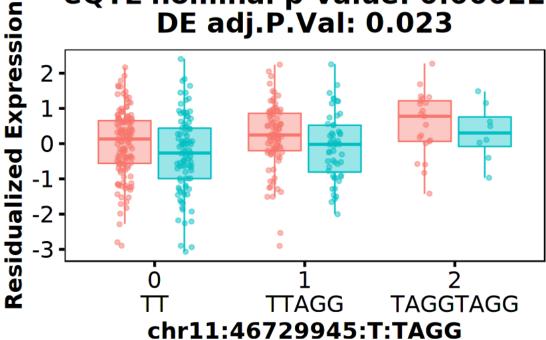
RERE chr1:8359987-8360111(-) SZ GWAS pvalue: 3.8e-09 SZ risk allele: A

eQTL nominal p-value: 3.7e-06 DE adj.P.Val: 0.02



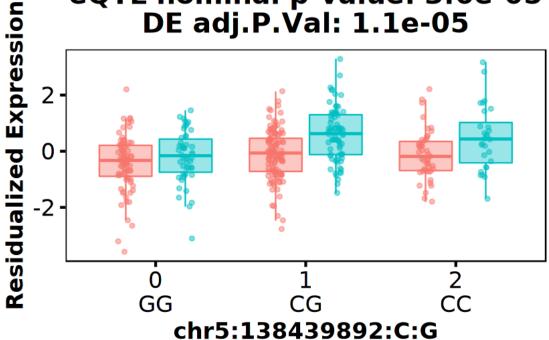
PACSIN3 chr11:47180691-47182402(-) SZ GWAS pvalue: 3.9e-09 SZ risk allele: TAGG

eQTL nominal p-value: 0.00022 DE adj.P.Val: 0.023



REEP2 chr5:138445599-138445682(+) SZ GWAS pvalue: 1e-08 SZ risk allele: C

eQTL nominal p-value: 3.6e-05 DE adj.P.Val: 1.1e-05

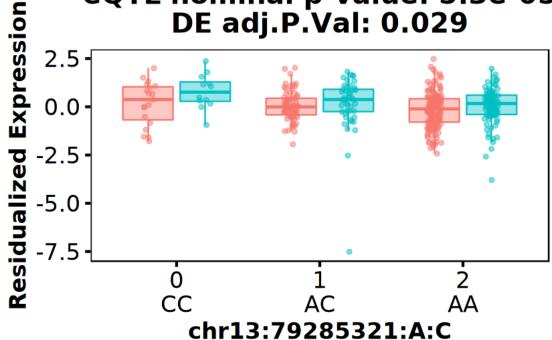


Dx 🖶 CTL 🖶 SZ

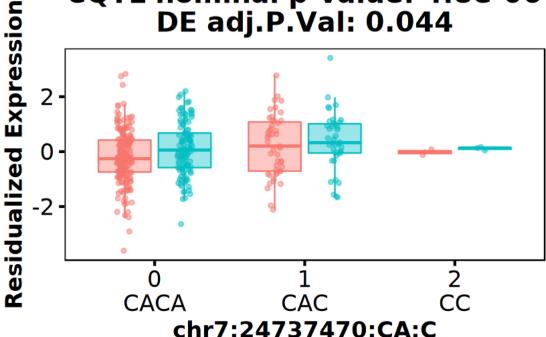
NDFIP2 chr13:79551123-79552515(+) SZ GWAS pvalue: 1.2e-08

SZ risk allele: A

eQTL nominal p-value: 5.3e-05 DE adj.P.Val: 0.029



MPP6 chr7:24641869-24649611(+) SZ GWAS pvalue: 1.6e-08 SZ risk allele: C eQTL nominal p-value: 4.8e-06 DE adj.P.Val: 0.044



Dx 😑 CTL 😑 SZ

1.3 Session Info

```
[14]: Sys.time()
    proc.time()
    options(width = 120)
    sessioninfo::session_info()

[1] "2021-09-08 11:24:25 EDT"

    user system elapsed
    8671.188 4339.813 1869.688

    Session info
    setting value
```

version R version 4.0.3 (2020-10-10)

os Arch Linux

system x86_64, linux-gnu

ui X11 language (EN)

collate en_US.UTF-8
ctype en_US.UTF-8
tz America/New_York

date 2021-09-08

Packages

package	*	version	date	lib	sourc	ce
abind		1.4-5	2016-07-21	[1]	CRAN	(R 4.0.2)
assertthat		0.2.1	2019-03-21	[1]	CRAN	(R 4.0.2)
backports		1.2.1	2020-12-09	[1]	CRAN	(R 4.0.2)
base64enc		0.1-3	2015-07-28	[1]	CRAN	(R 4.0.2)
broom		0.7.9	2021-07-27	[1]	CRAN	(R 4.0.3)
cachem		1.0.6	2021-08-19	[1]	CRAN	(R 4.0.3)
Cairo		1.5-12.2	2020-07-07	[1]	CRAN	(R 4.0.2)
car		3.0-11	2021-06-27	[1]	CRAN	(R 4.0.3)
carData		3.0-4	2020-05-22	[1]	CRAN	(R 4.0.2)
cellranger		1.1.0	2016-07-27	[1]	CRAN	(R 4.0.2)
cli		3.0.1	2021-07-17	[1]	CRAN	(R 4.0.3)
colorspace		2.0-2	2021-06-24	[1]	CRAN	(R 4.0.3)
crayon		1.4.1	2021-02-08	[1]	CRAN	(R 4.0.3)
curl		4.3.2	2021-06-23	[1]	CRAN	(R 4.0.3)
data.table		1.14.0	2021-02-21	[1]	CRAN	(R 4.0.3)
DBI		1.1.1	2021-01-15	[1]	CRAN	(R 4.0.2)
dbplyr		2.1.1	2021-04-06	[1]	CRAN	(R 4.0.3)
digest		0.6.27	2020-10-24	[1]	CRAN	(R 4.0.2)
dplyr	*	1.0.7	2021-06-18	[1]	CRAN	(R 4.0.3)
ellipsis		0.3.2	2021-04-29	[1]	CRAN	(R 4.0.3)
evaluate		0.14	2019-05-28	[1]	CRAN	(R 4.0.2)
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- [1] /home/jbenja13/R/x86_64-pc-linux-gnu-library/4.0
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