GSE90102 tutorial

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This vignette describes how to use the wBHa and other procedures on a GWAS dataset, and performs analysis of the results obtained. The files this script works with are pulled from the Gene Expression Omnibus (GEO) webpage and contain 659,636 SNPs and 98 individuals.

As a part of Quality Control (QC) measures, only SNPs located on the autosome chromosomes were kept (13,793 SNPs were omitted). Next, 20,983 SNPs with call rate less than 95% and samples with genotyping rates less than 95% were excluded from analysis. Then, 1,330 SNPs with Hardy-Weinberg equilibrium p-value less than 1×10^{-5} were eliminated. At last, 15,810 SNPs with minor allele frequency less than 0.10 were ejected. After all exclusion, 98 Japanese individuals including and 607,720 SNPs were analyzed for GWAS, in which we tested the association between the percentage of Paneth cell defect (quantitative phenotype) and genotype using a linear regression model. The p-values (GSE90102_01$rawp) and Minor Allele Frequencies (GSE90102_01$MAF) of the SNPs from this association test are available in the wBHa package (GSE90102_01).

Loading of used libraries

```
set.seed(123)
library(IHW)
library(qvalue)
library(swfdr)
library(FDRreg)
library(CAMT)
library(wBHa)
library(UpSetR)
library(venn)
library(RColorBrewer)
```

Application of procedures

```
data("GSE90102_01") # load the dataset from the wBHa package

# Initialization of parameters
alpha <- 0.05 # alpha significance level set at 5%
pvalues <- GSE90102_01$rawp # extraction of the p-values
covariates <- GSE90102_01$MAF # extraction of the covariates


# wBHa procedure
res_wBHa <- wBHa(pvalues, covariates, alpha) # use of the wBHa method
pval_wBHa <- res_wBHa$adjusted_pvalues # saving of adjusted p-values
rej_wBHa <- which(pval_wBHa<=alpha) # saving the rejected SNPs
```

```r
# BH procedure
pval_BH <- p.adjust(pvalues, method="BH")
rej_BH <- which(pval_BH<=alpha)

# IHW procedure
res_IHW <- ihw(pvalues~covariates, alpha=alpha)
pval_IHW <- adj_pvalues(res_IHW)
rej_IHW <- which(pval_IHW<alpha)

# wBH procedure
pval_wBH <- p.adjust(pvalues/((length(pvalues)/sum(1/covariates))*(1/covariates)),
                     method="BH")
rej_wBH <- which(pval_wBH<=alpha)

# Qvalue procedure
res_qvalue <- qvalue(pvalues)
pval_qvalue <- res_qvalue$qvalues
rej_qvalue <- which(pval_qvalue<alpha)

# Swfdr procedure
res_qvalue <- lm_qvalue(pvalues, covariates)
pval_swfdr <- res_qvalue$qvalue
rej_swfdr <- which(pval_swfdr<alpha)

# FDRreg procedure
pvalues[pvalues==1]<-(1-10^-7)
zscores <- qnorm(pvalues)
res_FDRreg <- FDRreg(zscores, as.matrix(covariates))
pval_FDRreg <- res_FDRreg$FDR
rej_FDRreg <- which(pval_FDRreg<alpha)

# CAMT procedure
res_CAMT <- camt.fdr(pvals=pvalues,pi0.var=covariates)
pval_CAMT <- res_CAMT$fdr
rej_CAMT <- which(c(pval_CAMT<alpha))

rej_list <- list(BH=rej_BH, wBH=rej_wBH, wBHa=rej_wBHa, IHW=rej_IHW,
                 qvalue=rej_qvalue, swfdr=rej_swfdr, FDRreg=rej_FDRreg,
                 CAMT=rej_CAMT) # list of rejected SNPs for each procedure
```

