main

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1 Plotting eQTLs, increase font sizes

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[1]:
```
import re
import functools
import subprocess
import numpy as np
import pandas as pd
from plotnine import *
from pandas_plink import read_plink
from warnings import filterwarnings
from matplotlib.cbook import mplDeprecation

filterwarnings("ignore",category=mplDeprecation)
filterwarnings('ignore', category=UserWarning, module='plotnine.*')
filterwarnings('ignore', category=DeprecationWarning, module='plotnine.*')
```

1.1 Configuration

[2]:
```
tissue = "hippocampus"; feature = "genes"
config = {
    'biomart_file': '../_h/biomart.csv',
    'residual_expression_file': "../../../../prep_eqtl_analysis/%s/%s/
 ↪covariates/" % (tissue, feature)+\
    "residualized_expression/_m/%s_residualized_expression.csv" % feature,
    'phenotype_file': '/ceph/projects/v4_phase3_paper/inputs/phenotypes/_m/
 ↪merged_phenotypes.csv',
    'plink_file_prefix': '/ceph/projects/v4_phase3_paper/inputs/genotypes/_m/
 ↪LIBD_Brain_TopMed',
    'eqtl_output_file': '../../../summary_table/_m/
 ↪Brainseq_sex_interacting_4features_3regions.eFeatures.txt.gz',
    'gwas_snp_file': '/ceph/projects/v4_phase3_paper/inputs/sz_gwas/pgc2_clozuk/
 ↪map_phase3/_m/libd_hg38_pgc2sz_snps_p5e_minus8.tsv'
}
```

1.2 Functions

1.2.1 Expression functions

[3]:
```
@functools.lru_cache()
def tissue_map(tissue):
    return {"caudate": "Caudate", "dlpfc": "DLPFC",
            "hippocampus": "Hippocampus"}[tissue]


@functools.lru_cache()
def feature_map(feature):
    return {"genes": "Gene", "transcripts": "Transcript",
            "exons": "Exon", "junctions": "Junction"}[feature]


@functools.lru_cache()
def get_biomart_df():
    biomart = pd.read_csv(config['biomart_file'], index_col=0)
    biomart['description'] = biomart['description'].str.replace('\[Source.
 ↪*$','', regex=True)
    return biomart


@functools.lru_cache()
def get_residual_expression_df():
    return pd.read_csv(config['residual_expression_file'], index_col=0).
 ↪transpose()


@functools.lru_cache()
def get_pheno_df():
    return pd.read_csv(config['phenotype_file']).set_index("BrNum").loc[:,␣
 ↪["RNum", "Sex", "Dx"]]


@functools.lru_cache()
def get_expression_and_pheno_df():
    return pd.merge(get_pheno_df(), get_residual_expression_df(),
                    left_index=True, right_index=True)


@functools.lru_cache()
def get_gene_id_df():
    return pd.DataFrame({'gene_id': get_residual_expression_df().columns,
                         'ensembl_gene_id': get_residual_expression_df().
 ↪columns.str.replace('\..+$','', regex=True)})
```

```
@functools.lru_cache()
def gene_info_from_symbol(gene_symbol):
    return␣
 ↪get_biomart_df()[get_biomart_df()['external_gene_name']==gene_symbol]\
        .merge(get_gene_id_df(), on='ensembl_gene_id', how='left')


@functools.lru_cache()
def gene_id_from_symbol(gene_symbol):
    df = gene_info_from_symbol(gene_symbol)
    assert df.shape[0] == 1
    return df[['gene_id']].iloc[0].values[0]
```

1.2.2 Genotype and eQTL functions

[4]:
```
def letter_snp(number, a0, a1):
    '''
    Example:
    letter_snp(0, 'A', 'G') is 'AA'
    letter_snp(1, 'A', 'G') is 'AG'
    letter_snp(2, 'A', 'G') is 'GG'
    '''
    if np.isnan(number):
        return np.nan
    if len(a0)==1 and len(a1)==1:
        sep = ''
    else:
        sep = ' '
    return sep.join(sorted([a0]*int(number) + [a1]*(2-int(number))))


@functools.lru_cache()
def get_plink_tuple():
    '''
    Usage: (bim, fam, bed) = get_plink_tuple()
    '''
    return read_plink(config['plink_file_prefix'])


@functools.lru_cache()
def get_eFeature_df():
    eqtl_df = pd.read_csv(config["eqtl_output_file"], sep='\t')
    return eqtl_df[(eqtl_df["Type"] == feature_map(feature)) &
                   (eqtl_df["Tissue"] == tissue_map(tissue))]
```

```
@functools.lru_cache()
def get_gwas_snps():
    return pd.read_csv(config['gwas_snp_file'], sep='\t', index_col=0)


@functools.lru_cache()
def get_risk_allele(snp_id):
    gwas_snp = get_gwas_snp(snp_id)
    if gwas_snp['OR'].iloc[0] > 1:
        ra = gwas_snp['A1'].iloc[0]
    else:
        ra = gwas_snp['A2'].iloc[0]
    return ra


@functools.lru_cache()
def get_snp_df(snp_id):
    '''
    Returns a dataframe containing the genotype on snp snp_id.
    The allele count is the same as in the plink files.

    Example:
    get_snp_df('rs653953').head(5)

            rs653953_num rs653953_letter rs653953
    Br5168             0              GG    0\nGG
    Br2582             1              AG    1\nAG
    Br2378             1              AG    1\nAG
    Br5155             2              AA    2\nAA
    Br5182             2              AA    2\nAA
    '''
    (bim, fam, bed) = get_plink_tuple()
    brain_ids = list(set(get_expression_and_pheno_df().index).
↪intersection(set(fam['fid'])))
    snp_info = bim[bim['snp']==snp_id]
    snp_pos = snp_info.iloc[0]['i']
    fam_pos = list(fam.drop_duplicates(subset="fid").set_index('fid').
↪loc[brain_ids]['i'])
    dfsnp = (pd.DataFrame(bed[[snp_pos]].compute()[:,fam_pos],
                          columns=brain_ids, index=[snp_id + '_num'])
             .transpose().dropna())
    my_letter_snp = functools.partial(letter_snp, a0=snp_info.iloc[0]['a0'],␣
↪a1=snp_info.iloc[0]['a1'])
    dfsnp[[snp_id + '_num']] = 2 - dfsnp[[snp_id + '_num']].astype('int')
    dfsnp[snp_id + '_letter'] = dfsnp[snp_id + '_num'].apply(my_letter_snp)
    dfsnp[snp_id] = (dfsnp[snp_id + '_num'].astype('str') + '\n' +
                     dfsnp[snp_id + '_letter'].astype('str')).astype('category')
```

```
    return dfsnp


@functools.lru_cache()
def get_gwas_ordered_snp_df(snp_id):
    '''
    Returns a dataframe containing the genotype on snp snp_id.
    The allele count is the number of risk alleles according to GWAS.

    Example:
    get_gwas_ordered_snp_df('rs653953').head(5)

            rs653953_num rs653953_letter rs653953
    Br5168             2              GG    2\nGG
    Br2582             1              AG    1\nAG
    Br2378             1              AG    1\nAG
    Br5155             0              AA    0\nAA
    Br5182             0              AA    0\nAA
    '''
    pgc = get_gwas_snps()
    dfsnp = get_snp_df(snp_id).copy()
    gwas_snp = get_gwas_snp(snp_id)
    if gwas_snp['pgc2_a1_same_as_our_counted'].iloc[0]:
        if gwas_snp['OR'].iloc[0] > 1:
            pass
        else:
            dfsnp[[snp_id + '_num']] = 2 - dfsnp[[snp_id + '_num']]
    else:
        if gwas_snp['OR'].iloc[0] > 1:
            dfsnp[[snp_id + '_num']] = 2 - dfsnp[[snp_id + '_num']]
        else:
            pass
    dfsnp[snp_id] = (dfsnp[snp_id + '_num'].astype('str') + '\n' +
                     dfsnp[snp_id + '_letter'].astype('str')).astype('category')
    return dfsnp
```

