Introduction to the gact R package

From integrative genomics to polygenic risk scoring

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https://pdrohde.github.io/

Section 1

Setting up *gact* the first time

Install *gact*

Install gact from our GitHub (https://psoerensen.github.io/gact/)

```
# Prepare gact
# only do once!
  library(gact)

  GAlist <- gact(version="hsa.0.0.1", dbdir="../gact", task="download")

# Download 1000G reference data
  GAlist <- downloadDB(GAlist=GAlist, what="1000G")

  saveRDS(GAlist, file=".../gact/hsa.0.0.1/GAlist_hsa.0.0.1.rds")
```


```
> names(GAlist)
 [1] "version"     "dbdir"       "dirs"        "features"    "markerfiles"
 [6] "rsids"       "cpra"        "gsetsfiles"  "gseafiles"   "study"
[11] "studies"     "studyfiles"  "gwasfiles"   "gsets"       "targets"
[16] "drug2atc"    "atc"
```

Included annotations

```
List of 10
 $ ENSG00000223972: chr [1:18] "rs575272151" "rs544419019" "rs540538026" "rs62635286" ...
 $ ENSG00000227232: chr [1:19] "rs575272151" "rs544419019" "rs540538026" "rs62635286" ...
 $ ENSG00000243485: chr [1:19] "rs575272151" "rs544419019" "rs540538026" "rs62635286" ...
 $ ENSG00000237613: chr [1:19] "rs575272151" "rs544419019" "rs540538026" "rs62635286" ...
 $ ENSG00000268020: chr [1:29] "rs564023708" "rs533090414" "rs806731" "rs542415070" ...
 $ ENSG00000186092: chr [1:35] "rs542415070" "rs559500163" "rs528344458" "rs551668143" ...
 $ ENSG00000241670: chr [1:6] "rs201347561" "rs144169752" "rs112455420" "rs141415251" ...
 $ ENSG00000237094: chr [1:3] "rs576317820" "rs541569731" "rs182870673"
 $ ENSG00000235249: chr [1:2] "rs541569731" "rs182870673"
 $ ENSG00000185097: chr [1:8] "rs561532399" "rs113167131" "rs111824286" "rs369953380" ...

List of 10
 $ R-HSA-1059683: chr [1:141] "ENSG00000096968" "ENSG00000096968" "ENSG00000105397" "ENSG00000105397" ...
 $ R-HSA-109704 : chr [1:249] "ENSG00000033327" "ENSG00000051382" "ENSG00000066468" "ENSG00000068078" ...
 $ R-HSA-110056 : chr [1:74] "ENSG00000096968" "ENSG00000102882" "ENSG00000105397" "ENSG00000134352" ...
 $ R-HSA-110312 : chr [1:108] "ENSG00000009413" "ENSG00000035928" "ENSG00000049541" "ENSG00000106399" ...
 $ R-HSA-110314 : chr [1:190] "ENSG00000035928" "ENSG00000049541" "ENSG00000062822" "ENSG00000070950" ...
 $ R-HSA-110320 : chr [1:125] "ENSG00000010072" "ENSG00000035928" "ENSG00000049541" "ENSG00000070010" ...
 $ R-HSA-110328 : chr [1:303] "ENSG00000065057" "ENSG00000076248" "ENSG00000092330" "ENSG00000102977" ...
 $ R-HSA-110329 : chr [1:303] "ENSG00000065057" "ENSG00000076248" "ENSG00000092330" "ENSG00000102977" ...
 $ R-HSA-110330 : chr [1:497] "ENSG00000092330" "ENSG00000092330" "ENSG00000102977" "ENSG00000102977" ...
 $ R-HSA-110331 : chr [1:497] "ENSG00000092330" "ENSG00000092330" "ENSG00000102977" "ENSG00000102977" ...
```

Ingest GWAS summary data

```
GAlist <- updateStatDB(GAlist = GAlist,
                       stat = stat,                 # R-object
                       source = "...",              # markers file name
                       trait = "...",               # name of trait
                       type = "...",                # quantitative or binary
                       gender = "...",              # male, female, or both
                       ancestry = "...",            # ancestry
                       build = "...",               # genome build, GRCh37 or GRCh38
                       reference = "...",           # PMID
                       n = NA,                      # total sample size
                       ncase = NA,                  # if binary, how many cases
                       ncontrol = NA,               # if binary, how many controls
                       comments = "..."             # comments
                       )
```

Ingest GWAS summary data, example

```
# Load GWAS data
  fname_stat <- "./Mahajan.NatGenet2018b.T2D-noUKBB.European.zip"
  stat <- fread(fname_stat, data.table = FALSE)

# Modify columns according to required format
  stat <- stat[, c("SNP", "Chr", "Pos", "EA", "NEA", "Beta", "SE", "Pvalue")]
  colnames(stat) <- c("marker", "chr", "pos", "ea", "nea", "b", "seb", "p")

# Update database
  GAlist <- updateStatDB(GAlist = GAlist,
                         stat = stat,
                         source = "Mahajan.NatGenet2018b.T2D-noUKBB.European.zip",
                         trait = "T2D",
                         type = "binary",
                         gender = "both",
                         ancestry = "EUR",
                         build = "GRCh37",
                         reference = "PMID:30297969",
                         n = 456236,
                         ncase = 55927,
                         ncontrol = 400309,
                         comments = "Exclude UK biobank",
                         writeStatDB = TRUE)

# Save updated database
  saveRDS(GAlist, file = "./gact/hsa.0.0.1/GAlist_hsa.0.0.1.rds", compress = FALSE)
```

Collecting information and performing QC

```
Collecting information on external summary statistics
Perform quality control of external summary statistics
Map markers based on cpra
Number of markers in stat mapped to marker ids in GAlist: 9060453
Number of markers in stat not mapped to marker ids in GAlist: 12448245
Number of markers in stat also found in bimfiles: 9060453

Number of effect alleles aligned with first allele in bimfiles: 5056308
Number of effect alleles not aligned with first allele in bimfiles: 4004145

Number of markers excluded by large difference between MAF difference: 621

Writing processed summary statistics to internal file: GWAS1.txt
```

gstat

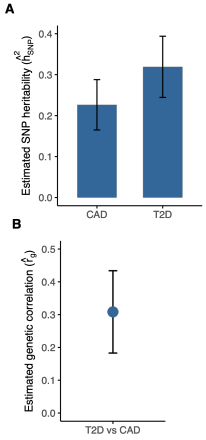
id	file	trait	type	gender	n	ncase	ncontrol	neff	reference	source	ancestry	build	comments
GWAS1	GWAS1.txt	T2DM	binary	both	456236	55927	400309	49071.27329	PMID:30297969	Mahajan.NatGenet2018b.T2D-noUKBB.Eur	EUR	GRCh37	Exclude UK biobank
GWAS2	GWAS2.txt	CAD	binary	both	184305	60801	123504	40743.1524	PMID:26343387	CARDIoGRAMplusC4D.txt.gz	EUR	GRCh37	Exclude UK biobank
GWAS3	GWAS3.txt	T2DM	binary	both	933970	80154	853816	73275.12411	PMID:35551307	DIAMANTE-EUR.sumstat.txt.gz	EUR	GRCh37	Include UK biobank
GWAS4	GWAS4.txt	T2DM	binary	males	425662	41846	383816	37732.20146	PMID:30297969	Mahajan.NatGenet2018b.T2D.MALE.Europ	EUR	GRCh37	Include UK biobank

Section 2

Example analyses

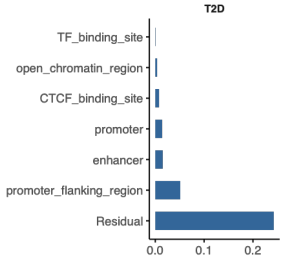
Estimating genetic parameters - 1

```r
# Load GAlist
  GAlist <- readRDS(file="./gact/hsa.0.0.1/GAlist_hsa.0.0.1.rds")

# Select GWAS study IDs
  studyIDs <- c("GWAS1","GWAS2")

# Get GWAS summary statistics for studyIDs (e.g. z and n) from gact database
  stat <- getMarkerStat(GAlist=GAlist, studyID=studyIDs)

# Get ldscores matched to the ancestry of GWAS data
  ldscores <- getLDscoresDB(GAlist=GAlist, ancestry="EUR", version="1000G")

# Estimate heritability and genetic correlation using using ldsc
  fit.h2 <- ldsc(z=stat$z, n=stat$n, ldscores=ldscores, what="h2", SE.h2=T)
  fit.rg <- ldsc(z=stat$z, n=stat$n, ldscores=ldscores, what="rg", SE.rg=T)
```



Estimating genetic parameters - 2

```r
# Partitioned h2 across regulatory categories
  sets <- getMarkerSets(GAlist=GAlist, feature="Regulatory Categories")
  fit <- ldsc(z=stat$z, n=stat$n, ldscores=ldscores, sets=sets, what="h2",
              method="bayesC", residual=TRUE)
```



Gene-level association (VEGAS)

```
# Load Glist with information on 1000G matched to the ancestry of GWAS data
  GAlist <- readRDS(file="./hsa.0.0.1/GAlist_hsa.0.0.1.rds")
  Glist <- readRDS(file.path(GAlist$dirs["marker"],"Glist_1000G_eur_filtered.rds"))

# Extract gene-marker sets (include markers 40kb/10kb upstream/downstream)
  markerSets <- getMarkerSets(GAlist = GAlist, feature = "Genesplus")

# Select study1
  studyID <- "GWAS1"

# Get GWAS summary statistics from gact database
  stat <- getMarkerStat(GAlist=GAlist, studyID=studyID)

# Check and align summary statistics based on marker information in Glist
  stat <- checkStat(Glist=Glist, stat=stat)

# Gene analysis using VEGAS
  res <- vegas(Glist=Glist, sets=markerSets, stat=stat, verbose=TRUE)
```

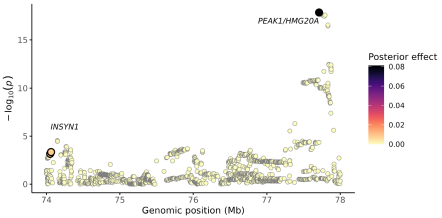
```
EnsemblID        Chr  m    X2          z         p
ENSG00000237491   1  26 12.16659 -0.6649650 0.7375987
ENSG00000177757   1  33 12.92801 -0.6622818 0.7355755
ENSG00000225880   1  37 13.57057 -0.6788080 0.7480649
ENSG00000230368   1  50 22.41127 -0.7223630 0.7812910
```

Gene-set enrichment analysis (MAGMA)

```
# Get gene sets
  sets <- getFeatureSets(GAlist = GAlist, feature="Pathways", minsets=25)

# Get VEGAS results
  z <- getVEGAS(GAlist,studyID="GWAS1")

# Run standard MAGMA
  fitST.m <- magma(stat=z, sets=sets, method="marginal")
  fitST.j <- magma(stat=z, sets=sets, method="joint")

# Run Bayesian MAGMA
  fitST.b <- magma(stat=z, sets=sets, method="bayesC", pi=0.01, nit=10000, nburn=1000)

# Run Bayesian multi-trait MAGMA
  z <- getVEGAS(GAlist,studyID=c("GWAS1","GWAS2")
  fitMT.b <- magma(stat=z, sets=sets, method="bayesC", pi=0.01, nit=10000, nburn=1000)
```

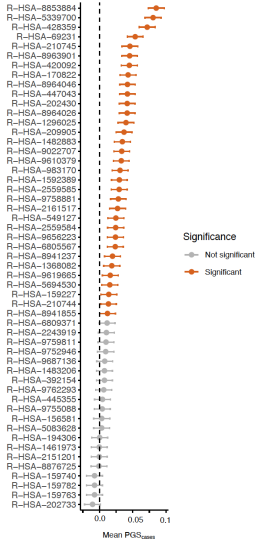
Statistical Fine Mapping

```
res <- vector(22,mode="list")

for(CHR in 1:22){
  ldscores <- Glist$ldscores[[CHR]]
  ldscores <- ldscores[names(ldscores) %in% stat$rsids]
  sets <- createLDsets(ldscores=ldscores,
                       maxsize=3000, msize=100, verbose=TRUE)

  fit <- gmap(Glist=Glist, stat=stat, sets=sets,
              method="bayesR", algorithm="mcmc-eigen",
              nit=10000, nburn=1000, cs_threshold=0.5, cs_r2=0.5,
             eigen_threshold=c(0.99, 0.97,0.95,0.9), verbose=TRUE)
res[[CHR]] <- fit
}
```



Polygenic scoring

```
# Finemap based on 1kG
  stat <- readRDS("./finemap_gwas1.rds")

# Load Glist for UKB
  Glist <- readRDS("./Glist_eur_ukb.rds")

# Match GWAS effects with allele effects in UKB
  stat <- checkStat(Glist=Glist, stat=stat,
                    excludeMAF=0.05,
                    excludeMAFDIFF=0.05,
                    excludeINFO=0.8,
                    excludeCGAT=TRUE,
                    excludeINDEL=TRUE,
                    excludeDUPS=TRUE,
                    excludeMHC=FALSE,
                    excludeMISS=0.05,
                    excludeHWE=1e-12)

# Compute PGS
  pgs <- gscore(Glist=Glist, stat=stat)

# Pathway-specific scores
  sets <- getMarkerSets(GAlist = GAlist, feature="Pathways")
  pgs.pathway <- gscore(Glist=Glist, stat=stat,sets=sets)
```



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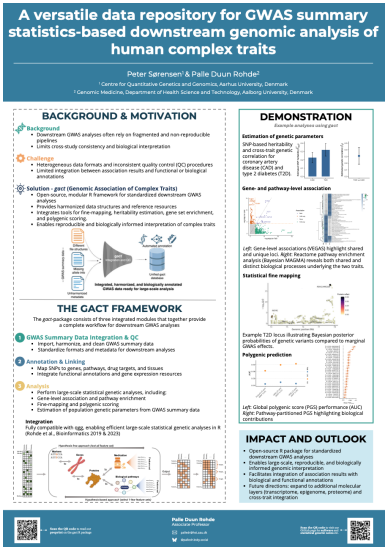

Section 3

Discussion - jigsaw

Initiating the discussion