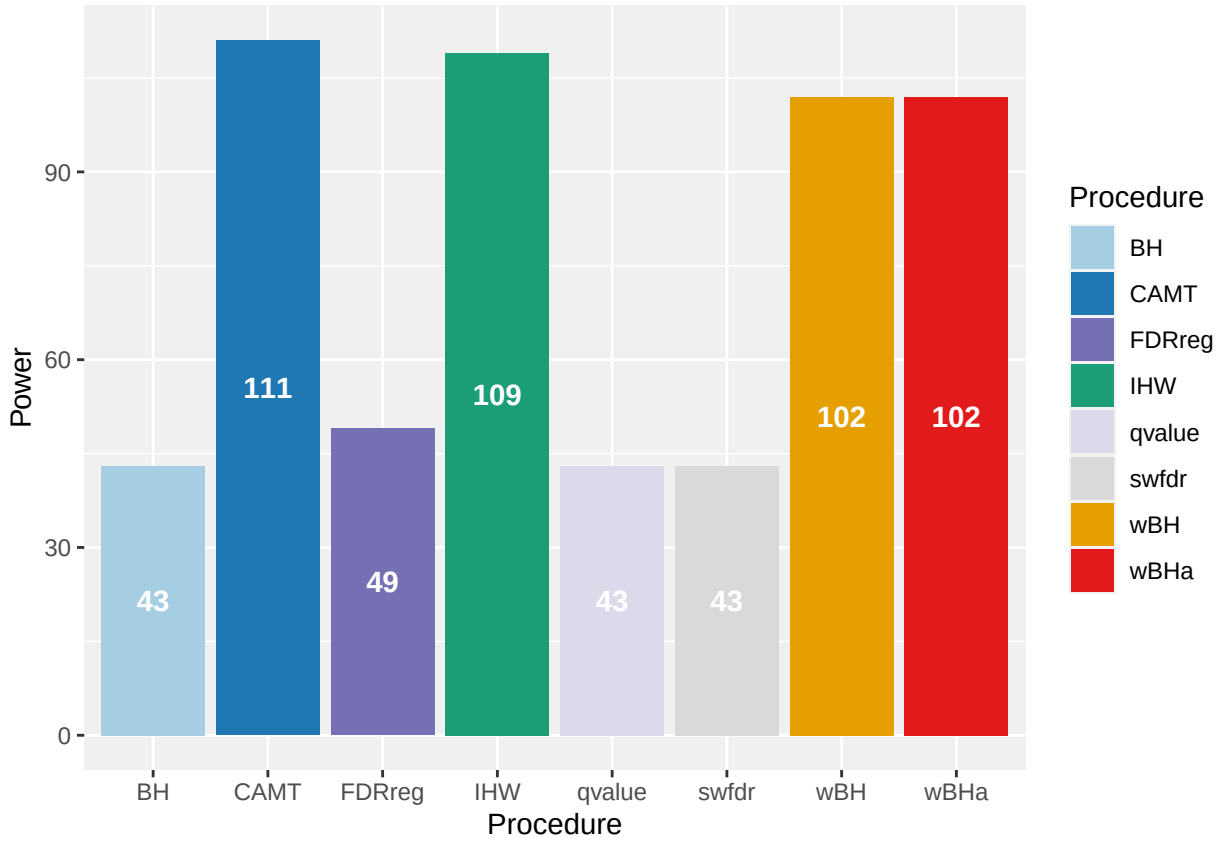
Graphs

Overall power

```r
rej_tab <- data.frame(Procedure=c("BH", "wBH", "wBHa", "IHW", "qvalue", "swfdr",
                                  "FDRreg", "CAMT"),
                      Power=unlist(lapply(rej_list, length)))

rej_histogram <- ggplot(data=rej_tab, aes(x=Procedure, y=Power, fill=Procedure)) +
  geom_bar(stat="identity") +
  scale_fill_manual(values=c("#A6CEE3","#1F78B4","#7570B3","#1B9E77","#DADAEB",
```