1.2.3 Plotting functions

[5]:
```
def get_snp_gene_pheno_df(snp_id, gene_id, snp_df_func):
    pheno_columns = list(get_pheno_df().columns)
    expr_df = get_expression_and_pheno_df()[pheno_columns + [gene_id]]
    snp_df =  snp_df_func(snp_id)
    return expr_df.merge(snp_df, left_index=True, right_index=True)


def simple_snp_expression_plot_impl(snp_id, gene_id, snp_df_func):
    df = get_snp_gene_pheno_df(snp_id, gene_id, snp_df_func)
```

```
    y0 = df[gene_id].quantile(.01) - 0.26
    y1 = df[gene_id].quantile(.99) + 0.26
    p = ggplot(df, aes(x=snp_id, y=gene_id, fill='Sex')) \
    + geom_boxplot(alpha=0.4, outlier_alpha=0) \
    + geom_jitter(position=position_jitterdodge(jitter_width=0.25),
                  stroke=0, alpha=0.6) \
    + ylim(y0, y1) \
    + theme_bw(base_size=15) \
    + theme(panel_grid=element_blank(),
            axis_title=element_text(face="bold"))
    return p


def simple_snp_expression_plot(snp_id, gene_id):
    return simple_snp_expression_plot_impl(snp_id, gene_id, get_snp_df)


def simple_gwas_ordered_snp_expression_plot(snp_id, gene_id):
    return simple_snp_expression_plot_impl(snp_id, gene_id,␣
 ↪get_gwas_ordered_snp_df)


def get_gene_symbol(gene_id, biomart=get_biomart_df()):
    ensge = re.sub('\..+$','', gene_id)
    ggg = biomart[biomart['ensembl_gene_id']==ensge]
    if ggg.shape[0]==0:
        return '', ''
    gs = ggg['external_gene_name'].values[0]
    de = ggg['description'].values[0]
    if type(de)!=str:
        de = ''
    de = re.sub('\[Source:.*$','',de)
    return gs, de


def get_gwas_snp(snp_id):
    gwas = get_gwas_snps()
    r = gwas[gwas['our_snp_id']==snp_id]
    assert len(r) == 1
    return r


def gwas_annotation(snp_id):
    return 'SZ GWAS pvalue: %.1e' % get_gwas_snp(snp_id).iloc[0]['P']


def eqtl_annotation(snp_id, gene_id):
```

```
    eqtl_df = get_eFeature_df()
    r = eqtl_df[(eqtl_df['variant_id']==snp_id) & (eqtl_df['gene_id']==gene_id)]
    assert len(r)==1
    return 'eQTL adjusted p-value: %.1e' % r.iloc[0]['BF']


def risk_allele_annotation(snp_id):
    return 'SZ risk allele: %s' % get_risk_allele(snp_id)


def annotated_eqtl_plot(snp_id, gene_id):
    p = simple_snp_expression_plot(snp_id, gene_id)
    gene_symbol, gene_description = get_gene_symbol(gene_id)
    title ="\n".join([gene_symbol,
                      eqtl_annotation(snp_id, gene_id)
                      ])
    p += ggtitle(title) + ylab('Residualized Expression')
    return p


def gwas_annotated_eqtl_plot(snp_id, gene_id):
    p = simple_gwas_ordered_snp_expression_plot(snp_id, gene_id)
    gene_symbol, gene_description = get_gene_symbol(gene_id)
    title ="\n".join([gene_symbol,
                      eqtl_annotation(snp_id, gene_id),
                      gwas_annotation(snp_id),
                      risk_allele_annotation(snp_id)
                      ])
    p += ggtitle(title) + ylab('Residualized Expression')
    return p


def save_plot(p, fn):
    for ext in ['png', 'pdf', 'svg']:
        p.save(fn + '.' + ext)
```

1.3 Plot eQTLs

1.3.1 DRD2

[6]:
```
get_eFeature_df()[(get_eFeature_df()["gene_id"] == gene_id_from_symbol('DRD2'))]
```

[6]:
```
Empty DataFrame
Columns: [variant_id, gene_id, gencodeID, slope, statistic, pval_nominal, BF,
eigenMT_BH, TESTS, Type, Tissue]
Index: []
```

1.3.2 Top 5 eQTLs

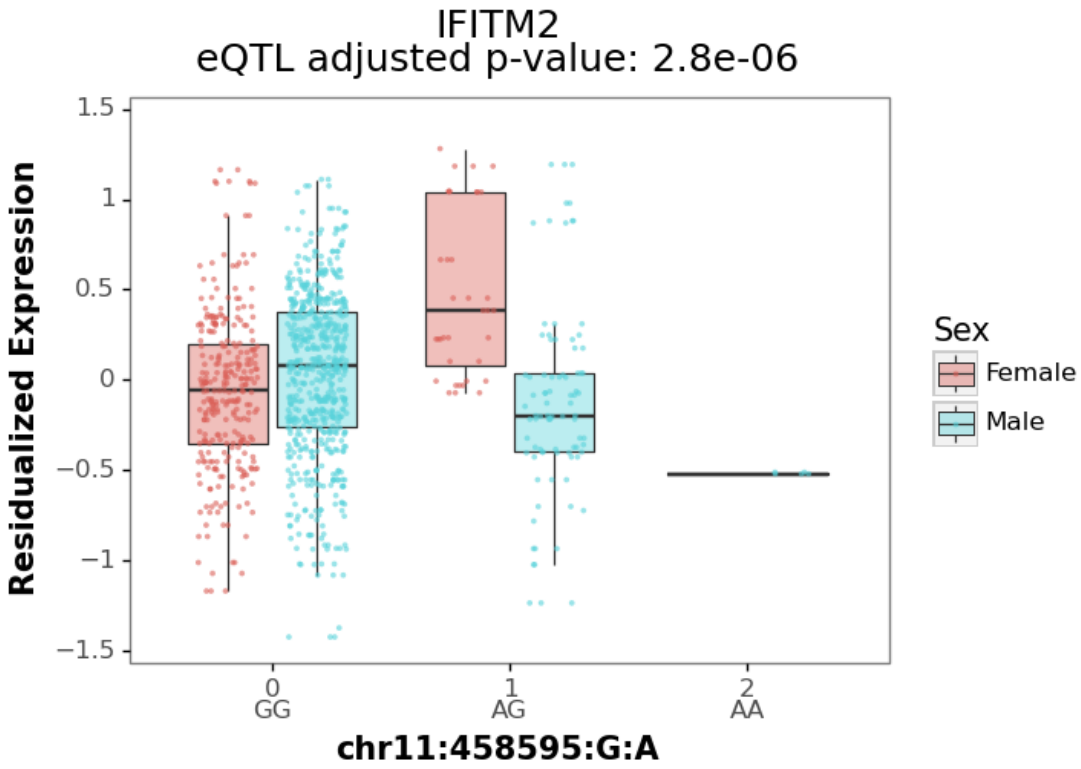
[7]:
```
eqtl_df = get_eFeature_df()
eqtl_df.head()
```

[7]:

