

# *gwascat*: structuring and querying the NHGRI GWAS catalog

VJ Carey\*

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# 1 Introduction

NHGRI maintains and routinely updates a database of selected genome-wide association studies. This document describes R/Bioconductor facilities for working with contents of this database.

## 1.1 Installation

The package can be installed using Bioconductor's *BiocInstaller* package, with the sequence

```
library(BiocInstaller)
biocLite("gwascat")
```

## 1.2 Attachment and access to documentation

Once the package has been installed, use `library(gwascat)` to obtain interactive access to all the facilities. After executing this command, use `help(package="gwascat")` to obtain an overview. The current version of this vignette can always be accessed at [www.bioconductor.org](http://www.bioconductor.org), or by suitably navigating the web pages generated with `help.start()`.

Some noteworthy limitations: As of 2012.09.22, there are 243 records in the database for which no SNP is identified. NA chromosomal position of the associated locus is given.

## 1.3 Illustrations: computing

Available functions are:

```
> library(gwascat)
> objects("package:gwascat")

[1] "chklocs"           "elementMetadata"  "getRsids"
[4] "getTraits"         "gwcex2gviz"       "locs4trait"
[7] "makeCurrentGwascat" "obo2graphNEL"     "ranges"
[10] "riskyAlleleCount"  "subsetByChromosome" "subsetByTraits"
[13] "topTraits"         "traitsManh"
```

The GRanges instance with all SNP-disease associations is:

```
> gwrngs
```

gwasloc instance with 8723 records and 35 attributes per record.

Extracted: 2012.09.22

Excerpt:

GRanges with 5 ranges and 3 metadata columns:

```

      seqnames          ranges strand |          Disease.Trait
      <Rle>            <IRanges> <Rle> |          <factor>
[1]   chr4 [116196306, 116196306]   * |          Resistin levels
[2]   chr1 [ 75235317,  75235317]   * |          Resistin levels
[3]   chr1 [ 57243454,  57243454]   * |          Resistin levels
[4]  chr19 [ 7734511,   7734511]   * |          Resistin levels
[5]  chr17 [ 13062795,  13062795]   * | Cannbis use (initiation)
      SNPs  p.Value
      <factor> <numeric>
[1] rs13144478    6e-18
[2] rs3931020    6e-12
[3] rs17372114    5e-07
[4] rs3745367    3e-06
[5] rs9900808    2e-06

```

---

seqlengths:

```

      chr1      chr2      chr3      chr4 ...      chr21      chr22      chrX
249250621 243199373 198022430 191154276 ... 48129895 51304566 155270560

```

To determine the most frequently occurring traits:

```
> topTraits(gwrngs)
```

```

      Height          Type 2 diabetes          Crohn's disease
      304                    176                    138
Coronary heart disease          Multiple sclerosis          HDL cholesterol
      135                    129                    118
      Bipolar disorder          Body mass index          Ulcerative colitis
      109                    109                    106
      LDL cholesterol
      102

```

For a given trait, obtain a GRanges with all recorded associations; here only three associations are shown:

```
> subsetByTraits(gwrngs, tr="LDL cholesterol")[1:3]
```

gwasloc instance with 3 records and 35 attributes per record.

Extracted: 2012.09.22

Excerpt:

GRanges with 3 ranges and 3 metadata columns:

```

      seqnames          ranges strand |          Disease.Trait          SNPs
      <Rle>            <IRanges> <Rle> |          <factor> <factor>
[1]   chr2 [20903015, 20903015]   * | LDL cholesterol rs4971516

```

```

[2] chr2 [20903015, 20903015] * | LDL cholesterol rs4971516
[3] chr8 [ 9185146,  9185146] * | LDL cholesterol rs2126259
      p.Value
      <numeric>
[1] 2e-40
[2] 2e-52
[3] 7e-12
---
seqlengths:
      chr1      chr2      chr3      chr4 ...      chr21      chr22      chrX
249250621 243199373 198022430 191154276 ... 48129895 51304566 155270560

```

## 2 Some visualizations

### 2.1 Basic Manhattan plot

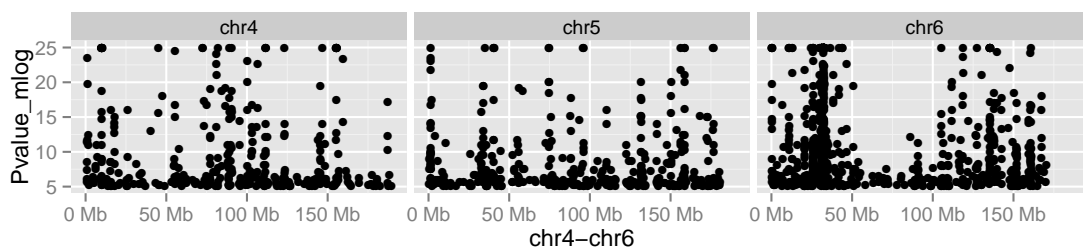
A basic Manhattan plot is easily constructed with the `ggbio` package facilities. Here we confine attention to chromosomes 4:6. First, we create a version of the catalog with  $-\log_{10}p$  truncated at a maximum value of 25.

```

> gwtrunc = gwrngs
> mlpv = values(gwrngs)$Pvalue_mlog
> mlpv = ifelse(mlpv > 25, 25, mlpv)
> values(gwtrunc)$Pvalue_mlog = mlpv
> gwlit = gwtrunc[ which(seqnames(gwtrunc) %in% c("chr4", "chr5", "chr6")) ]
> library(ggbio)
> mlpv = values(gwlit)$Pvalue_mlog
> mlpv = ifelse(mlpv > 25, 25, mlpv)
> values(gwlit)$Pvalue_mlog = mlpv

> methods:::bind_activation(FALSE)
> autoplot(gwlit, geom="point", aes(y=Pvalue_mlog), xlab="chr4-chr6")

```



## 2.2 Annotated Manhattan plot

A simple call permits visualization of GWAS results for a small number of traits. Note the defaults in this call.

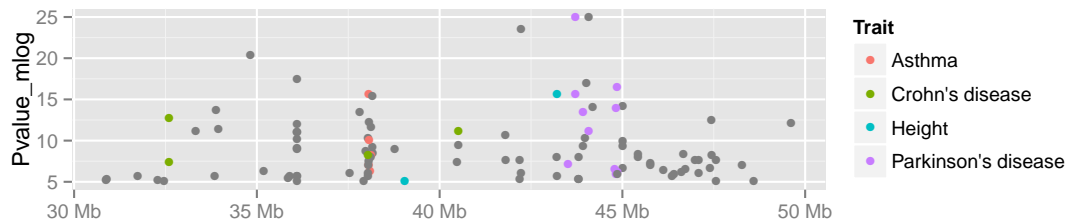
```
> args(traitsManh)
```

```
function (gwr, selr = GRanges(seqnames = "chr17", IRanges(3e+07,
  5e+07)), traits = c("Asthma", "Parkinson's disease", "Height",
  "Crohn's disease"), truncmlp = 25, ...)
```

```
NULL
```

```
> traitsManh(gwtrunc)
```

```
Object of class "ggbio"
```



## 2.3 Integrative view of potential genetic determinants

The following chunk uses GFF3 data on eQTL and related phenomena distributed at the GBrowse instance at [eqtl.uchicago.edu](http://eqtl.uchicago.edu). A request for all information at 43-45 Mb was made on 2 June 2012, yielding the GFF3 referenced below. Of interest are locations and scores of genetic associations with DNaseI hypersensitivity (scores identifying dsQTL, see Degner et al 2012).

```
> gffpath = system.file("gff3/chr17_43000000_45000000.gff3", package="gwascat")
> library(rtracklayer)
> c17t = import(gffpath)
> c17tg = as(c17t, "GRanges")
```

We make a Gviz DataTrack of the dsQTL scores.

```
> c17td = c17tg[ which(values(c17tg)$type == "Degner_dsQTL") ]
> library(Gviz)
> dsqs = DataTrack( c17td, chrom="chr17", genome="hg19", data="score",
+   name="dsQTL")
```

We start the construction of the graph here.

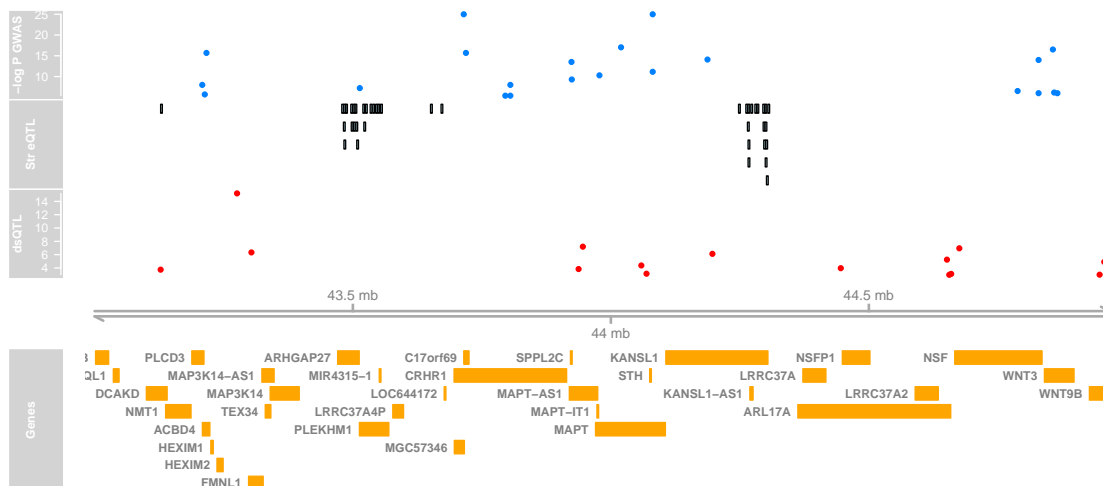
```
> g2 = GRanges(seqnames="chr17", IRanges(start=4.3e7, width=2e6))
> basic = gwcx2gviz(contextGR=g2, plot.it=FALSE)
```

We also collect locations of eQTL in the Stranger 2007 multipopulation eQTL study.

```
> c17ts = c17tg[ which(values(c17tg)$type == "Stranger_eqtl" ) ]
> eqloc = AnnotationTrack(ranges(c17ts), chrom="chr17", genome="hg19", name="Str eQT
> displayPars(eqloc)$col = "black"
> displayPars(dsqs)$col = "red"
> integ = list(basic[[1]], eqloc, dsqs, basic[[2]], basic[[3]])
```

Now use Gviz.

```
> plotTracks(integ)
```



### 3 SNP sets and trait sets

#### 3.1 SNPs by name

We can regard the content of a SNP chip as a set of SNP, referenced by name. The `pd.genomewidesnp.6` package describes the Affymetrix SNP 6.0 chip. We can determine which traits are associated with loci interrogated by the chip as follows. We work with a subset of the 1 million loci for illustration.

The `locon6` data frame has information on 10000 probes, acquired through the following code (not executed here to reduce dependence on the `pd.genomewidesnp.6` package, which is very large).

```
> library(pd.genomewidesnp.6)
> con = pd.genomewidesnp.6@getdb()
> locon6 = dbGetQuery(con,
+   "select dbsnp_rs_id, chrom, physical_pos from featureSet limit 10000")
```

Instead use the serialized information:

```
> data(locon6)
> rson6 = as.character(locon6[[1]])
> rson6[1:5]

[1] "rs2887286" "rs1496555" "rs41477744" "rs3890745" "rs10492936"
```

We subset the GWAS ranges structure with rsids that are common to both the chip and the GWAS catalog. We then tabulate the diseases associated with the common loci.

```
> intr = gwrngs[ intersect(getRsids(gwrngs), rson6) ]
> sort(table(getTraits(intr)), decreasing=TRUE)[1:10]
```

```
          Select biomarker traits
          3
          Height
          2
Immune reponse to smallpox (secreted IFN-alpha)
          2
          Metabolic traits
          2
          Schizophrenia
          2
          Ulcerative colitis
          2
Age-related macular degeneration (CNV vs. GA)
          1
          Aging traits
          1
          Alcohol dependence
          1
          Alzheimer's disease
          1
```

### 3.2 Traits by genomic location

We will assemble genomic coordinates for SNP on the Affymetrix 6.0 chip and show the effects of identifying the trait-associated loci with regions of width 1000bp instead of 1bp.

The following code retrieves coordinates for SNP interrogated on 10000 probes (to save time) on the 6.0 chip, and stores the results in a GRanges instance.

```

> gr6.0 = GRanges(seqnames=ifelse(is.na(locon6$chrom),0,locon6$chrom),
+               IRanges(ifelse(is.na(locon6$phys),1,locon6$phys), width=1))
> elementMetadata(gr6.0)$rsid = as.character(locon6$db SNP_rs_id)
> seqlevels(gr6.0) = paste("chr", seqlevels(gr6.0), sep="")

```

Here we compute overlaps with both the raw disease-associated locus addresses, and with the locus address  $\pm 500$ bp.

```

> ag = function(x) as(x, "GRanges")
> ovraw = suppressWarnings(subsetByOverlaps(ag(gwrngs), gr6.0))
> length(ovraw)

[1] 63

> ovaug = suppressWarnings(subsetByOverlaps(ag(gwrngs+500), gr6.0))
> length(ovaug)

[1] 90

```

To acquire the subset of the catalog to which 6.0 probes are within 500bp, use:

```

> rawrs = elementMetadata(ovraw)$SNPs
> augrs = elementMetadata(ovaug)$SNPs
> gwrngs[augrs]

```

gwasloc instance with 90 records and 35 attributes per record.

Extracted: 2012.09.22

Excerpt:

GRanges with 5 ranges and 3 metadata columns:

	seqnames	ranges	strand		Disease.Trait	SNPs	p.Value
	<Rle>	<IRanges>	<Rle>		<factor>	<factor>	<numeric>
[1]	chr10	[ 64187564, 64187564]	*		Breast size	rs7089814	3e-09
[2]	chr10	[124214448, 124214448]	*		Age-related macular degeneration (CNV vs. GA)	rs10490924	7e-14
[3]	chr10	[124214448, 124214448]	*		Age-related macular degeneration (CNV vs. GA)	rs10490924	7e-14
[4]	chr10	[124214448, 124214448]	*		Age-related macular degeneration (CNV vs. GA)	rs10490924	7e-14
[5]	chr10	[124214448, 124214448]	*		Age-related macular degeneration (CNV vs. GA)	rs10490924	7e-14

---

seqlengths:

chr1	chr2	chr3	chr4	...	chr21	chr22	chrX
249250621	243199373	198022430	191154276	...	48129895	51304566	155270560



Relaxing the intersection criterion in this limited case leads to a larger set of traits.

```
> setdiff( getTraits(gwrngs[augrs]), getTraits(gwrngs[rawrs]) )

[1] "Venous thromboembolism"
[2] "Fasting glucose-related traits (interaction with BMI)"
[3] "Response to angiotensin II receptor blocker therapy"
[4] "Response to hepatitis C treatment"
[5] "Response to antidepressant treatment"
[6] "Bipolar disorder"
[7] "Phospholipid levels (plasma)"
[8] "Endometrial cancer"
[9] "Neuroblastoma"
[10] "MRI atrophy measures"
[11] "Menarche (age at onset)"
[12] "Self-rated health"
[13] "Neonatal lupus"
[14] "Crohn's disease"
[15] "Optic disc size (cup)"
[16] "Response to statin therapy"
[17] "Tanning"
[18] "Obesity"
[19] "Osteonecrosis of the jaw"
[20] "Hip geometry"
[21] "Parkinson's disease"
```

## 4 Counting alleles associated with traits

We can use `riskyAlleleCount` to count risky alleles enumerated in the GWAS catalog. This particular function assumes that we have genotyped at the catalogued loci. Below we will discuss how to impute from non-catalogued loci to those enumerated in the catalog.

```
> data(gg17N) # translated from GGdata chr 17 calls using ABmat2nuc
> gg17N[1:5,1:5]
```

	rs6565733	rs1106175	rs17054921	rs8064924	rs8070440
NA06985	"G/G"	"A/G"	"C/C"	"G/G"	"G/G"
NA06991	"G/G"	"A/A"	"C/C"	"G/G"	"G/G"
NA06993	"G/G"	"A/A"	"C/C"	"G/G"	"G/G"
NA06994	"A/G"	"A/G"	"C/C"	"A/G"	"G/G"
NA07000	"G/G"	"A/A"	"C/C"	"G/G"	"G/G"

This function can use genotype information in the A/B format, assuming that B denotes the alphabetically later nucleotide. Because we have direct nucleotide coding in our matrix, we set the `matIsAB` parameter to false in this call.

```
> h17 = riskyAlleleCount(gg17N, matIsAB=FALSE, chr="ch17")
> h17[1:5,1:5]
```

```
      rs7217319 rs2360111 rs12150338 rs4790881 rs1231206
NA06985      0      0      0      1      1
NA06991      0      1      0      2      0
NA06993      0      2      0      1      1
NA06994      0      2      0      2      2
NA07000      0      0      0      2      2
```

```
> table(as.numeric(h17))
```

```
  0    1    2
10436 4226 2888
```

It is of interest to bind the counts back to the catalog data.

```
> gwr = gwrngs
> gwr = gwr[colnames(h17),]
> elementMetadata(gwr) = cbind(elementMetadata(gwr), DataFrame(t(h17)))
> sn = rownames(h17)
> gwr[,c("Disease.Trait", sn[1:4])]
```

gwasloc instance with 195 records and 5 attributes per record.

Extracted: 2012.09.22

Excerpt:

GRanges with 5 ranges and 5 metadata columns:

seqnames	ranges	strand	Disease.Trait
<Rle>	<IRanges>	<Rle>	<factor>
[1] chr17	[ 38924, 38924]	*	AIDS progression
[2] chr17	[ 831667, 831667]	*	Economic and political preferences
[3] chr17	[1634104, 1634104]	*	Calcium levels
[4] chr17	[2068932, 2068932]	*	Bone mineral density
[5] chr17	[2125605, 2125605]	*	Coronary heart disease
NA06985	NA06991	NA06993	NA06994
<integer>	<integer>	<integer>	<integer>
[1] 0	0	0	0
[2] 0	1	2	2
[3] 0	0	0	0
[4] 1	2	1	2

```
[5]          1          0          1          2
----
seqlengths:
      chr1      chr2      chr3      chr4 ...      chr21      chr22      chrX
249250621 243199373 198022430 191154276 ... 48129895 51304566 155270560
```

Now by programming on the `elementMetadata`, we can identify individuals with particular risk profiles.

## 5 Imputation to unobserved loci

If we lack information on a specific locus  $s$ , but have reasonably dense genotyping on a subject, population genetics may allow a reasonable guess at the genotype at  $s$  for this subject. Many algorithms for genotype imputation have been proposed. Here we use a very simple approach due to David Clayton in the `snpStats` package.

We use the “low coverage” 1000 genomes genotypes for the CEU (central European) HapMap cohort as a base for constructing imputation rules. We focus on chromosome 17 for illustration.

The base data are

```
> data(low17)
> low17

A SnpMatrix with 60 rows and 196327 columns
Row names:  NA06985 ... NA12874
Col names:  chr17:1869 ... chr17:78654554
```

A somewhat sparser set of genotypes (HapMap phase II, genomewide 4 million loci) on chromosome 17 is archived as `g17SM`. This has a compact `SnpMatrix` encoding of genotypes.

```
> data(g17SM)
> g17SM

A SnpMatrix with 90 rows and 89701 columns
Row names:  NA06985 ... NA12892
Col names:  rs6565733 ... rs4986109
```

For a realistic demonstration, we use the subset of these loci that are present on the Affy 6.0 SNP array.

```
> data(gw6.rs_17)
> g17SM = g17SM[, intersect(colnames(g17SM), gw6.rs_17)]
> dim(g17SM)
```

```
[1] 90 20359
```

The base data were used to create a set of rules allowing imputation from genotypes in the sparse set to the richer set. Some rules involve only a single locus, some as many as 4. The construction of rules involves tuning of modeling parameters. See `snp.imputation` in `snpStats` for details.

```
> if (!exists("rules_6.0_1kg_17")) data(rules_6.0_1kg_17)
> rules_6.0_1kg_17[1:5,]
```

```
chr17:1869 ~ rs9915268+rs11247571+rs9895105+rs6598837 (MAF = 0.06666667, R-squared = 0.706)
chr17:2220 ~ rs4790867+rs10454094+rs2586238+rs7207284 (MAF = 0.125, R-squared = 0.592)
chr17:6689 ~ rs4424950+rs4790867+rs7225087+rs11658347 (MAF = 0.11666667, R-squared = 0.26)
rs34663111 ~ rs11658079+rs1609550+rs4985594+rs9788983 (MAF = 0.125, R-squared = 0.26)
rs62054999 ~ rs17609440+rs2740351+rs2589492+rs16956017 (MAF = 0.125, R-squared = 0.26)
```

The summary of rules shows the degree of association between the predictors and predictands in terms of  $R^2$ . Many potential targets are not imputed.

```
> summary(rules_6.0_1kg_17)
```

R-squared	SNPs used				<NA>
	1 tags	2 tags	3 tags	4 tags	
[0,0.1)	655	785	276	56	0
[0.1,0.2)	7	664	926	868	0
[0.2,0.3)	0	158	916	3054	0
[0.3,0.4)	0	28	411	5104	0
[0.4,0.5)	0	20	203	6365	0
[0.5,0.6)	0	21	121	6052	0
[0.6,0.7)	0	29	104	5623	0
[0.7,0.8)	0	54	108	6330	0
[0.8,0.9)	0	141	225	9506	0
[0.9,0.95)	652	700	572	8056	0
[0.95,0.99)	7274	1689	1388	6158	0
[0.99,1]	33660	1353	2326	10152	0
<NA>	0	0	0	0	53601

The overlap between the 6.0-resident `g17SM` loci and the catalog is

```
> length(intersect(colnames(g17SM), values(gwrngs)$SNPs))
```

```
[1] 83
```

The new expected B allele counts are

```
> exg17 = impute.snps(rules_6.0_1kg_17, g17SM)
```

The number of new loci that coincide with risk loci in the catalog is:

```
> length(intersect(colnames(exg17), values(gwrngs)$SNPs))
```

```
[1] 111
```

## 6 Formal management of trait vocabularies

### 6.1 Diseases: Disease Ontology

The Disease Ontology project Osborne et al. (2009) formalizes a vocabulary for human diseases. Bioconductor's DO.db package is a curated representation.

```
> library(DO.db)
> DO()
```

Quality control information for DO:

This package has the following mappings:

```
DOANCESTOR has 6284 mapped keys (of 6285 keys)
DOCHILDREN has 1789 mapped keys (of 6285 keys)
DOOBSOLETE has 2371 mapped keys (of 2371 keys)
DOOFFSPRING has 1789 mapped keys (of 6285 keys)
DOPARENTS has 6284 mapped keys (of 6285 keys)
DOTERM has 6285 mapped keys (of 6285 keys)
```

Additional Information about this package:

```
DB schema: DO_DB
DB schema version: 1.0
```

All tokens of the ontology are acquired via:

```
> alltob = unlist(mget(mappedkeys(DOTERM), DOTERM))
> allt = sapply(alltob, Term)
> allt[1:5]
```

```
          DOID:0000000          DOID:0000405          DOID:0001816
"gallbladder disease" "vascular tissue disease"          "angiosarcoma"
          DOID:0002116          DOID:0014667
          "pterygium"    "disease of metabolism"
```

Direct mapping from disease trait tokens in the catalog to this vocabulary succeeds for a modest proportion of records.

```
> cattra = elementMetadata(gwrngs)$Disease.Trait
> mat = match(tolower(cattra), tolower(allt))
> catDO = names(allt)[mat]
> catDO[1:50]
```

```
[1] NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA
[26] NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA NA
```

```
> mean(is.na(catDO))
```

```
[1] 0.7522641
```

Approximate matching of unmatched tokens can proceed by various routes. Some traits are not diseases, and will not be mappable using Disease Ontology. However, consider

```
> unique(cattr[is.na(catDO)])[1:20]
```

```
[1] Resistin levels
[2] Cannabis use (initiation)
[3] Central corneal thickness
[4] Renal function-related traits (BUN)
[5] Renal function-related traits (eGRFcrea)
[6] Renal function-related traits (sCR)
[7] Renal function-related traits (urea)
[8] C-reactive protein and white blood cell count
[9] Insulin-related traits
[10] Gambling
[11] Aging
[12] IgG levels
[13] Asthma (bronchodilator response)
[14] Bone mineral density
[15] Blood pressure
[16] Cortical thickness
[17] Response to citalopram treatment
[18] Insomnia (caffeine-induced)
[19] Breast size
[20] Lean body mass and age at menarche (combined)
721 Levels: 5-HTT brain serotonin transporter levels ... YKL-40 levels
```

```
> nomatch = cattr[is.na(catDO)]
```

Manual searching shows that a number of these have very close matches.

## 6.2 Other phenotypic traits: Human Phenotype Ontology

Bioconductor does not possess an annotation package for phenotype ontology, but the standardized OBO format can be parsed and modeled into a graph.

```

> hpobo = gzfile(dir(system.file("obo", package="gwascat"), pattern="hpo", full=TRUE)
> HPOgraph = obo2graphNEL(hpobo)
> close(hpobo)

```

The phenotypic terms are obtained via:

```

> hpoterms = unlist(nodeData(HPOgraph, nodes(HPOgraph), "name"))
> hpoterms[1:10]

```

```

          HP:0000001
            "All"
          HP:0000002
    "Abnormality of body height"
          HP:0000003
    "Multicystic kidney dysplasia"
          HP:0000004
    "Onset and clinical course"
          HP:0000005
    "Mode of inheritance"
          HP:0000006
    "Autosomal dominant inheritance"
          HP:0000007
    "Autosomal recessive inheritance"
          HP:0000008
"Abnormality of female internal genitalia"
          HP:0000009
    "Functional abnormality of the bladder"
          HP:0000010
    "Recurrent urinary tract infections"

```

Exact hits to unmatched GWAS catalog traits exist:

```

> intersect(tolower(nomatch), tolower(hpoterms))

[1] "atrial fibrillation"      "stroke"
[3] "iga nephropathy"          "coronary artery calcification"
[5] "scoliosis"                 "glioma"
[7] "nephropathy"              "glomerulosclerosis"
[9] "autism"                    "hypertriglyceridemia"
[11] "freckling"                "knee osteoarthritis"
[13] "hearing impairment"

```

More work on formalization of trait terms is underway.

### 6.3 Curation of approximate matches

## 7 Appendix: Adequacy of location annotation

A basic question concerning the use of archived SNP identifiers is durability of the association between asserted location and SNP identifier. The `chklocs` function uses a current Bioconductor `SNPlocs` package to check this.

For example, to verify that locations asserted on chromosome 20 agree between the Bioconductor dbSNP image and the gwas catalog,

```
> if ("SNPlocs.Hsapiens.dbSNP.20111119" %in% installed.packages()[,1]) {  
+   library(SNPlocs.Hsapiens.dbSNP.20111119)  
+   suppressWarnings(chklocs("20"))  
+ }
```

```
[1] TRUE
```

This is not a fast procedure but has succeeded for all chromosomes 1-22 when checked off line.

## References

John D Osborne, Jared Flatow, Michelle Holko, Simon M Lin, Warren A Kibbe, Lihua Julie Zhu, Maria I Danila, Gang Feng, and Rex L Chisholm. Annotating the human genome with disease ontology. *BMC Genomics*, 10 Suppl 1:S6, Jan 2009. doi: 10.1186/1471-2164-10-S1-S6. URL <http://www.biomedcentral.com/1471-2164/10/S1/S6>.