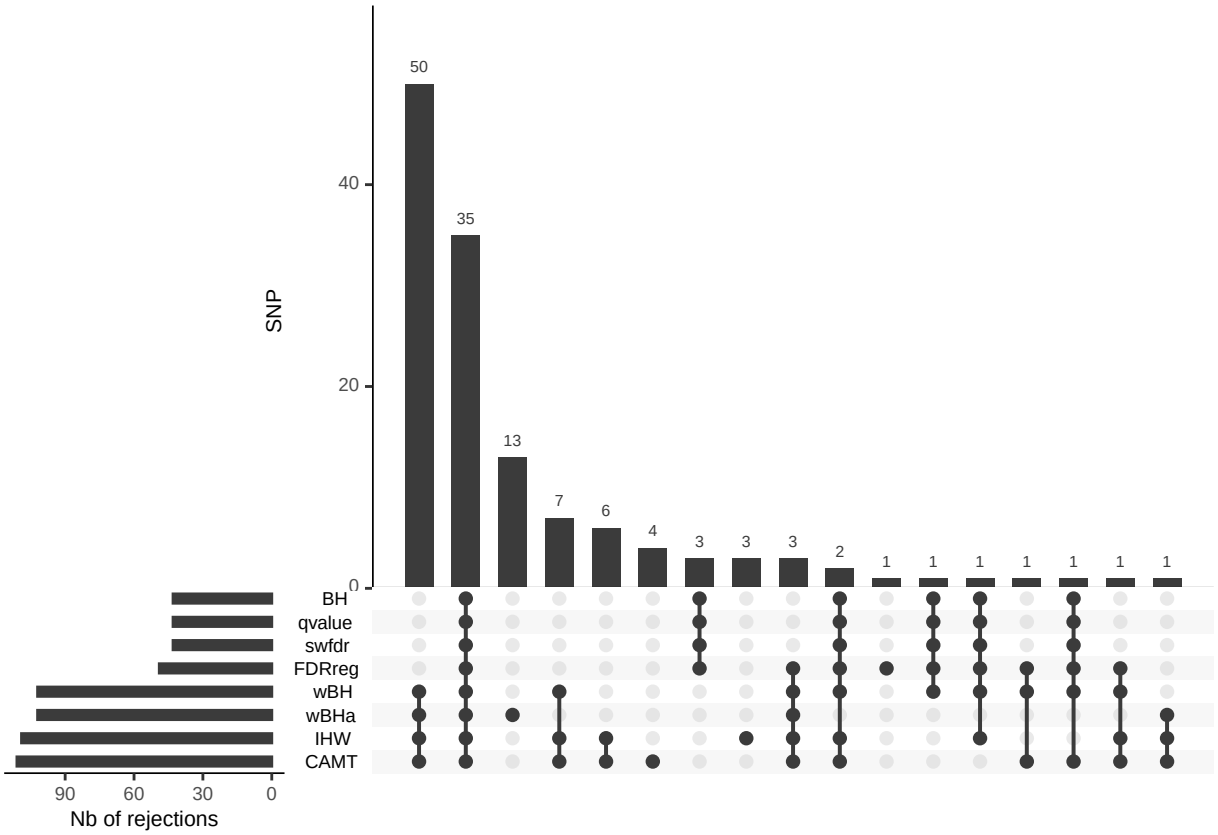
```
                                "#D9D9D9","#E69F00","#E31A1C")) +
  geom_text(aes(label=round(Power,digits=1)), position=position_stack(0.5),
            color="white", fontface=c("bold")) +
  theme(panel.background=element_rect(fill="#F0F0F0", colour="#F0F0F0",
                                      size=0.5, linetype="solid"),
        panel.grid.major=element_line(size=0.5, linetype="solid",
                                      colour="white"),
        panel.grid.minor=element_line(size=0.25, linetype="solid",
                                      colour="white"))
rej_histogram
```

Histogram of rejects




```
UpsetR_graph <- upset(fromList(rej_list), order.by="freq", mainbar.y.label="SNP",
                      sets.x.label="Nb of rejections", nsets=8)
UpsetR_graph
```

UpsetR graph



We note that BH, qvalue and swfdr procedures reject the same variants : reduction of the number of procedure. We also notice that the BH, qvalue and swfdr procedures reject the same variants ⇒ reduction of the number of procedures. Moreover, we note that the FDRreg procedure rejects a similar number of markers as the BH, qvalue and swfdr procedures.