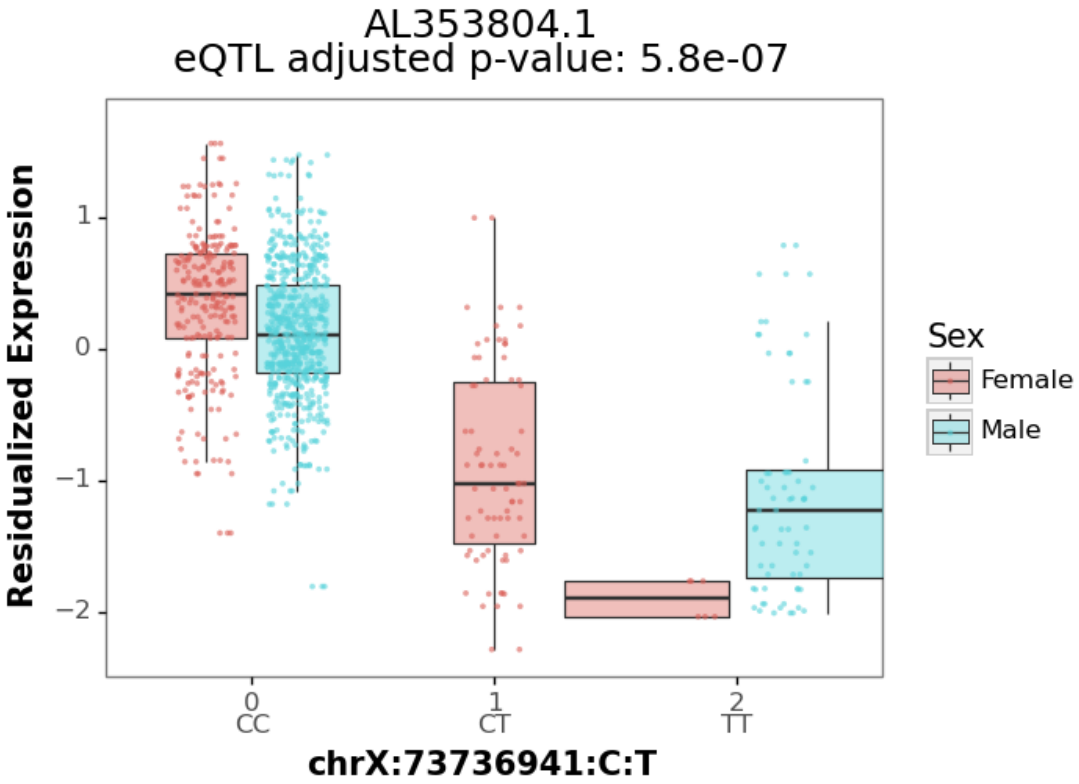
	variant_id	gene_id	gencodeID	slope	statistic	pval_nominal	BF	eigenMT_BH	TESTS	Type	Tissue
55266	chrX:100404152:G:A	ENSG00000000005.5	ENSG00000000005.5	0.497189	17.628291	0.000014	0.004420	0.478076	323	Gene	Hippocampus
55267	chr1:196610909:G:A	ENSG00000000971.15	ENSG00000000971.15	-0.476843	-11.561317	0.000013	0.001964	0.443931	151	Gene	Hippocampus
55268	chr1:24888756:T:C	ENSG00000001461.16	ENSG00000001461.16	-0.311761	-11.705099	0.000042	0.022525	0.634349	536	Gene	Hippocampus
55269	chr7:42749666:G:C	ENSG00000002746.14	ENSG00000002746.14	0.314297	5.959216	0.000077	0.033827	0.663881	440	Gene	Hippocampus
55270	chr17:38495906:AT:A	ENSG00000002834.17	ENSG00000002834.17	0.477555	11.402260	0.000025	0.015118	0.598413	608	Gene	Hippocampus

[8]:
```
top_5 = eqtl_df.sort_values('pval_nominal').reset_index(drop=True).head(5)
for x in top_5.itertuples():
    filename = "top_%d_eqtl_%s" % (x.Index, tissue)
    p = annotated_eqtl_plot(x.variant_id, x.gene_id)
    print(filename, x.Index, x.variant_id, x.gene_id)
    print(p)
    save_plot(p, filename)
```

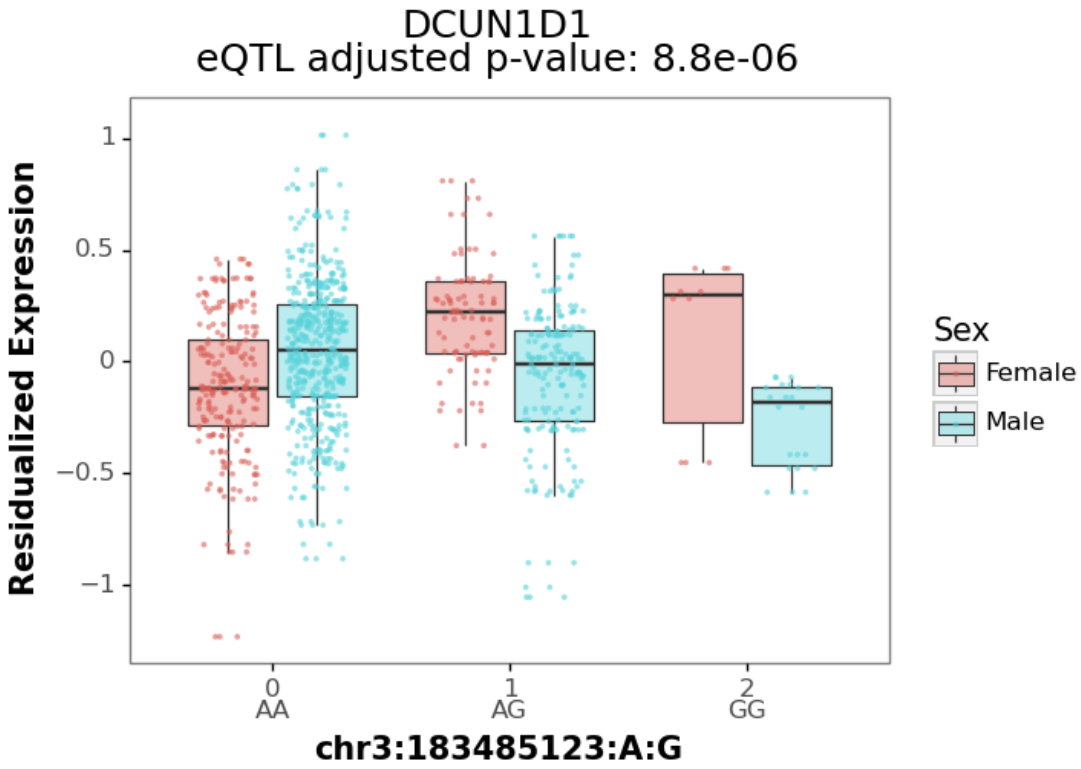
```
Mapping files: 100%|      | 3/3 [00:26<00:00,  8.72s/it]

top_0_eqtl_hippocampus 0 chr11:458595:G:A ENSG00000185201.16
```



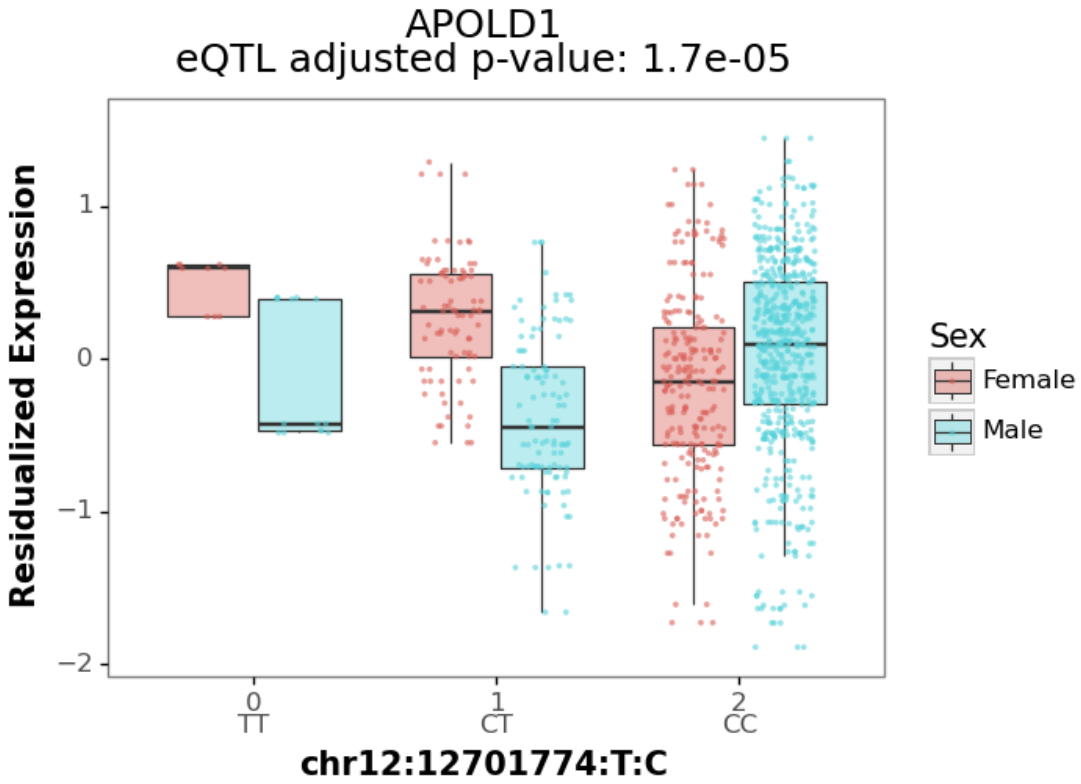

```
<ggplot: (8779724703820)>
top_1_eqtl_hippocampus 1 chrX:73736941:C:T ENSG00000228906.1
```