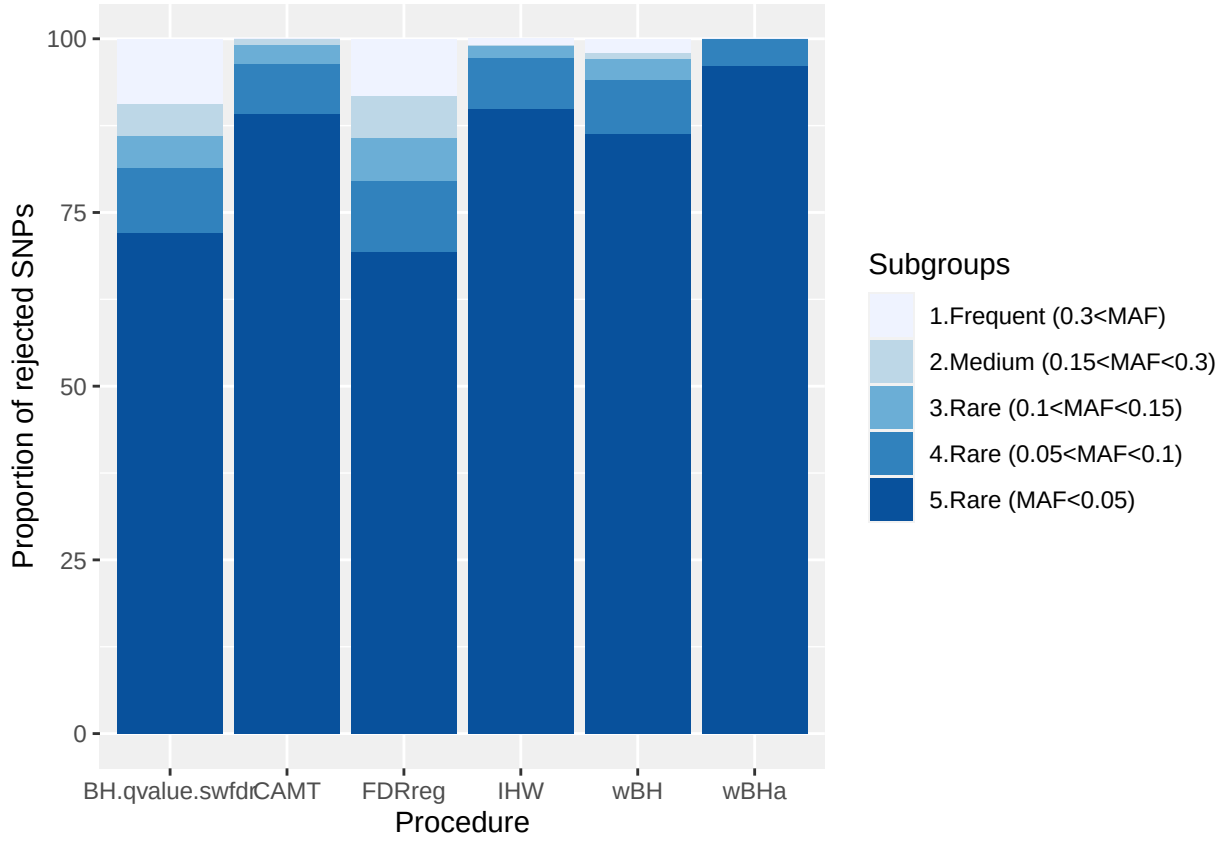
```
# reduction of the number of groups: 8 to 6
rej_list$qvalue==rej_list$BH
rej_list$swfdr==rej_list$BH
rej_list2 <- list(BH.qvalue.swfdr=rej_BH, wBH=rej_wBH, wBHa=rej_wBHa, IHW=rej_IHW,
                  FDRreg=rej_FDRreg, CAMT=rej_CAMT)
```