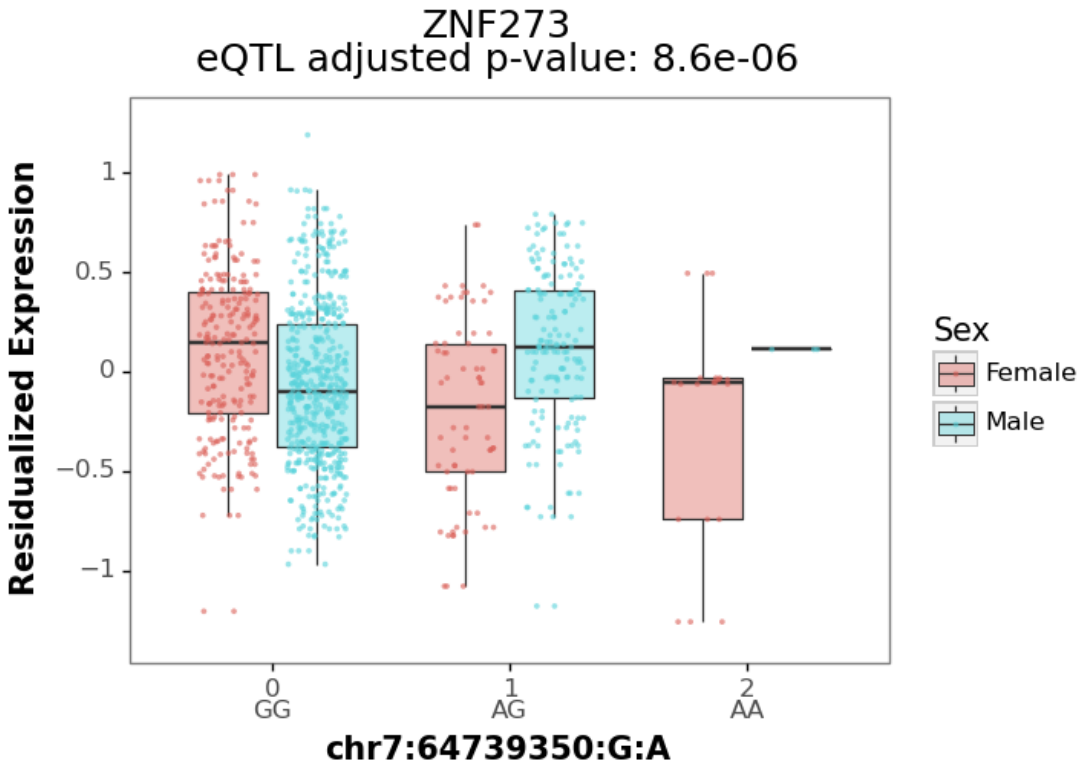

```
<ggplot: (8779724509281)>
top_2_eqtl_hippocampus 2 chr3:183485123:A:G ENSG00000043093.13
```




```
<ggplot: (8779724167918)>
top_3_eqtl_hippocampus 3 chr12:12701774:T:C ENSG00000178878.12
```




```
<ggplot: (8779723800450)>
top_4_eqtl_hippocampus 4 chr7:64739350:G:A ENSG00000198039.11
```

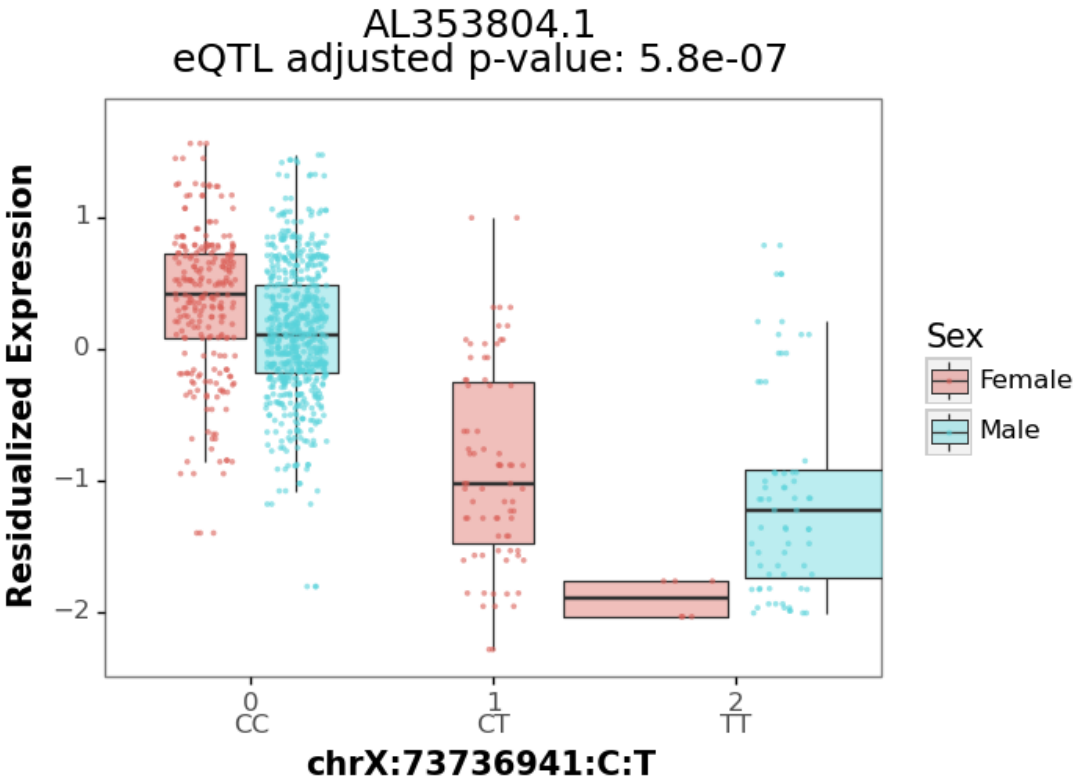


<ggplot: (8779723914810)>

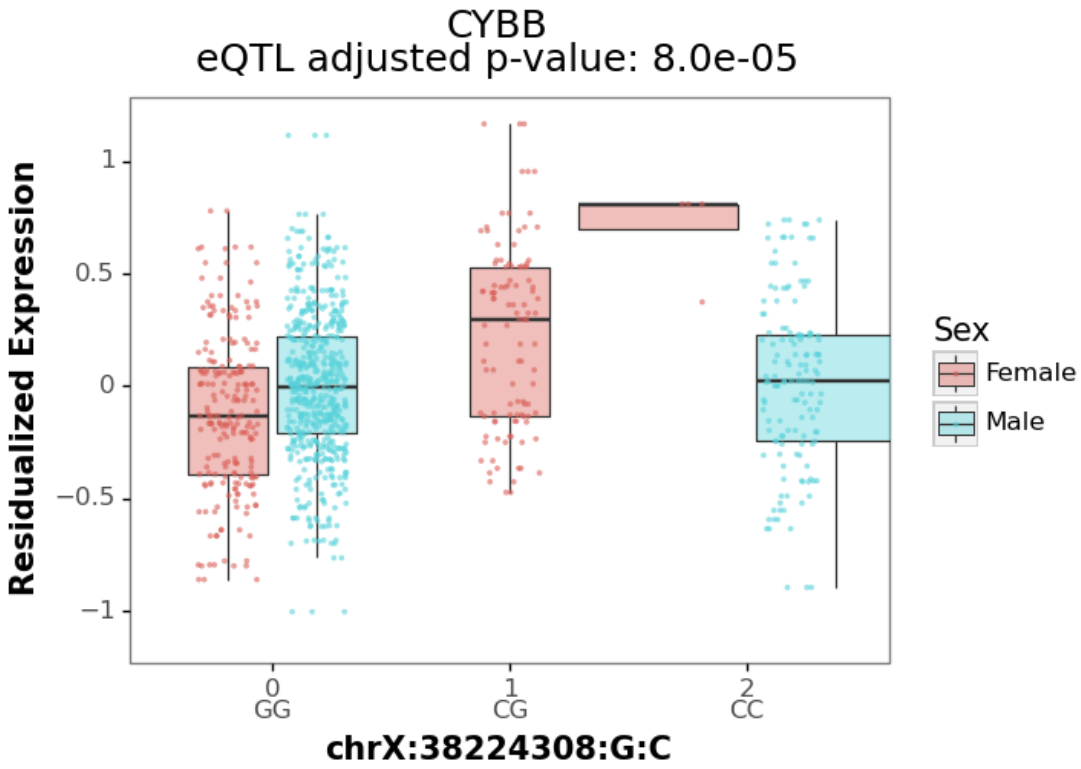
1.3.3 Top 5 X-linked genes

[9]:
```
top_5_x = eqtl_df[eqtl_df['variant_id'].str.contains("chrX")].
 ↪sort_values("pval_nominal").reset_index(drop=True).head(5)
for x  in top_5_x.itertuples():
    filename = "top_%d_eqtl_xlinked_%s" % (x.Index, tissue)
    p = annotated_eqtl_plot(x.variant_id, x.gene_id)
    print(filename, x.Index, x.variant_id, x.gene_id)
    print(p)
    save_plot(p, filename)
```

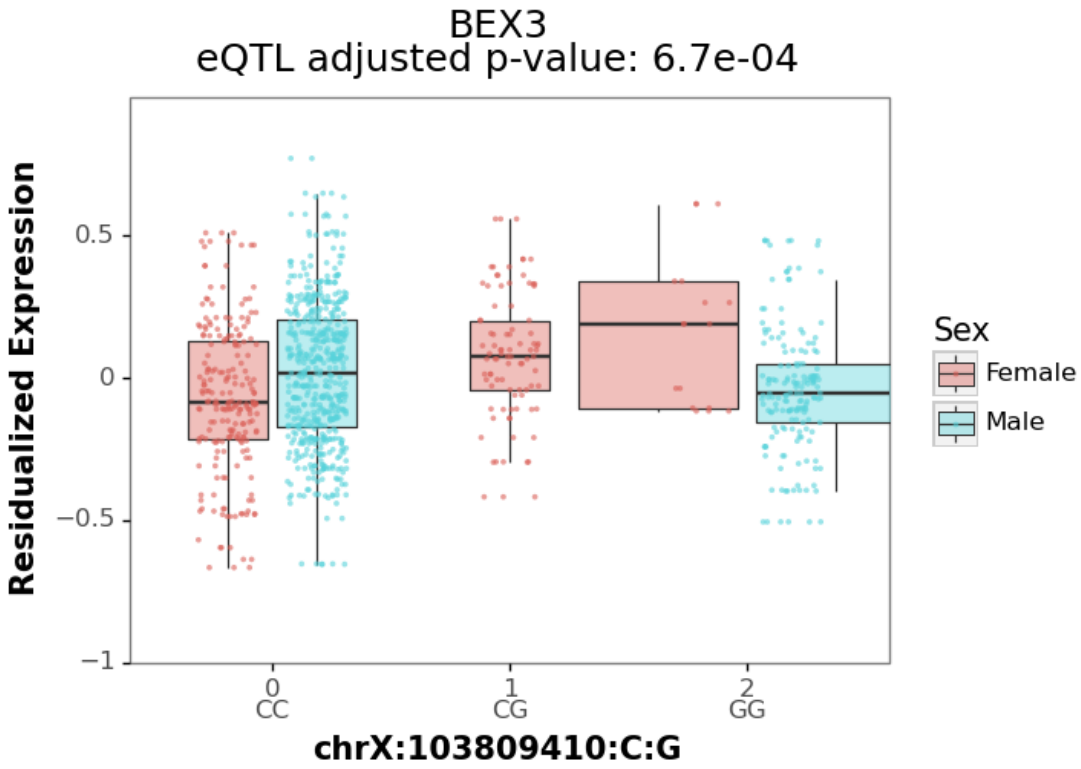
```
top_0_eqtl_xlinked_hippocampus 0 chrX:73736941:C:T ENSG00000228906.1
```



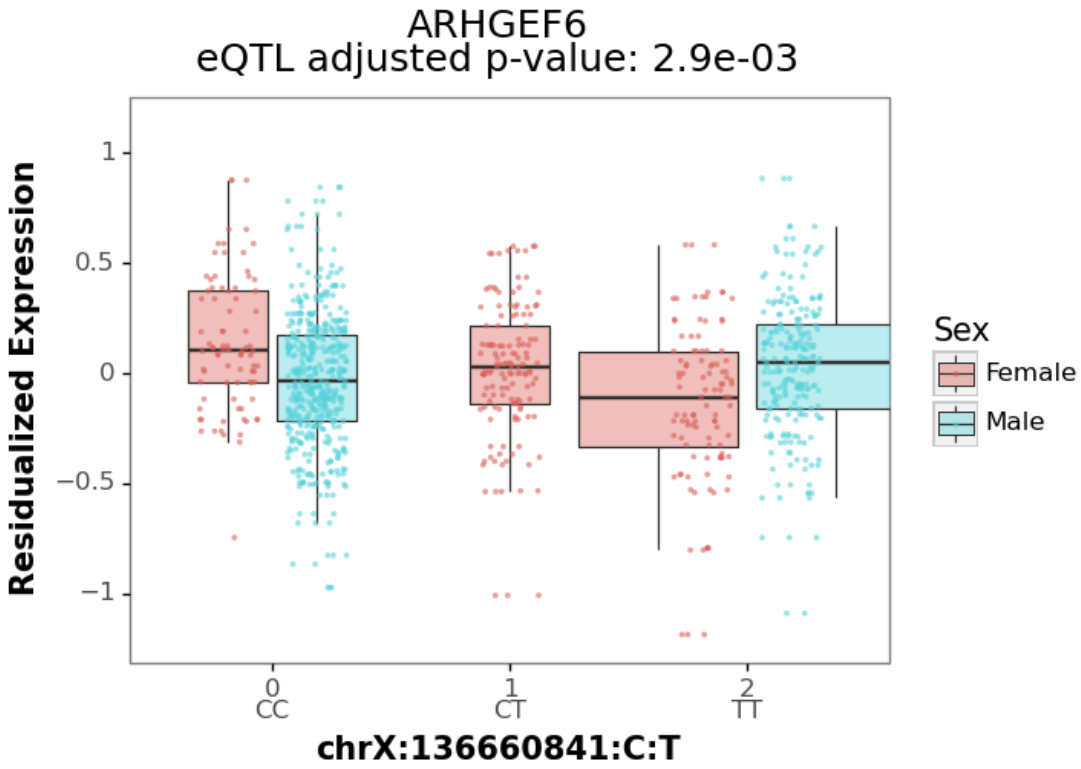

```
<ggplot: (8779849800602)>
top_1_eqtl_xlinked_hippocampus 1 chrX:38224308:G:C ENSG00000165168.7
```