Power of (causal) subgroups

```
calc_proportion_subgroup <- function(rej_vect){
  # Allows to compute the proportion of causal SNPs in each subgroup
  rares1 <- length(which((covariates[rej_vect]<0.05)==T))
  rares2 <- length(which((covariates[rej_vect]<0.10)==T))-(rares1)
  rares3 <- length(which((covariates[rej_vect]<0.15)==T))-(rares1+rares2)
  frequents <- length(which((covariates[rej_vect]>0.30)==T))
  medium <- length(rej_vect)-(rares1+rares2+rares3+frequents)
  nb<-c(rares1,rares2,rares3,medium,frequents)
  prop <- (nb/length(rej_vect))*100
  return(prop)
}

prop_subgroup_tab <- as.data.frame(cbind(c(rep("BH.qvalue.swfdr",5), rep("wBH",5),
                                           rep("wBHa",5), rep("IHW",5),
```

```
                                        rep("FDRreg",5), rep("CAMT",5)),
                                      c("5.Rare (MAF<0.05)",
                                        "4.Rare (0.05<MAF<0.1)",
                                        "3.Rare (0.1<MAF<0.15)",
                                        "2.Medium (0.15<MAF<0.3)",
                                        "1.Frequent (0.3<MAF)"),
                                      unlist(lapply(rej_list2,
                                                    calc_proportion_subgroup))))
colnames(prop_subgroup_tab) <- c("Procedure", "Subgroups", "Proportion")
prop_subgroup_tab$Proportion <- as.numeric(prop_subgroup_tab$Proportion)

subgroup_hist <- ggplot(data=prop_subgroup_tab, aes(x=Procedure, y=Proportion,
                                                    fill=Subgroups)) +
  geom_bar(stat="identity") +
  scale_fill_brewer(palette="Blues") +
  labs(y="Proportion of rejected SNPs") +
  theme(panel.background=element_rect(fill="#F0F0F0", colour="#F0F0F0",
                                      size=0.5, linetype="solid"),
        panel.grid.major=element_line(size=0.5, linetype="solid",
                                      colour="white"),
        panel.grid.minor=element_line(size=0.25, linetype="solid",
                                      colour="white"))

subgroup_hist
```

Histogram of rejects



We can note that wBHa focuses on rare markers (less than 5%). However, although this is also the case for the other weighted procedures combining the two types of approaches, these are less powerful for rare variants than wBHa.

Relationship to annotations SNPs found in the article present in our data and their respective coordinates:

- rs12494894 : 565881
- rs72622838 : 325191
- rs2238823 : 561177

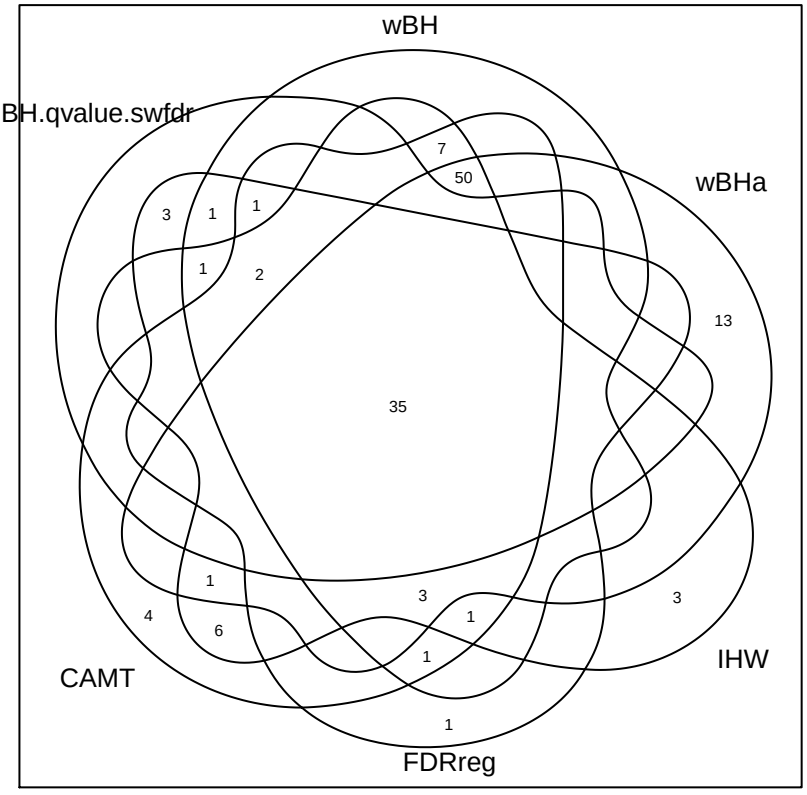
```
search_rank <- function(pval_vect,alpha=0.05){
  # Allows to search the rank of the 3 SNPs present in our data for a given procedure
  pval_rank_tab <- data.frame(rank=c(1:length(pval_vect)), pvalues=pval_vect)
  pval_rank_tab_order <- pval_rank_tab[order(pval_rank_tab$pvalues),]
  pval_rank_tab_order <- cbind(pval_rank_tab_order, c(1:length(pval_vect)))
  pval_rank_tab_order_interest <- pval_rank_tab_order[c("565881","325191","561177"),]
  pval_rank_tab_order_interest <- data.frame(SNP=c("rs12494894","rs72622838","rs2238823"),
                                             Rank=pval_rank_tab_order_interest[,3],
                                             Threshold=length(which((pval_vect<alpha))))
  return(pval_rank_tab_order_interest)
}

lapply(list(BH=pval_BH,CAMT=pval_CAMT,FDRreg=pval_FDRreg,IHW=pval_IHW,qvalue=pval_qvalue,
            swfdr=pval_swfdr, wBH=pval_wBH,wBHa=pval_wBHa), search_rank)
```

```
## $BH
##          SNP Rank Threshold
## 1 rs12494894   36        43
## 2 rs72622838   40        43
## 3  rs2238823   44        43
##
## $CAMT
##          SNP Rank Threshold
## 1 rs12494894   73       111
## 2 rs72622838  712       111
## 3  rs2238823  103       111
##
## $FDRreg
##          SNP Rank Threshold
## 1 rs12494894   36        49
## 2 rs72622838   41        49
## 3  rs2238823   43        49
##
## $IHW
##          SNP Rank Threshold
## 1 rs12494894   92       109
## 2 rs72622838  426       109
## 3  rs2238823  147       109
##
## $qvalue
##          SNP Rank Threshold
## 1 rs12494894   36        43
## 2 rs72622838   40        43
## 3  rs2238823   44        43
```

```
##
## $swfdr
##          SNP Rank Threshold
## 1 rs12494894   36        43
## 2 rs72622838   40        43
## 3  rs2238823   44        43
##
## $wBH
##          SNP Rank Threshold
## 1 rs12494894   66       102
## 2 rs72622838  117       102
## 3  rs2238823   96       102
##
## $wBHa
##          SNP Rank Threshold
## 1 rs12494894  175       102
## 2 rs72622838  721       102
## 3  rs2238823  284       102
```

Venn diagram

```
venn_diagram <- venn(rej_list2)
```



This diagram shows that a large number of the rejected SNPs by the wBHa procedure are specific to it.