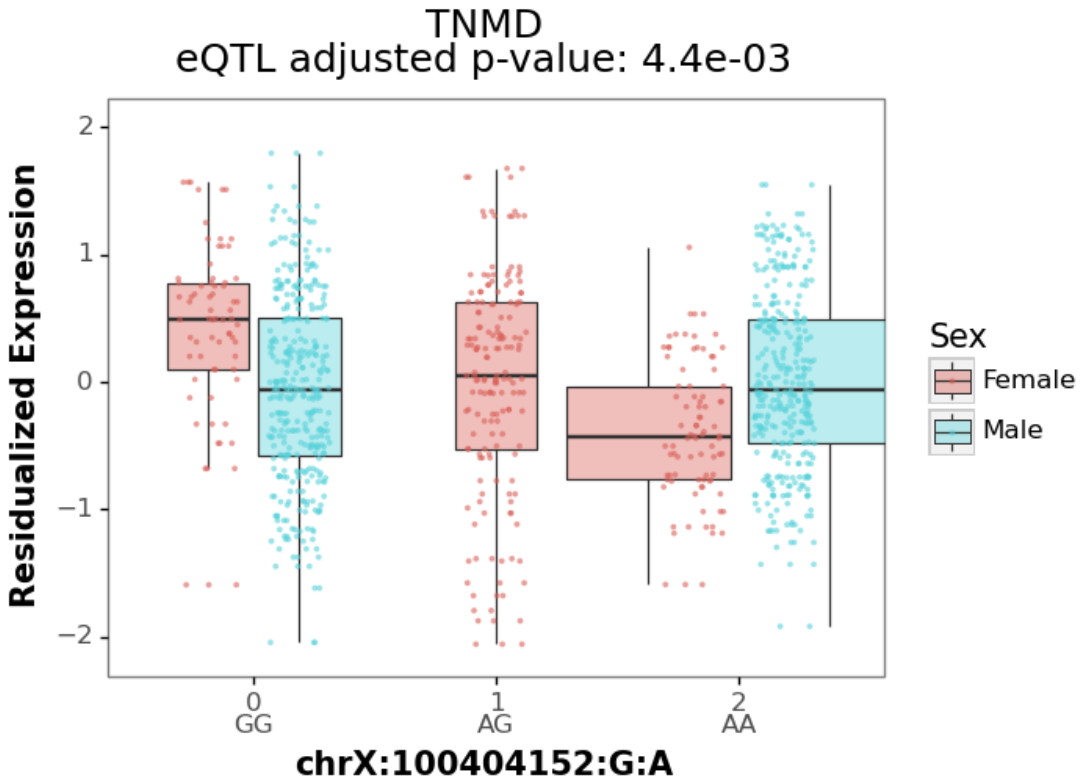

```
<ggplot: (8779723727951)>
top_2_eqtl_xlinked_hippocampus 2 chrX:103809410:C:G ENSG00000166681.13
```




```
<ggplot: (8779724630878)>
top_3_eqtl_xlinked_hippocampus 3 chrX:136660841:C:T ENSG00000129675.15
```




```
<ggplot: (8779724390310)>
top_4_eqtl_xlinked_hippocampus 4 chrX:100404152:G:A ENSG00000000005.5
```




```
<ggplot: (8779723814533)>
```

1.3.4 Top 5 eQTL with GWAS significant index SNP

[10]:
```
gwas_eqtl_df = eqtl_df.merge(get_gwas_snps(), left_on = 'variant_id',
                             right_on = 'our_snp_id', suffixes=['','_gwas'])
print(gwas_eqtl_df.shape)
gwas_eqtl_df.head()
```

```
(8, 33)
```

[10]:

	variant_id	gene_id	gencodeID	slope	\
0	chr6:28254038:A:G	ENSG00000182477.5	ENSG00000182477.5	-0.587888	
1	chr12:110405656:A:G	ENSG00000186298.11	ENSG00000186298.11	0.288399	
2	chr6:28800336:C:A	ENSG00000189298.13	ENSG00000189298.13	-0.706295	
3	chr6:32773079:A:C	ENSG00000196735.11	ENSG00000196735.11	-0.454907	
4	chr6:32719441:C:T	ENSG00000204231.10	ENSG00000204231.10	0.407413	

	statistic	pval_nominal	BF	eigenMT_BH	TESTS	Type	…	A2	\
0	-13.107428	0.000107	0.017435	0.615239	163	Gene	…	G	
1	9.113946	0.000173	0.033719	0.662886	195	Gene	…	G	
2	-12.810508	0.000069	0.013872	0.595893	200	Gene	…	A	

```
3 -14.436133      0.000049  0.038676    0.686868    794  Gene  …  C
4  13.634354      0.000014  0.009168    0.572569    672  Gene  …  T

        OR        SE             P  hg19chrc hg38chrc    hg38pos  \
0  0.86693  0.013949  1.350000e-24      chr6     chr6   28254038
1  1.06460  0.010544  2.960000e-09     chr12    chr12  110405656
2  1.17800  0.015035  1.220000e-27      chr6     chr6   28800336
3  1.07670  0.011079  2.590000e-11      chr6     chr6   32773079
4  1.11740  0.013233  4.780000e-17      chr6     chr6   32719441

  pgc2_a1_same_as_our_counted        rsid  is_index_snp
0                       False  rs10456362         False
1                       False  rs28813775         False
2                       False   rs7766107         False
3                       False   rs1480383         False
4                       False   rs9275680         False

[5 rows x 33 columns]
```

[11]:
```
top_gwas_eqtl_df = gwas_eqtl_df[(gwas_eqtl_df['is_index_snp'])].
↪sort_values(['BF', 'P'])
print(top_gwas_eqtl_df.shape)
top_gwas_eqtl_df.head()
```

```
(0, 33)
```

[11]:
```
Empty DataFrame
Columns: [variant_id, gene_id, gencodeID, slope, statistic, pval_nominal, BF,
eigenMT_BH, TESTS, Type, Tissue, chrN, our_snp_id, cm, pos, our_counted,
our_alt, chrom, SNP, Freq.A1, CHR, BP, A1, A2, OR, SE, P, hg19chrc, hg38chrc,
hg38pos, pgc2_a1_same_as_our_counted, rsid, is_index_snp]
Index: []

[0 rows x 33 columns]
```

[12]:
```
top_gwas_eqtl_df = gwas_eqtl_df.sort_values(['BF', 'P']).reset_index(drop=True)
print(top_gwas_eqtl_df.shape)
top_gwas_eqtl_df.head(10)
```

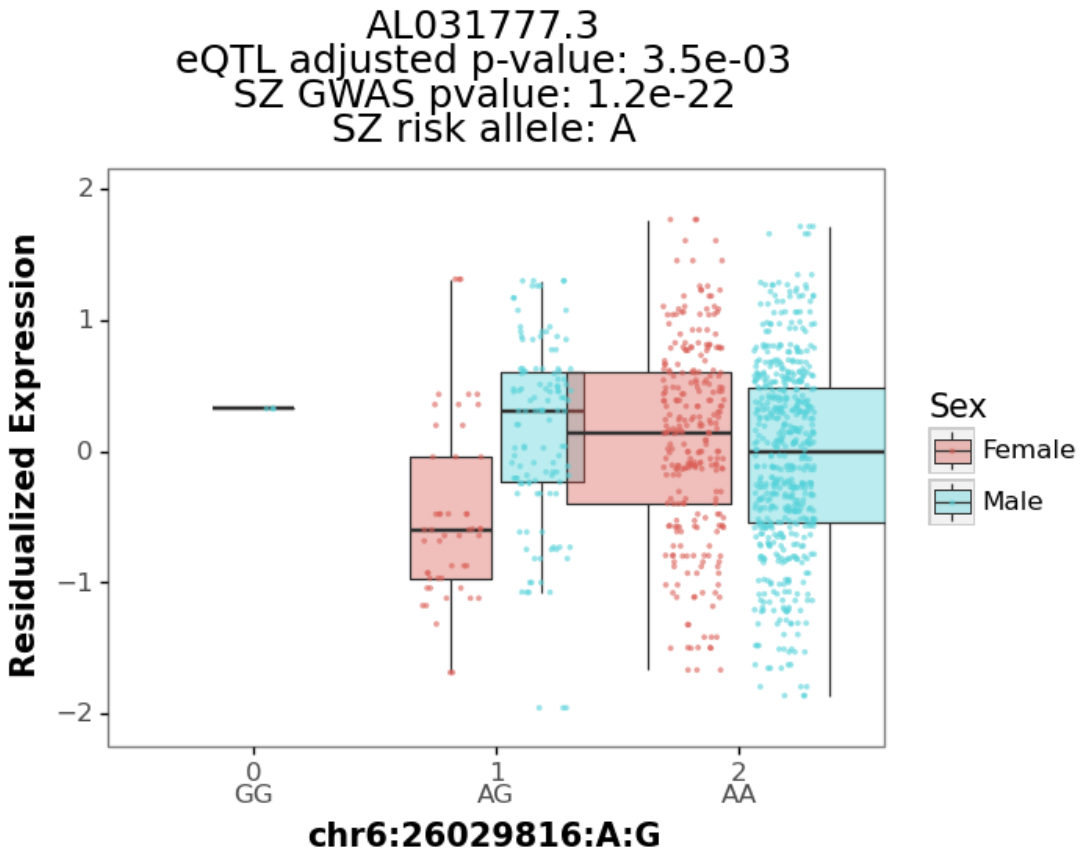
```
(8, 33)
```

[12]:
```
            variant_id             gene_id           gencodeID     slope  \
0    chr6:26029816:A:G   ENSG00000282988.1   ENSG00000282988.1  1.002980
1    chr6:32719441:C:T  ENSG00000204231.10  ENSG00000204231.10  0.407413
2    chr6:28800336:C:A  ENSG00000189298.13  ENSG00000189298.13 -0.706295
3    chr6:28254038:A:G   ENSG00000182477.5   ENSG00000182477.5 -0.587888
4    chr6:29404546:A:G   ENSG00000214922.9   ENSG00000214922.9 -0.815373
5    chr6:27096496:C:T   ENSG00000224843.6   ENSG00000224843.6  0.457570
```

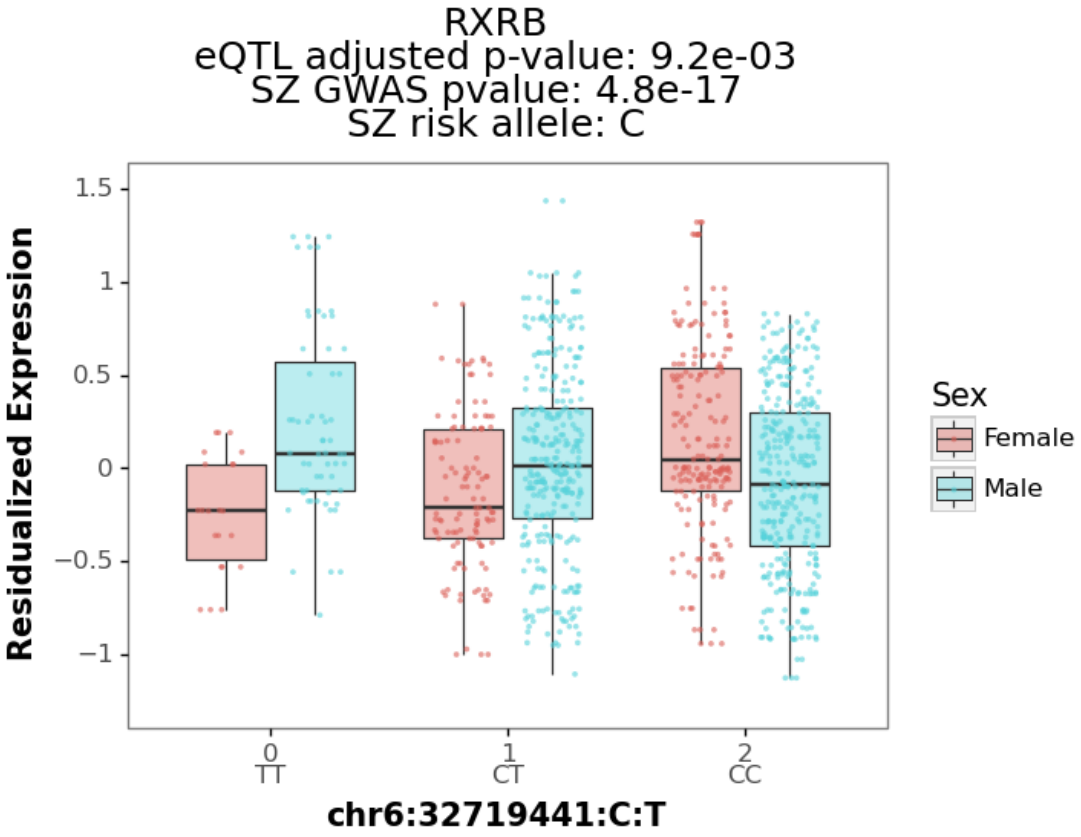
```
6  chr12:110405656:A:G  ENSG00000186298.11  ENSG00000186298.11  0.288399
7    chr6:32773079:A:C  ENSG00000196735.11  ENSG00000196735.11 -0.454907

   statistic  pval_nominal        BF  eigenMT_BH  TESTS  Type  … A2  \
0  12.397785      0.000014  0.003507    0.460288    257  Gene  …  G
1  13.634354      0.000014  0.009168    0.572569    672  Gene  …  T
2 -12.810508      0.000069  0.013872    0.595893    200  Gene  …  A
3 -13.107428      0.000107  0.017435    0.615239    163  Gene  …  G
4  -9.500715      0.000060  0.029938    0.658966    503  Gene  …  G
5  14.474000      0.000172  0.032596    0.662351    189  Gene  …  T
6   9.113946      0.000173  0.033719    0.662886    195  Gene  …  G
7 -14.436133      0.000049  0.038676    0.686868    794  Gene  …  C

        OR        SE             P  hg19chrc hg38chrc    hg38pos  \
0  1.17710  0.016649  1.200000e-22      chr6     chr6   26029816
1  1.11740  0.013233  4.780000e-17      chr6     chr6   32719441
2  1.17800  0.015035  1.220000e-27      chr6     chr6   28800336
3  0.86693  0.013949  1.350000e-24      chr6     chr6   28254038
4  1.24980  0.017875  1.000000e-35      chr6     chr6   29404546
5  1.11120  0.011646  1.430000e-19      chr6     chr6   27096496
6  1.06460  0.010544  2.960000e-09     chr12    chr12  110405656
7  1.07670  0.011079  2.590000e-11      chr6     chr6   32773079

  pgc2_a1_same_as_our_counted        rsid  is_index_snp
0                       False  rs28360595         False
1                       False   rs9275680         False
2                       False   rs7766107         False
3                       False  rs10456362         False
4                       False    rs429479         False
5                       False   rs9467989         False
6                       False  rs28813775         False
7                       False   rs1480383         False

[8 rows x 33 columns]
```

[13]:
```
top_5_gwas = top_gwas_eqtl_df.head(5)
for x  in top_5_gwas.itertuples():
    filename = "top_%d_eqtl_in_gwas_significant_snps_%s" % (x.Index, tissue)
    p = gwas_annotated_eqtl_plot(x.variant_id, x.gene_id)
    print(filename, x.Index, x.variant_id, x.gene_id)
    print(p)
    save_plot(p, filename)
```

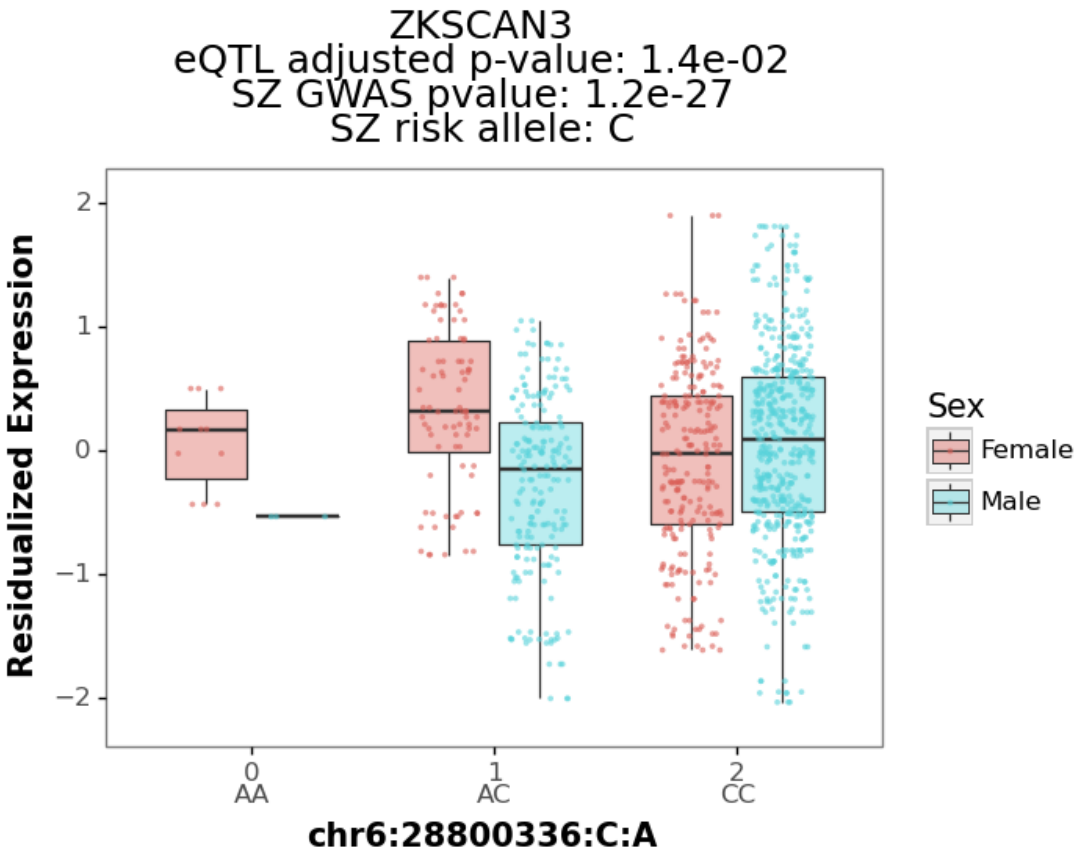
```
top_0_eqtl_in_gwas_significant_snps_hippocampus 0 chr6:26029816:A:G
ENSG00000282988.1
```



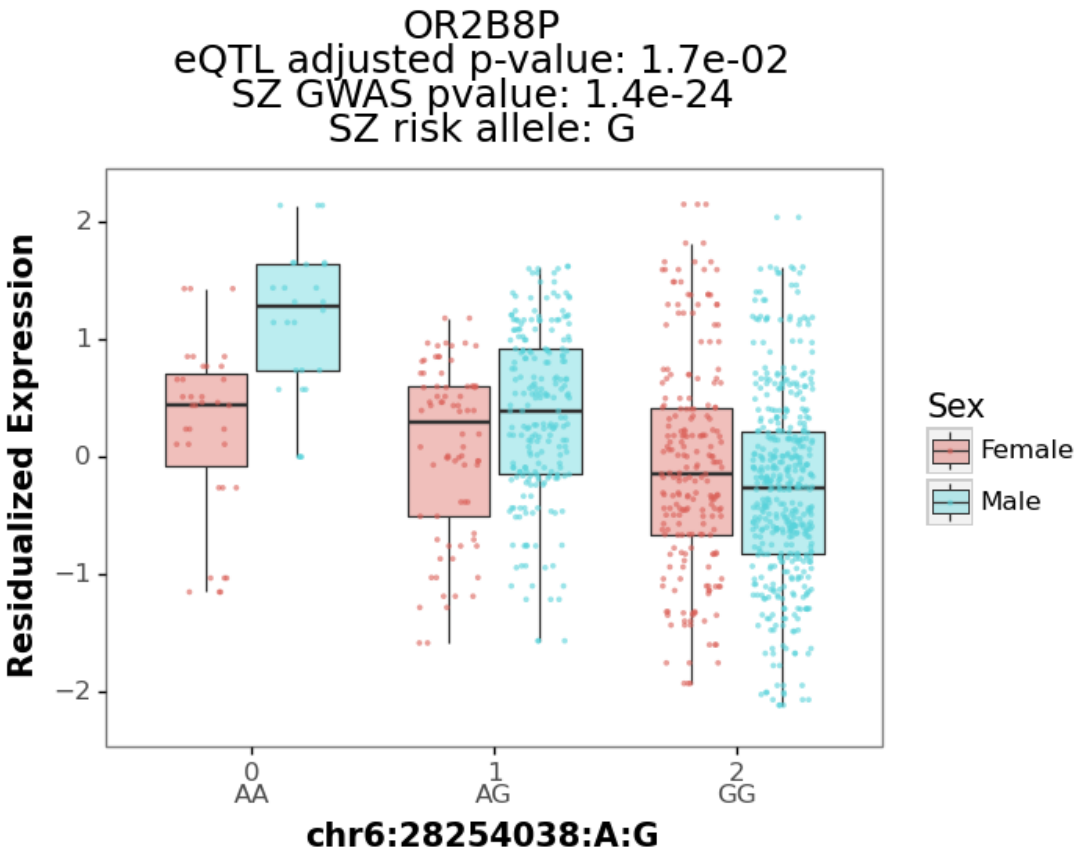

```
<ggplot: (8779722688901)>
top_1_eqtl_in_gwas_significant_snps_hippocampus 1 chr6:32719441:C:T
ENSG00000204231.10
```



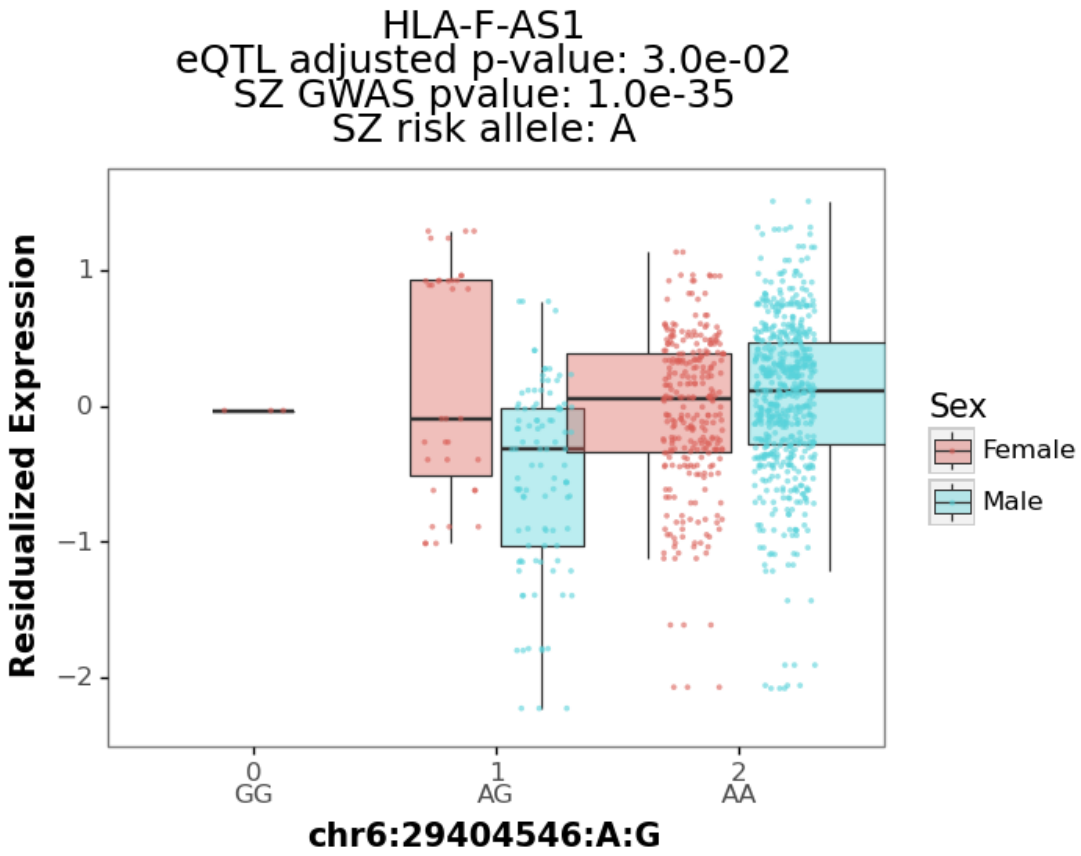

```
<ggplot: (8779723014166)>
top_2_eqtl_in_gwas_significant_snps_hippocampus 2 chr6:28800336:C:A
ENSG00000189298.13
```




```
<ggplot: (8779723004769)>
top_3_eqtl_in_gwas_significant_snps_hippocampus 3 chr6:28254038:A:G
ENSG00000182477.5
```




```
<ggplot: (8779723805260)>
top_4_eqtl_in_gwas_significant_snps_hippocampus 4 chr6:29404546:A:G
ENSG00000214922.9
```




```
<ggplot: (8779845294520)>
```

[ ]: