

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

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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 *BiocManager* package, with the sequence

```
library(BiocManager)
BiocManager::install("gwascats")
```

## 1.2 Attachment and access to documentation

Once the package has been installed, use `library(gwascats)` to obtain interactive access to all the facilities. After executing this command, use `help(package="gwascats")` 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()`.

## 1.3 Illustrations: computing

Available functions are:

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

```
[1] "bindcadd_snv"      "chklocs"          "ebicat37"
[4] "ebicat37UCSC"      "ebicat38"          "ebicat_b37"
[7] "ebicat_b38"        "efo.obo.g"         "g17SM"
[10] "getRsids"          "getTraits"         "gg17N"
[13] "gw6.rs_17"         "gwastagger"        "gwce2gviz"
[16] "gwdf_2014_09_08"   "gwrngs19"          "gwrngs38"
[19] "ldtagr"            "locon6"            "locs4trait"
[22] "low17"             "makeCurrentGwascats" "obo2graphNEL"
[25] "riskyAlleleCount"  "rules_6.0_1kg_17"  "si.hs.37"
[28] "si.hs.38"          "subsetByChromosome" "subsetByTraits"
[31] "topTraits"         "traitsManh"
```

The extended `GRanges` instance with all SNP-disease associations is obtained as follows, using the hg19 genome build (GRCh38/hg38-based ranges are also available as `ebicat38`).

```
> data(ebicat37)
```

To determine the most frequently occurring traits:

```
> topTraits(ebicat37)
```

Obesity-related traits	Height	IgG glycosylation
957	822	699
Type 2 diabetes	Rheumatoid arthritis	Crohn's disease
340	294	249
Schizophrenia	Blood metabolite levels	HDL cholesterol
248	245	220
Breast cancer		
199		

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

```
> subsetByTraits(ebicat37, tr="LDL cholesterol")[1:3]
```

gwasloc instance with 3 records and 36 attributes per record.

Extracted: 2016-01-18

Genome: GRCh37

Excerpt:

GRanges object with 3 ranges and 3 metadata columns:

	seqnames	ranges	strand	DISEASE/TRAIT	SNPS	P-VALUE
	<Rle>	<IRanges>	<Rle>	<character>	<character>	<numeric>
[1]	chr2	44072576	*	LDL cholesterol	rs4299376	4e-72
[2]	chr1	150958836	*	LDL cholesterol	rs267733	5e-09
[3]	chr2	21263900	*	LDL cholesterol	rs1367117	1e-182

-----  
seqinfo: 23 sequences from GRCh37 genome

## 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.

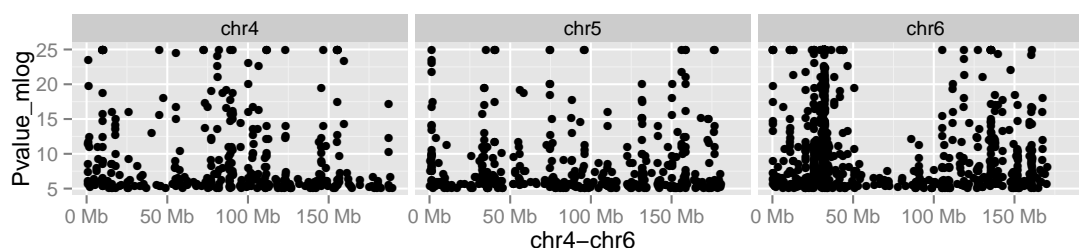
```
> gwtrunc = ebicat37
> requireNamespace("S4Vectors")
> mcols = S4Vectors::mcols
```

```

> mlpv = mcols(ebicat37)$PVALUE_MLOG
> mlpv = ifelse(mlpv > 25, 25, mlpv)
> S4Vectors::mcols(gwtrunc)$PVALUE_MLOG = mlpv
> library(GenomeInfoDb)
> seqlevelsStyle(gwtrunc) = "UCSC"
> gwlit = gwtrunc[ which(as.character(seqnames(gwtrunc)) %in% c("chr4", "chr5", "chr6")) ]
> library(ggbio)
> mlpv = mcols(gwlit)$PVALUE_MLOG
> mlpv = ifelse(mlpv > 25, 25, mlpv)
> S4Vectors::mcols(gwlit)$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.

July 2018: The following is unevaluated owing to ggbio.

```

> 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)

```

## 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)
> c17tg = import(gffpath)
```

We make a Gviz DataTrack of the dsQTL scores.

```
> c17td = c17tg[ which(S4Vectors::mcols(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.

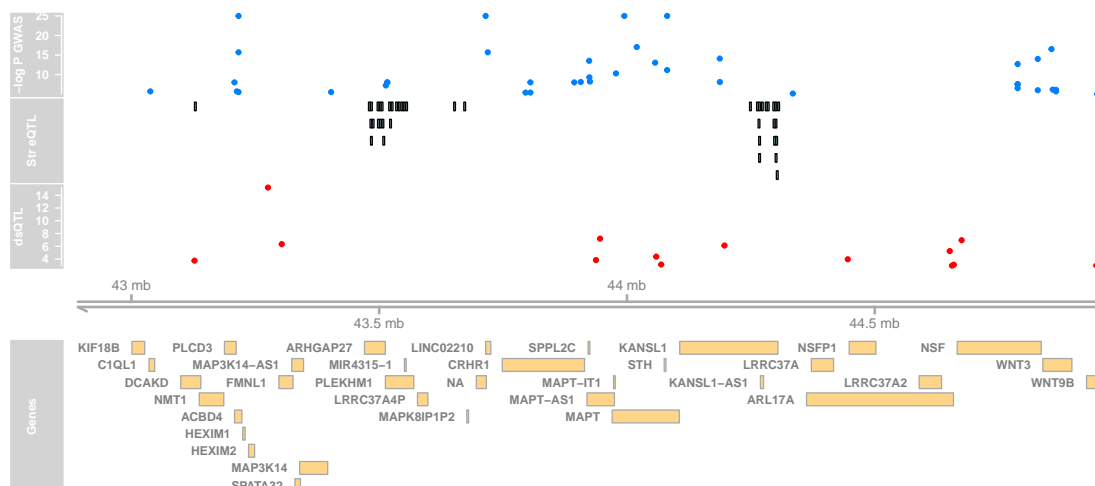
```
> g2 = GRanges(seqnames="chr17", IRanges(start=4.3e7, width=2e6))
> seqlevelsStyle(ebicat37) = "UCSC"
> basic = gwcex2gviz(basegr = ebicat37, contextGR=g2, plot.it=FALSE)
```

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

```
> c17ts = c17tg[ which(S4Vectors::mcols(c17tg)$type == "Stranger_eqtl") ]
> eqloc = AnnotationTrack(c17ts, chrom="chr17", genome="hg19", name="Str eQTL")
> displayPars(eqloc)$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 = ebicat37[ intersect(getRsids(ebicat37), rson6) ]
> sort(table(getTraits(intr)), decreasing=TRUE)[1:10]
```

Height	6
Select biomarker traits	3
Bipolar disorder	2
Dental caries	2
Homocysteine levels	2
IgG glycosylation	2
Immune reponse to smallpox (secreted IFN-alpha)	2

```

Metabolic traits
2
Mitochondrial DNA levels
2
Response to cytidine analogues (cytosine arabinoside)
2

```

## 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))
> S4Vectors::mcols(gr6.0)$rsid = as.character(locon6$dbSNP_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  $\pm$  500bp.

```

> ag = function(x) as(x, "GRanges")
> ovraw = suppressWarnings(subsetByOverlaps(ag(ebicat37), gr6.0))
> length(ovraw)

[1] 128

> ovaug = suppressWarnings(subsetByOverlaps(ag(ebicat37+500), gr6.0))
> length(ovaug)

[1] 207

```

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

```

> rawrs = mcols(ovraw)$SNPS
> augrs = mcols(ovaug)$SNPS
> ebicat37[augrs]

```

gwasloc instance with 207 records and 36 attributes per record.

Extracted: 2016-01-18

Genome: GRCh37

Excerpt:

GRanges object with 5 ranges and 3 metadata columns:

	seqnames	ranges	strand	
	<Rle>	<IRanges>	<Rle>	
[1]	chr11	4605195	*	
[2]	chr11	46761055	*	
[3]	chr1	169519049	*	
[4]	chr11	61640379	*	
[5]	chr1	8495945	*	

	DISEASE/TRAIT
	<character>
[1]	Response to serotonin reuptake inhibitors in major depressive disorder
[2]	Venous thromboembolism
[3]	Venous thromboembolism
[4]	Trans fatty acid levels
[5]	Optic cup area

	SNPS	P-VALUE
	<character>	<numeric>
[1]	rs2566255	2e-06
[2]	rs1799963	2e-09
[3]	rs6025	1e-96
[4]	rs174449	8e-07
[5]	rs301801	3e-08

-----

seqinfo: 23 sequences from GRCh37 genome

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

```
> setdiff( getTraits(ebicat37[augrs]), getTraits(ebicat37[rawrs]) )
```

```
[1] "Response to serotonin reuptake inhibitors in major depressive disorder"
[2] "Venous thromboembolism"
[3] "Hippocampal volume"
[4] "Red blood cell fatty acid levels"
[5] "Febrile seizures (MMR vaccine-related)"
[6] "Eosinophilic esophagitis"
[7] "QT interval"
[8] "Smoking cessation"
[9] "Systolic blood pressure (alcohol consumption interaction)"
[10] "QRS duration in Tripanosoma cruzi seropositivity"
[11] "Functional impairment in major depressive disorder, bipolar disorder and schizop
[12] "Periodontitis (CDC/AAP)"
[13] "Odorant perception (&beta;-damascenone)"
[14] "Bronchopulmonary dysplasia"
[15] "Self-reported allergy"
```



```

[16] "Migraine"
[17] "Reading and spelling"
[18] "Adverse response to chemotherapy (neutropenia/leucopenia) (carboplatin)"
[19] "Obesity"
[20] "Autism spectrum disorder, attention deficit-hyperactivity disorder, bipolar disorder"
[21] "Response to taxane treatment (docetaxel)"
[22] "Response to amphetamines"
[23] "Neuroblastoma"
[24] "Lentiform nucleus volume"
[25] "Capecitabine sensitivity"
[26] "Fasting glucose-related traits (interaction with BMI)"
[27] "Response to angiotensin II receptor blocker therapy"
[28] "Response to hepatitis C treatment"
[29] "Response to anti-depressant treatment in major depressive disorder"
[30] "Phospholipid levels (plasma)"
[31] "Endometrial cancer"
[32] "MRI atrophy measures"
[33] "Self-rated health"
[34] "Neonatal lupus"
[35] "Crohn's disease"
[36] "Response to statin therapy"
[37] "Tanning"
[38] "Osteonecrosis of the jaw"
[39] "Hip geometry"
[40] "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",
+ gwwl = ebicat37)
> h17[1:5,1:5]
```

	rs7217319	rs684232	rs623323	rs747685	rs747687
NA06985	0	0	2	1	1
NA06991	0	0	2	2	2
NA06993	0	0	2	1	1
NA06994	0	0	2	2	2
NA07000	0	0	2	2	2

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

0	1	2
23876	9954	7570

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

```
> gwr = ebicat37
> gwr = gwr[colnames(h17),]
> S4Vectors::mcols(gwr) = cbind(mcols(gwr), DataFrame(t(h17)))
> sn = rownames(h17)
> gwr[,c("DISEASE/TRAIT", sn[1:4])]
```

gwasloc instance with 460 records and 5 attributes per record.

Extracted: 2016-01-18

Genome: GRCh37

Excerpt:

GRanges object with 5 ranges and 5 metadata columns:

	seqnames	ranges	strand	DISEASE/TRAIT	NA06985	NA06991
	<Rle>	<IRanges>	<Rle>	<character>	<integer>	<integer>
[1]	chr17	38924	*	AIDS progression	0	0
[2]	chr17	618965	*	Prostate cancer	0	0
[3]	chr17	700020	*	Type 2 diabetes	2	2
[4]	chr17	775051	*	Blood pressure	1	2
[5]	chr17	775334	*	Blood pressure	1	2
	NA06993	NA06994				
	<integer>	<integer>				
[1]	0	0				
[2]	0	0				

[3]	2	2
[4]	1	2
[5]	1	2

-----

seqinfo: 23 sequences from GRCh37 genome

Now by programming on the metadata columns, 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
```

An object of class "SnpMatrix"

```
chr17:1869 chr17:2220 chr17:6689 rs34663111 rs62054999 chr17:13074
chr17:14008 chr17:19979 chr17:27268 chr17:31906 chr17:32249 chr17:32309
chr17:32311 chr17:32579 chr17:32869 chr17:33766 chr17:33817 chr17:33865
chr17:34206 chr17:34276 chr17:34401 chr17:36164 chr17:36169 chr17:36642
rs62054056 chr17:38761 chr17:44399 rs62057000 chr17:46107 rs34794059
rs35498575 rs11656530 rs12941744 chr17:48400 rs12945606 rs59865068
chr17:48474 rs7501441 chr17:48878 rs4890179 rs4890180 rs4890181
rs62057022 rs62057023 rs4890182 rs55715614 chr17:49783 rs56209223
chr17:49868 rs8070685 rs62057026 chr17:50776 rs11658619 rs11656429
rs9900783 chr17:51088 rs11657419 rs9911285 rs4890184 chr17:51196
rs4890185 rs1882990 rs1109902 rs4424950 rs56200345 rs7503116 rs4890188
rs1136388 chr17:53181 rs1609550 chr17:53324 rs34979521 rs9913041
chr17:54373 rs1109995 chr17:55518 chr17:55533 rs9903623 rs4305131
rs7213008 chr17:57029 chr17:57897 rs55639116 rs62057047 rs11654695
chr17:59056 chr17:59096 chr17:59137 chr17:59340 rs4353523 chr17:59389
rs11649979 chr17:60469 rs12938802 chr17:60733 chr17:61665 chr17:61849
rs1138504 rs11150884 rs9907477 chr17:63097 rs11150885 rs11150886
chr17:63683 chr17:63824 chr17:63927 rs62057048 rs8077096 chr17:64175
```

rs62057049 rs7226358 chr17:65360 rs62057050 rs7207457 rs11868664  
rs4417592 rs4417593 chr17:66507 rs62057051 rs8066107 chr17:68293  
chr17:68317 chr17:68329 rs62057055 rs56377713 rs12941133 rs55767019  
rs55737141 chr17:69067 rs62057059 rs62059560 rs62059561 rs62059562  
rs62059563 rs12450789 chr17:71465 chr17:71471 rs12943724 rs56871222  
rs62059580 rs9915268 rs35292180 chr17:72213 chr17:72267 chr17:72335  
chr17:72338 rs12450662 rs28698090 rs4442878 rs9890183 rs8078223  
rs9896436 rs35147412 rs11867332 rs34778113 rs36016398 rs35147390  
rs11867900 rs35698541 chr17:74922 chr17:75264 rs61618085 chr17:75839  
chr17:76431 rs12939784 chr17:76628 rs9915328 rs34372025 rs12452457  
chr17:77285 rs11150887 rs8081881 rs8078929 rs8069524 rs9675043  
rs28521142 rs8075539 chr17:80061 chr17:80433 rs11150888 rs11150889  
rs4890193 rs4550502 rs11150890 rs11150891 rs12945036 rs11150892  
rs55708782 chr17:81113 rs4890194 rs4890195 chr17:81254 chr17:81349  
chr17:81369 rs9674467 chr17:81659 rs9674571 chr17:81768 chr17:81921  
chr17:81922 chr17:81923 rs8075084 rs8075208 chr17:82229 chr17:82312  
rs34314694 rs4890196 rs4890171 chr17:82992 rs4890197 rs4890198  
rs12941826 rs28529202 rs28690679 chr17:84521 rs8073847 rs35286566  
chr17:84936 rs8076034 chr17:85592 chr17:85776 rs4531790 rs3923019  
chr17:85842 rs11655874 rs11651610 rs3923018 rs11651800 rs3923017  
rs11654890 chr17:86853 rs9905036 chr17:86925 rs55708732 rs11652984  
rs35315427 rs11150893 rs11150894 rs11653255 rs12603796 chr17:87964  
rs34347588 rs8074031 rs7213583 rs7213702 rs12449638 rs7217872  
chr17:89055 rs12937656 chr17:90050 rs62056563 rs9912863 rs9908467  
rs9908519 rs9894303 rs9913392 rs9909439 rs9892331 rs35026216 rs55904681  
rs34170095 rs35445227 rs12942097 rs12949408 chr17:92005 chr17:93709  
chr17:94243 rs12150065 chr17:94595 chr17:94869 rs12150077 chr17:94873  
rs9896350 rs58055127 chr17:95303 chr17:95332 rs9892040 rs7207284  
rs62622824 rs58153628 rs57953101 rs7405600 rs4985571 rs4352099  
chr17:97378 rs4353524 rs4426400 chr17:97720 rs12948758 rs12449506  
rs12451407 rs4357997 chr17:98250 rs11651297 rs4395128 chr17:98469  
chr17:98717 rs59337913 chr17:98915 rs4129926 rs56252542 chr17:100246  
rs7406880 chr17:100371 rs62056571 rs56384259 chr17:100691 rs7405713  
rs12451219 rs12451236 rs12600698 rs12602957 chr17:101766 rs9901911  
chr17:102171 rs7208985 rs58485634 rs7223759 rs7209151 rs58315634  
rs9892618 rs7209688 rs7221298 rs7217222 rs7214608 rs28747076 rs7214637  
rs12451029 rs4458053 rs28515912 rs28706104 rs28556780 rs62056574  
rs9900685 rs60727688 rs12601375 rs4890202 rs4890203 chr17:108015  
rs12452527 rs11150870 rs9906110 chr17:109220 chr17:109235 rs9907635  
rs7406768 chr17:109423 rs4985595 rs7224163 rs7215219 chr17:110522  
rs7219680 rs7212156 rs9903116 rs8073479 rs8073513 rs10454094  
chr17:111460 chr17:111519 chr17:111665 rs56702013 rs28468376 rs28404325

chr17:112970 rs7208188 rs55695413 rs6565702 rs4985594 chr17:113584  
chr17:113604 rs34427628 rs4985593 rs4985592 chr17:113738 rs12947571  
rs12449625 chr17:114530 rs4617924 rs8075999 chr17:115031 chr17:115115  
rs60794269 rs4985591 rs4985590 rs4247500 rs4985589 rs4371209 rs4471739  
chr17:115802 rs4471740 rs7224768 rs7224674 rs12940704 chr17:116375  
chr17:116431 chr17:116499 chr17:117204 chr17:117452 rs28593623  
rs56960944 chr17:118657 rs12451051 chr17:118962 rs7504058 rs7501898  
chr17:119999 rs4985588 rs12937990 chr17:122582 rs8079261 rs9789021  
chr17:123540 rs9891976 chr17:123961 rs9915796 rs59849037 chr17:125579  
rs7207517 chr17:126030 rs7211665 rs9902230 rs10871511 rs9915647  
rs9915649 chr17:126885 chr17:127753 rs56101945 rs12936802 rs7223270  
rs9789059 rs9789037 rs9789038 rs9788983 chr17:129697 rs35128325  
rs56210084 rs56005157 rs7208824 chr17:130149 chr17:130369 chr17:130451  
chr17:130529 rs4985587 chr17:130892 rs12949507 rs9894715 rs12449754  
rs12942829 rs11150871 rs12451279 rs12452629 rs9906685 chr17:132008  
rs9901478 rs12453152 rs9891894 rs9891903 chr17:132276 rs10871512  
rs11657652 chr17:132364 rs35035943 rs4985586 rs9913843 rs35478781  
rs9909445 rs12936617 chr17:133111 rs12949092 chr17:133392 chr17:133497  
rs12451101 rs9889392 rs9901577 rs11650789 rs11650933 rs10871513  
rs55995547 rs55856972 rs62052705 chr17:135075 rs55868427 rs12951184  
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rs11657374 rs58249801 chr17:78618888 chr17:78619033 chr17:78619313
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[ reached getOption("max.print") -- omitted 60 rows ]

```

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

```

An object of class "Snpmatrix"

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      rs6565733 rs1106175 rs17054921 rs8064924 rs8070440 rs3794811 rs8066551
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      rs7215271 rs7224313 rs7217319 rs17055015 rs4890199 rs10459967 rs4890183
NA06985      02      01      02      01      03      01      02
      rs11654491 rs1882990 rs4424950 rs7503116 rs1136388 rs1609550 rs12937885

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	rs1808939	rs9907305	rs165105	rs165103	rs165102	rs356054	rs356053
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	rs3826519	rs354995	rs171395	rs11656206	rs11078638	rs8079402	rs12604075
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	rs16944149	rs4792092	rs4791449	rs4792093	rs4792094	rs9303268	rs9890597
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	rs2323284	rs4792496	rs4792497	rs4792498	rs11651613	rs9900777	rs11651617
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	rs7946	rs1020697	rs4646408	rs16961834	rs9900054	rs3785499	rs4609908
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	rs4646406	rs12373156	rs12103822	rs4646405	rs4646404	rs4244593	rs4646402
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	rs897455	rs748724	rs1108579	rs4646401	rs897456	rs748196	rs8182244
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	rs9896989	rs4924768	rs4924922	rs8078513	rs4646399	rs4646398	rs9894937
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	rs4646389	rs8081961	rs11651487	rs4646387	rs4646386	rs11651620	rs6502603
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	rs13342397	rs4924962	rs9890856	rs11654842	rs7225421	rs8082417	rs1531100
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	rs4646367	rs897451	rs9902092	rs9902188	rs4646365	rs4646364	rs4646362
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	rs4244598	rs4646350	rs4646348	rs729975	rs12948060	rs11078389	rs8068641
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	rs2124344	rs8070432	rs4591203	rs7224725	rs956967	rs9944423	rs2278952
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	rs3760188	rs7214988	rs4646344	rs4646343	rs4244599	rs4646342	rs4646341
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	rs4646340	rs4646339	rs7215880	rs7216985	rs7217764	rs7217778	rs8066046
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	rs8079802	rs9897309	rs9904351	rs4925103	rs4925104	rs4244601	rs8081913
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	rs9915059	rs9896221	rs9904928	rs9896709	rs12603372	rs3850780	rs13339688
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	rs9325894	rs2034110	rs11654025	rs767751	rs12601273	rs9892080	rs7207611
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	rs2165897	rs8071665	rs7502896	rs8068720	rs8070401	rs9908418	rs7223476
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	rs9913007	rs2694201	rs4985930	rs8076285	rs6650602	rs2449922	rs4485420
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	rs671827	rs9908604	rs7223920	rs4985807	rs4990805	rs11657211	rs12452283
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	rs1657744	rs5021703	rs5028197	rs2362326	rs2002591	rs3866980	rs5002954
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	rs1969373	rs1521563	rs12103473	rs11657456	rs7225143	rs12453728	
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	rs1975980	rs1402726	rs2061893	rs8074736	rs1851267	rs16972661	rs16972676
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	rs6505225	rs8070811	rs178672	rs188914	rs322198	rs322199	rs322200
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	rs1695668	rs1676582	rs1676583	rs1695670	rs1676587	rs322192	rs322193
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	rs7217148	rs9989456	rs2086033	rs2100894	rs2100895	rs10853139	rs10853140



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	rs7218503	rs7215192	rs1319660	rs1551851	rs1038024	rs1551855	rs1551854
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	rs11649814	rs11649888	rs17184147	rs7212997	rs11869847	rs7218135	
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	rs319788	rs16968157	rs319789	rs1817964	rs2275	rs2278	rs11867871
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	rs12952455	rs371634	rs16968175	rs319769	rs319768	rs319767	rs319766
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	rs319758	rs319757	rs319755	rs2346690	rs319754	rs2068586	rs7501476
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	rs4795758	rs17248874	rs17836744	rs12952139	rs17248888	rs4795759	
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	rs12601597	rs1002317	rs4795760	rs1391076	rs2346687	rs1497359	rs1497358
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	rs7218456	rs10512459	rs12949335	rs11870580	rs1548508	rs1003837	
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	rs1548507	rs7207803	rs7225966	rs755612	rs982849	rs2214450	rs11080250
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	rs11870384	rs957373	rs11653822	rs1003916	rs1003915	rs9303674	rs929260
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	rs10512460	rs9914754	rs9913938	rs9914385	rs9912762	rs9915666	rs12948726
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	rs2158262	rs16969224	rs2158261	rs4795868	rs12950879	rs12940154	

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	rs9903752	rs9903975	rs11080252	rs17193375	rs17193382	rs2097762	
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	rs9901065	rs9899087	rs9901756	rs9900973	rs9907895	rs8071866	rs9907476
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	rs8076754	rs929259	rs929258	rs9895553	rs4795871	rs4795872	rs4795873
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	rs17193396	rs16969242	rs11656508	rs2107150	rs16969250	rs11657866	
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	rs8082206	rs17250896	rs8064367	rs17193410	rs9911097	rs3744513	rs3744512
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	rs7218031	rs10512461	rs7218036	rs1548509	rs8070143	rs11080254	rs2228990
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	rs2228989	rs9891330	rs757224	rs2097761	rs8064963	rs8064745	rs8069494
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	rs12449674	rs8067623	rs8069516	rs763781	rs9911364	rs17250931	rs17250938
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	rs8077171	rs2368698	rs3744511	rs3744510	rs8069624	rs17250959	rs8070119
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	rs17784068	rs1078170	rs2368697	rs758292	rs2005314	rs10512462	rs4795883
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	rs2079662	rs2003533	rs740562	rs750289	rs731971	rs4794990	rs11867166
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	rs7218501	rs7217519	rs12938546	rs3785907	rs11652429	rs11658512	
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	rs12150657	rs11080256	rs17614093	rs16969340	rs7502094	rs4328493	
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	rs6505397	rs4794992	rs9903934	rs8079587	rs8065802	rs8080487	rs16963804
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	rs1024613	rs12939473	rs2108826	rs17542175	rs8066047	rs7213460	rs7215649
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	rs11657810	rs11653971	rs7207653	rs1860179	rs12452818	rs17542274	
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	rs9891243	rs9910730	rs8066215	rs2017180	rs12941188	rs7359541	rs7359592
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	rs7215001	rs7215324	rs887074	rs12601112	rs4794993	rs887072	rs887071
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	rs12601658	rs2368473	rs4299196	rs9889846	rs9909870	rs9896676	rs11658977

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	rs1019113	rs1019112	rs10491109	rs1024612	rs11651806	rs17652000	
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	rs2159220	rs1029720	rs1029719	rs11654788	rs16969373	rs9906713	
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	rs17652139	rs12950076	rs4340374	rs6505400	rs8070055	rs12944577	
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	rs2215183	rs13380798	rs9893808	rs16969376	rs16969377	rs7215541	
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	rs8071803	rs11868941	rs9890372	rs9893096	rs9897821	rs758294	rs2017629
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	rs740563	rs8182355	rs9902605	rs7223422	rs7223451	rs9889296	rs9890014
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	rs11649832	rs7213978	rs7214171	rs17652343	rs11652585	rs11656026	
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	rs7210316	rs11656271	rs6505402	rs8068314	rs4795893	rs2857653	rs11867200
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	rs3917891	rs3917894	rs2530797	rs3917895	rs991804	rs11575018	rs8074043
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	rs3091318	rs7224013	rs3091319	rs3744509	rs3091237	rs3091321	rs2302160
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	rs3091326	rs3091327	rs1860187	rs8081047	rs6505403	rs3091331	rs3091330
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	rs3091328	rs8067889	rs12948058	rs4795895	rs4795896	rs17735961	
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	rs16969415	rs17809012	rs3744508	rs1860184	rs3815341	rs4795898	rs1019109
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	rs12601294	rs12601396	rs714910	rs1860182	rs1860181	rs12453516	rs9913706
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	rs11656007	rs11656109	rs11652256	rs8075846	rs9905791	rs2215185	
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	rs12453746	rs16969457	rs12449657	rs12452741	rs4100073	rs1233653	
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	rs1233652	rs1233651	rs3848464	rs3848465	rs3848466	rs891753	rs12602687
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	rs12602707	rs12602722	rs885691	rs12453143	rs1233650	rs3890641	rs3138034
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	rs8082480	rs8081376	rs4374216	rs4795910	rs12449308	rs3138035	rs3138036
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	rs3138037	rs1133763	rs16969479	rs4310920	rs11575056	rs11575057	
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	rs11575059	rs11575060	rs1821142	rs1946589	rs3138039	rs1346998	rs3138040
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	rs12453585	rs1897349	rs12601344	rs2217553	rs9913364	rs4795000	rs9914367
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	rs9915877	rs8072865	rs16969497	rs12602195	rs2339004	rs8066789	rs9909184
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	rs399240	rs9895412	rs408121	rs365654	rs12600832	rs210838	rs8074206
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	rs1431991	rs3136674	rs3136675	rs3136676	rs3136677	rs159313	rs2072069
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	rs2072070	rs159314	rs159315	rs159316	rs11575025	rs159317	rs159318
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	rs159319	rs3136680	rs3136681	rs3136682	rs2282692	rs2282691	rs3138031
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	rs159271	rs3138032	rs159272	rs159273	rs159274	rs159278	rs159279
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	rs867132	rs867133	rs159280	rs159284	rs159285	rs159286	rs159288
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	rs7502772	rs12603353	rs12603965	rs17653433	rs17574949	rs159289	rs159290
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	rs159305	rs159306	rs159307	rs4552064	rs1347000	rs1367954	rs159308
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	rs159311	rs159312	rs17654117	rs212451	rs295076	rs167170	rs212453
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	rs16969689	rs159255	rs159256	rs159257	rs159258	rs159259	rs295078
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	rs16969695	rs295079	rs159261	rs12947391	rs212454	rs212455	rs212456
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	rs17576095	rs159262	rs159263	rs212457	rs159264	rs212458	rs212461
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	rs212462	rs212463	rs212464	rs212465	rs212466	rs169862	rs167171
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	rs212469	rs212470	rs212472	rs212473	rs7207094	rs212476	rs7501695
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	rs2028036	rs7224986	rs212478	rs212480	rs212482	rs295081	rs159266
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	rs212485	rs1034610	rs113881	rs212489	rs212491	rs212492	rs212498
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	rs159268	rs159269	rs295086	rs1619833	rs210837	rs159250	rs159248
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	rs159247	rs150509	rs150511	rs150512	rs150514	rs2118232	rs150516
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	rs150517	rs159246	rs210835	rs7503575	rs150518	rs150519	rs150520
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	rs159245	rs150521	rs4795917	rs7217062	rs159244	rs16969797	rs17577327
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	rs16969801	rs886160	rs886161	rs12953164	rs756882	rs7208805	rs7207706
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	rs9907428	rs11658990	rs9916329	rs1978685	rs4041613	rs4795921	rs159242
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	rs159243	rs183309	rs12603249	rs4795923	rs9912429	rs1431994	rs969979
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	rs11658008	rs7214375	rs1545118	rs2289161	rs2289159	rs2289158	rs2289157
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	rs213136	rs12952020	rs8064381	rs213137	rs213138	rs9916697	rs213139
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	rs213140	rs172482	rs1437214	rs190038	rs4306569	rs169889	rs11653563
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	rs740635	rs12941013	rs740634	rs740633	rs740632	rs9900616	rs7207105
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	rs16970009	rs917499	rs917498	rs7220773	rs917497	rs16970010	rs9891590
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	rs1990281	rs11867341	rs11870430	rs7211991	rs16970011	rs4258672	rs980173
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	rs7225598	rs11659016	rs7207172	rs11080279	rs12940745	rs1016125	
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	rs4795933	rs990510	rs11871515	rs9910185	rs4435304	rs9891921	rs740631
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	rs740630	rs731855	rs9897813	rs12600895	rs2191050	rs8068550	rs9908111
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	rs12449660	rs7216837	rs7215699	rs2191057	rs7220351	rs12942229	
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	rs887229	rs887228	rs4996565	rs16970084	rs11654085	rs11080285	rs7215934
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	rs986819	rs11651582	rs11080286	rs11080287	rs8068807	rs2338967	rs1029742
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	rs3948672	rs4795011	rs12951315	rs4795012	rs758409	rs758408	rs12600677



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	rs11654609	rs11654945	rs2240729	rs3903117	rs12453171	rs16970095	
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	rs12951344	rs4795014	rs758407	rs933390	rs4795015	rs12450904	rs989606
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	rs9916362	rs8074684	rs4795952	rs4795016	rs2009472	rs9900451	rs7222334
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	rs758403	rs2058164	rs730815	rs998637	rs998638	rs1558208	rs1558207
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	rs7208546	rs12602358	rs8066795	rs16970114	rs17587637	rs17587658	
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	rs16970117	rs16970127	rs9916211	rs1860279	rs1860278	rs10459951	
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	rs1860277	rs1860276	rs17587841	rs4990638	rs758406	rs758405	rs4636954
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	rs11869649	rs7217051	rs12451648	rs9904056	rs4795955	rs13380821	
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	rs4341789	rs11658457	rs9893682	rs11650565	rs11650365	rs7406221	
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	rs12952924	rs4332785	rs3922677	rs8182290	rs11649794	rs4547381	
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	rs12952122	rs4378662	rs12601259	rs9897634	rs8071265	rs12948504	
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	rs8071398	rs12602813	rs12601404	rs4795957	rs4795958	rs8071766	rs9906943
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	rs8068898	rs12451356	rs12953242	rs4795018	rs17664516	rs11654964	
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	rs7406955	rs11653884	rs17664623	rs10491112	rs6505421	rs3937444	
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	rs17588051	rs2190982	rs7503024	rs2190980	rs12601721	rs6416978	rs9891116
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	rs7504004	rs4795021	rs9896785	rs8070015	rs917444	rs16970206	rs917443
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	rs10491113	rs9911700	rs7405664	rs4795963	rs8066088	rs2014965	rs2079665
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	rs7212990	rs2098049	rs1860197	rs1860195	rs2190979	rs12450148	rs4795969
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	rs12946866	rs4795971	rs4795972	rs1029722	rs2190978	rs11653134	rs2215188
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	rs2339213	rs2339212	rs12451076	rs4795028	rs4795029	rs4795030	rs4795031
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	rs9898011	rs11658392	rs11658425	rs7219954	rs12326018	rs4795979	
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	rs1019115	rs17665518	rs17589074	rs12600627	rs8067298	rs16970273	
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	rs1019114	rs1990264	rs1990263	rs7215529	rs11656182	rs11652872	
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	rs887078	rs8075272	rs7216816	rs4795987	rs4795988	rs4795989	rs10221192
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	rs8065356	rs16970292	rs8065683	rs12945413	rs7207454	rs7209339	rs7215517
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	rs887082	rs11654601	rs8065705	rs2041191	rs2012926	rs1029721	rs12940855
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	rs12946986	rs8082524	rs8069940	rs4795043	rs8065738	rs8064667	rs12452160
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	rs17666879	rs4795998	rs8067477	rs4795999	rs12451550	rs11080297	rs723704

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	rs11655495	rs4796000	rs12451007	rs758302	rs16970352	rs758301	rs7207633
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	rs7214396	rs11871853	rs8076256	rs9893071	rs16970359	rs11080299	
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	rs8082403	rs740569	rs740055	rs17603809	rs7216020	rs4796002	rs16970375
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	rs16970378	rs9652888	rs16970379	rs7225050	rs7225391	rs714895	rs11080300
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	rs11080303	rs10512465	rs4796004	rs11080304	rs17544779	rs11656880	
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	rs11655780	rs1860199	rs1860198	rs1153926	rs16970398	rs8068834	rs8069018
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	rs11080305	rs7221264	rs11650778	rs16970400	rs234808	rs11650925	
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	rs12936984	rs17627603	rs1482102	rs16970402	rs11657254	rs734612	rs758299
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	rs17544975	rs8081228	rs234822	rs1005596	rs53782	rs11652355	rs4796009
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	rs12938847	rs11869882	rs11652634	rs11656251	rs11656105	rs11080306	
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	rs12941800	rs11080308	rs9674871	rs714666	rs739741	rs744298	rs11080309
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	rs9675202	rs1564562	rs7216238	rs12948069	rs12938711	rs2840067	
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	rs383170	rs383171	rs1482105	rs11654070	rs11655366	rs234810	rs234811
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	rs234812	rs12937658	rs12937660	rs234813	rs7215527	rs877092	rs1482100
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	rs234814	rs234815	rs4993370	rs10512466	rs11657617	rs7208412	rs234816
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	rs4796014	rs12945282	rs1482104	rs9910965	rs4280300	rs7209401	rs11655339
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	rs12150324	rs9897282	rs11656268	rs11651685	rs4795049	rs12150439	
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	rs8249	rs7208342	rs8075549	rs8076878	rs4041564	rs2339120	rs1351554
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	rs3135965	rs3744356	rs3135966	rs3135967	rs3135968	rs3135969	rs3135970
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	rs9905150	rs899940	rs12150168	rs11080333	rs9895923	rs16970806	
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	rs4796067	rs772115	rs10512468	rs9905107	rs4795069	rs9892409	rs772121
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	rs11656557	rs772122	rs8068941	rs16970816	rs7223034	rs772106	rs7219774
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	rs7220738	rs1081685	rs4796069	rs1081686	rs772110	rs812800	rs7223900
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	rs11656369	rs11652130	rs7209244	rs1548182	rs1546583	rs9898340	
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	rs12449840	rs1554044	rs1554046	rs4503848	rs4338833	rs4074590	rs4074591
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	rs4286151	rs7212097	rs1047268	rs3803860	rs7211677	rs7212322	rs8064546
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	rs1849738	rs1828836	rs2263090	rs2681065	rs2671828	rs12937141	rs2671827

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	rs12950933	rs9901457	rs9911083	rs12946189	rs9889442	rs12946685	
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	rs8066379	rs1545283	rs8073702	rs8072772	rs722375	rs722374	rs11653309
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	rs2671817	rs2586514	rs1849733	rs9303686	rs9303687	rs9892864	rs12941487
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	rs12950950	rs772297	rs3021400	rs9913995	rs997656	rs997655	rs997654
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	rs772296	rs772291	rs7220689	rs3760323	rs2376263	rs7210421	rs1031107
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	rs9896086	rs1822403	rs3744371	rs11657183	rs2681066	rs2586506	rs3098957
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	rs16970912	rs8076768	rs11652532	rs17549508	rs16970972	rs16970975	
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	rs10512469	rs10512470	rs9896246	rs7216628	rs8072510	rs12943866	
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	rs7214197	rs11871195	rs8081729	rs9913882	rs12601979	rs7219934	rs961134
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	rs7223250	rs9916629	rs4239251	rs12953115	rs12937961	rs11655913	
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	rs16971026	rs16971028	rs11654381	rs7223043	rs7221374	rs16971029	
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	rs4796090	rs6505478	rs12450474	rs8077662	rs9904992	rs8070473	rs8066424
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	rs9907489	rs4796093	rs8077228	rs2376179	rs4795078	rs7221507	rs986419



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	rs17550632	rs12452797	rs17637907	rs2840044	rs321601	rs9891887	
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	rs225283	rs2301731	rs2376177	rs11656872	rs9303689	rs11650225	rs1634684
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	rs225272	rs225273	rs225274	rs225275	rs225276	rs225277	rs225278
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	rs11657908	rs11653051	rs11653282	rs9889274	rs7223601	rs2735482	
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	rs9899870	rs2735480	rs9900236	rs2242597	rs2526324	rs2702947	rs2702949
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	rs2376287	rs2526325	rs7213636	rs9904675	rs7218953	rs4796136	rs2251660
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	rs7222534	rs12939392	rs7207527	rs12945833	rs2526327	rs2280787	rs9913559
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	rs12603185	rs1051838	rs1051849	rs1016678	rs5022318	rs5022313	rs1016679

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	rs2074407	rs2074411	rs9901644	rs12450416	rs12453417	rs7207076	rs2158235
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	rs8079983	rs8065395	rs8071473	rs3110627	rs1416	rs9914221	rs1045000
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	rs8074971	rs1048701	rs11542276	rs2189269	rs17576667	rs7210385	
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	rs12453595	rs7221482	rs13755	rs3254	rs4405583	rs4416046	rs12451694
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	rs3744076	rs12453656	rs1882472	rs12944738	rs9907595	rs2091763	rs6503745
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	rs3942176	rs3744078	rs12453897	rs4794802	rs11651481	rs3744077	rs1922176
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	rs1882473	rs7501787	rs6503746	rs12602945	rs12600774	rs12150445	
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	rs12150584	rs8074750	rs7503446	rs4077061	rs4077060	rs4299185	rs12939016
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	rs7207737	rs8065762	rs11653174	rs11079075	rs12603914	rs9893861	
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	rs8077608	rs4795348	rs8066109	rs4795349	rs7350954	rs3936022	rs11870664
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	rs11870701	rs7501692	rs4254363	rs17705467	rs757319	rs757320	rs16964972
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	rs9905211	rs3744350	rs3744351	rs3744352	rs7213676	rs17705646	rs1989955
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	rs16229	rs16491	rs3025159	rs8064237	rs16230	rs3025160	rs3025161
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	rs3025162	rs11871779	rs16232	rs16233	rs16492	rs3025164	rs17632667
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	rs16237	rs3785744	rs3025167	rs16238	rs16968617	rs16239	rs16494
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	rs498973	rs16495	rs12940574	rs16500	rs490044	rs16501	rs3025179
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							rs645167

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	rs4252664	rs4252665	rs8066837	rs12947109	rs8078056	rs2941518	rs4794818
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	rs8065156	rs2016793	rs9891131	rs12946510	rs907091	rs907092	rs16965328
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	rs16965330	rs9893628	rs9893933	rs9894370	rs9652840	rs1510474	rs2017438
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	rs9889993	rs2304946	rs3890865	rs9907548	rs7502908	rs4134992	rs4134998
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	rs7222102	rs7217852	rs7219013	rs9904270	rs1348380	rs12946680	rs7503453

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	rs525217	rs507564	rs11655408	rs16965783	rs8077355	rs10852940	rs9890917
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	rs584828	rs10305285	rs4890114	rs10305288	rs535058	rs9895954	rs10305291
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	rs10305292	rs1009727	rs1009728	rs10305301	rs538399	rs10305308	
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	rs17745391	rs2643026	rs12602344	rs1156287	rs11658717	rs11079143	
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	rs1982760	rs1894936	rs17210022	rs9675081	rs9912810	rs12450558	
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	rs12450607	rs2787507	rs11079152	rs16955527	rs16955531	rs2541247	
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	rs8079259	rs732646	rs8076795	rs2079229	rs4239206	rs8067386	rs7221286
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	rs12602586	rs17833633	rs8066415	rs6503777	rs8069808	rs9905327	
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	rs7222971	rs11650135	rs7224874	rs11651533	rs12451385	rs9914199	
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	rs792393	rs792392	rs16958244	rs792391	rs16958250	rs16958255	rs7226136
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	rs9897351	rs11652629	rs11079318	rs12948117	rs11651503	rs8079116	
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	rs12952205	rs12939474	rs12943284	rs9893613	rs17762121	rs12600761	
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	rs4793558	rs1005631	rs3910244	rs16942124	rs4530197	rs4793887	rs9899614
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	rs8065120	rs758142	rs8067590	rs13341026	rs13342413	rs11079321	



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	rs1003313	rs16942160	rs4793892	rs2286359	rs12938108	rs17730996	
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	rs740442	rs740441	rs740440	rs11868170	rs16942197	rs7226098	rs7226133
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	rs8078458	rs17658521	rs6503827	rs7223010	rs16942211	rs16942213	
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	rs9895869	rs6504246	rs6416940	rs7222724	rs7502347	rs6504248	rs1320079
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	rs9901569	rs2684521	rs7208266	rs7225193	rs2903890	rs9893433	rs11870704
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	rs232141	rs232142	rs232144	rs232145	rs232146	rs8080748	rs8182293
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	rs1443272	rs11869865	rs11079641	rs1914644	rs1899582	rs9911923	rs9914461
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	rs9916234	rs8066422	rs9914216	rs9903594	rs12938160	rs12936730	rs9899247
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	rs1518267	rs230571	rs2109471	rs2159556	rs230568	rs7216429	rs9911039
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	rs4791035	rs3848417	rs7223532	rs7223517	rs4791034	rs8067166	rs9900495
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	rs873417	rs2363128	rs8079150	rs9891883	rs758657	rs4791031	rs17711579
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	rs758658	rs755369	rs8068915	rs7209239	rs6504463	rs1476813	rs12603665
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	rs16960285	rs3848414	rs3859213	rs3848413	rs3848412	rs4791022	rs4791021
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	rs1395826	rs1395825	rs17713225	rs11870521	rs9899635	rs7221351	rs740804
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	rs7221048	rs872719	rs2363838	rs740558	rs740557	rs740556	rs8070371
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	rs2570051	rs2642032	rs10459946	rs11658071	rs2642036	rs2706665	rs2642037
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	rs4496197	rs11652682	rs4496198	rs4496196	rs7215161	rs6504520	rs11657839
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	rs817543	rs817541	rs732322	rs817559	rs4968857	rs817556	rs7209210
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	rs817555	rs12601741	rs731606	rs7226269	rs707247	rs817566	rs817565
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	rs817564	rs6501325	rs817563	rs12451722	rs11077447	rs9905795	rs2365493
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	rs9910030	rs12453226	rs16973997	rs1972933	rs12946388	rs2365494	

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	rs2165887	rs11870230	rs2586548	rs2715810	rs9894539	rs7213686	rs8080760
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	rs2716227	rs2521367	rs2716225	rs2715812	rs2715813	rs12950595	rs12945375
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	rs2715814	rs9895446	rs2521342	rs2716224	rs9896967	rs2028048	rs2028049
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	rs2715815	rs9893349	rs11651488	rs2715816	rs9907575	rs4500787	rs11869073
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	rs7224115	rs1548444	rs7222898	rs16974045	rs9302900	rs8078890	rs8077944
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	rs2715817	rs16974063	rs8065100	rs2521344	rs2716223	rs2716222	rs2249009
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	rs9913842	rs739559	rs9893273	rs8065373	rs2716219	rs2716218	rs2715819
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	rs16974102	rs12051558	rs2521349	rs2716212	rs9900464	rs2716211	rs2715822
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	rs11867183	rs16974110	rs2715824	rs17769598	rs2251862	rs2251855	
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	rs2521355	rs2251160	rs2521356	rs3729920	rs2716206	rs17691066	rs2521358
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	rs12603781	rs2074029	rs3729922	rs2074031	rs3729925	rs2074032	rs7225903
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	rs2716201	rs2715828	rs4968792	rs11869376	rs2715830	rs2716197	rs2715831
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	rs2715832	rs2715833	rs2716195	rs16974160	rs2715834	rs8067307	rs8072070
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	rs16974166	rs2716194	rs756944	rs2716193	rs3815035	rs2521365	rs16974184
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	rs16974193	rs17823190	rs17223054	rs11867261	rs1989854	rs17823202	
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	rs11654541	rs10512573	rs11868542	rs2188699	rs8072325	rs990231	rs7216405
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	rs2947862	rs10445226	rs10445206	rs10445207	rs9903306	rs2947887	
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	rs9892291	rs9892758	rs3922321	rs9895243	rs8074090	rs8079768	rs9909905
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	rs12051608	rs998580	rs9913355	rs9906557	rs9302912	rs9302913	rs9916760
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	rs17702078	rs758036	rs12949270	rs7217293	rs7217947	rs4405595	rs4497742
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	rs16975242	rs7208531	rs16975251	rs9916550	rs9912069	rs9896573	rs8080893

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	rs8075963	rs12451657	rs12936668	rs12945558	rs8081486	rs7224025	
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	rs11077477	rs11077478	rs8066863	rs9889883	rs9897832	rs236512	rs993242
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	rs236513	rs1468472	rs7221086	rs173135	rs9302914	rs9302915	rs9895478
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	rs9894661	rs3815306	rs643637	rs1544489	rs1544490	rs4328485	rs236518
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	rs1468473	rs12947618	rs8082135	rs1473905	rs9891877	rs236585	rs11871843
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	rs236523	rs1514235	rs236524	rs236525	rs11077480	rs9898954	rs236527
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	rs16977017	rs16977018	rs16977019	rs7211642	rs2190494	rs7213040	
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	rs16977022	rs11868906	rs16977023	rs4793391	rs2015816	rs2015730	
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	rs12948260	rs7217932	rs11650567	rs9895376	rs2190493	rs9895224	rs7215570
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	rs11077587	rs11077588	rs11869595	rs12950751	rs9903612	rs11077589	
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	rs8069518	rs6501514	rs9904985	rs11652803	rs2190492	rs1005576	rs8064772
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	rs2342299	rs4793393	rs11077590	rs7218087	rs7218949	rs12103869	
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	rs12451606	rs2193055	rs2193054	rs759497	rs759496	rs759495	rs9892959
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	rs2241174	rs11657075	rs2241173	rs12951737	rs7219056	rs7218051	
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	rs11867583	rs7209172	rs7502459	rs2342303	rs9892101	rs9892132	rs9912994
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	rs8064641	rs8077585	rs1558748	rs11871723	rs12019079	rs1047956	rs975772
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	rs17181304	rs17779161	rs2159009	rs4793406	rs4793407	rs4793408	rs4793409
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	rs8068580	rs1859929	rs1859928	rs4793276	rs7220150	rs4793277	rs12451603
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	rs11652467	rs17182483	rs9891641	rs11651456	rs9907951	rs4432291	
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	rs11655612	rs16977301	rs16977302	rs4417585	rs4271633	rs4563075	
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	rs7220850	rs4789201	rs8065160	rs8067986	rs6501797	rs6501798	rs6501800
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	rs4073422	rs7222559	rs4789208	rs7222924	rs9909269	rs9910576	rs7502597
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	rs2305528	rs1671036	rs4789213	rs1671035	rs936061	rs1671033	rs2305527
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	rs1671022	rs1661721	rs1671021	rs2305526	rs16968009	rs1661716	rs1661715
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	rs16967307	rs11655698	rs7209626	rs10512610	rs2304922	rs2304921	
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	rs8070864	rs9890158	rs9892510	rs4788931	rs11077835	rs10852771	
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	rs9893133	rs4788932	rs4789318	rs3940647	rs4788933	rs4238998	rs4575559
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	rs4633757	rs8070870	rs7212413	rs7214155	rs7212569	rs2532443	rs11654499
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	rs16969140	rs16969144	rs16969146	rs7218347	rs719430	rs16969149	
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	rs2410994	rs1117060	rs1117059	rs4788937	rs2098092	rs7223597	rs7210275
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	rs11077851	rs9897045	rs7221855	rs9910053	rs9910052	rs2410997	rs2159358
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	rs9899887	rs6565549	rs8069730	rs4969428	rs7214675	rs7219431	rs9906351
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	rs2048058	rs2056439	rs8074153	rs12951328	rs12952372	rs12943170	
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	rs7212109	rs7208059	rs7208247	rs9911063	rs6565550	rs2659037	rs8076437
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NA06985	03	03	03	02	01	03	03
	rs2264574	rs2459704	rs2243416	rs1056534	rs12943159	rs2248533	rs2264578
NA06985	03	03	03	03	03	01	03
	rs12453281	rs2451216	rs2451215	rs2451214	rs12936505	rs11867468	rs652265
NA06985	01	03	01	03	01	00	03
	rs2677913	rs583245	rs589978	rs590315	rs12453529	rs11868704	rs11657878
NA06985	03	03	01	03	03	01	03
	rs599314	rs615630	rs2292809	rs11078011	rs1317360	rs635999	rs3791174
NA06985	03	02	03	03	03	01	01
	rs1320299	rs2379358	rs8078282	rs8066848	rs663033	rs12601113	rs619712
NA06985	01	03	03	01	03	03	03
	rs7224961	rs633017	rs11650019	rs12952016	rs630945	rs632276	rs665574
NA06985	03	01	01	03	01	01	01
	rs11655811	rs659602	rs7215667	rs11651441	rs7209308	rs635996	rs623209
NA06985	03	03	01	01	03	01	01
	rs629246	rs868203	rs656969	rs8074430	rs626637	rs594829	rs610516
NA06985	03	01	03	01	03	01	03
	rs3791168	rs582192	rs3791166	rs3791160	rs3791159	rs668990	rs2292972
NA06985	03	03	03	03	03	03	03
	rs4986110	rs607544	rs622789	rs2460467	rs666404	rs7504023	rs3744162
NA06985	01	00	01	03	03	01	01
	rs11652093	rs11871918	rs2677919	rs2460468	rs12603804	rs2263123	
NA06985	03	01	03	03	01	03	
	rs2681122	rs2677930	rs662669	rs668133	rs603016	rs11658083	rs605054
NA06985	03	03	03	03	01	01	00
	rs8079088	rs601997	rs601555	rs601533	rs681595	rs997921	rs11078015
NA06985	01	01	03	01	03	01	01
	rs12452833	rs9891304	rs6502134	rs12948179	rs8074277	rs12450046	
NA06985	01	01	01	01	02	02	
	rs3744165	rs11077947	rs12948188	rs10163502	rs9906115	rs11654320	
NA06985	03	03	03	01	02	03	
	rs10163478	rs11655395	rs9897676	rs9903208	rs3803769	rs7225515	rs4986113
NA06985	03	03	03	03	03	02	01
	rs8069699	rs4075209	rs7219521	rs11655723	rs4986114	rs4986117	rs7216324
NA06985	03	02	01	01	01	03	03
	rs4986118	rs7215939	rs7214952	rs11077948	rs9897951	rs7223204	rs9913679

NA06985	03	03	03	03	02	01	03
	rs9911685	rs9303013	rs8076360	rs6502007	rs12452622	rs733342	rs11869432
NA06985	03	01	03	03	01	01	03
	rs8067902	rs2199111	rs11870134	rs9894705	rs9789034	rs9303014	rs7210902
NA06985	03	02	01	02	01	03	01
	rs7224427	rs12946560	rs4986121	rs4986122	rs4986083	rs9892064	rs7222931
NA06985	01	01	01	02	03	03	03
	rs9894419	rs8065975	rs9900369	rs7406011	rs7221138	rs7214035	rs898093
NA06985	03	01	02	02	03	03	03
	rs6502010	rs8078446	rs12945629	rs11650335	rs7218196	rs7222963	rs8067926
NA06985	01	03	03	02	01	03	02
	rs8072584	rs4986125	rs7220642	rs9747334	rs9747279	rs4986127	rs11870340
NA06985	03	03	01	01	03	01	03
	rs3744159	rs11658422	rs7218786	rs1317809	rs8075894	rs6502011	rs4986129
NA06985	01	03	01	00	02	03	03
	rs4986131	rs11870094	rs8077706	rs898101	rs4986085	rs4986086	rs4986133
NA06985	01	03	01	03	01	03	01
	rs9891862	rs11869888	rs9894906	rs4986134	rs4986135	rs7210153	rs7208393
NA06985	01	03	03	01	01	03	03
	rs7209726	rs7209736	rs11869396	rs12453162	rs11869416	rs7212980	
NA06985	01	03	03	02	03	01	
	rs2271918	rs11651826	rs9905146	rs2292971	rs8068572	rs4986136	rs2085616
NA06985	02	03	01	01	01	02	03
	rs8073910	rs8074371	rs2271916	rs4359479	rs3803768	rs6502013	rs6502014
NA06985	01	03	01	03	01	03	01
	rs8078148	rs9912684	rs8064687	rs8070801	rs8069773	rs9899957	rs9902635
NA06985	03	02	03	01	01	03	03
	rs12601021	rs1551627	rs12942419	rs8080847	rs8067859	rs8067463	rs1551625
NA06985	03	03	01	01	03	01	03
	rs3744155	rs2279064	rs2279063	rs11868138	rs10163476	rs3826308	
NA06985	03	01	01	01	03	03	
	rs10163477	rs1011007	rs754639	rs898096	rs1078334	rs11657837	rs3785512
NA06985	03	01	02	03	02	03	01
	rs3785513	rs8072406	rs8072518	rs729123	rs729124	rs1127986	rs2034962
NA06985	02	01	03	03	02	03	02
	rs2380172	rs6502015	rs3785514	rs7208020	rs3785515	rs3785516	rs7208520
NA06985	02	01	02	03	01	01	01
	rs2125479	rs898095	rs12103580	rs7406464	rs11652232	rs11869930	rs7218129
NA06985	02	02	03	02	03	01	02
	rs3785518	rs3785519	rs3785520	rs3785521	rs3785522	rs17856082	rs11077949
NA06985	03	01	02	02	02	03	01
	rs3744156	rs8073471	rs9896933	rs9916526	rs2292969	rs2292968	rs6416854

NA06985	01	01	02	03	01	03	02
	rs7213006	rs2292966	rs3603	rs1044661	rs8180	rs11077950	rs12940475
NA06985	02	01	03	02	02	01	01
	rs9896263	rs1065144	rs898097	rs898098	rs7225887	rs3744157	rs3744158
NA06985	02	00	02	02	01	03	01
	rs7222745	rs7222773	rs8079082	rs6502021	rs9906163	rs12949939	rs2380173
NA06985	02	02	01	02	02	01	02
	rs8074284	rs12937252	rs9916545	rs2380176	rs4271625	rs1531281	rs1001865
NA06985	02	01	01	01	01	03	01
	rs8078866	rs11077951	rs12942128	rs7215871	rs12449872	rs12947014	
NA06985	03	01	03	02	01	01	
	rs11868453	rs6502026	rs9747676	rs12952892	rs8065638	rs4986144	rs9303015
NA06985	01	02	02	03	01	01	03
	rs9303016	rs7209936	rs4986137	rs12936476	rs4986089	rs11650407	
NA06985	03	02	03	03	02	03	
	rs10775371	rs1551628	rs4986090	rs6416855	rs9898649	rs9890216	rs7503536
NA06985	02	02	03	02	03	03	02
	rs7503605	rs7503408	rs9891371	rs7405583	rs7405607	rs12603409	rs9905027
NA06985	02	02	03	02	02	01	02
	rs12603456	rs9906258	rs9907989	rs7214627	rs12943585	rs7406895	rs7406865
NA06985	01	02	02	02	03	03	02
	rs9893833	rs4986146	rs11870793	rs11870684	rs11656634	rs9911294	
NA06985	03	03	02	03	02	02	
	rs9912207	rs9910113	rs9911830	rs731447	rs9916813	rs9897919	rs6502033
NA06985	02	02	02	03	03	03	03
	rs7406848	rs12936735	rs7226076	rs7221410	rs7221423	rs12601298	rs9901757
NA06985	02	03	02	01	02	02	02
	rs9915799	rs751409	rs8068883	rs11658065	rs12939139	rs7405903	rs2168935
NA06985	02	02	02	01	02	03	01
	rs9893868	rs12603171	rs12946056	rs9892565	rs11650383	rs9899748	
NA06985	02	01	03	01	01	03	
	rs9899884	rs7213238	rs11868851	rs9915904	rs898099	rs7212102	rs12948347
NA06985	03	03	01	01	01	02	02
	rs9907767	rs7208987	rs7222550	rs9915460	rs7210722	rs9899855	rs9897674
NA06985	01	03	01	03	01	01	01
	rs7406067	rs8072951	rs8078193	rs4986140	rs898105	rs7405957	rs8081673
NA06985	02	01	01	02	01	02	01
	rs16940609	rs9889817	rs9890099	rs11656152	rs1471196	rs8065396	rs9908845
NA06985	01	03	02	01	01	03	02
	rs9894730	rs9903292	rs9903731	rs967825	rs9890149	rs12453381	rs9908243
NA06985	01	02	02	01	02	03	03
	rs7224733	rs10852789	rs1143006	rs7406119	rs9890743	rs7405834	rs6502040

```

NA06985      01      01      03      01      03      03      02
      rs3935099 rs12103530 rs4986100 rs4986075 rs4986103 rs7503665 rs7503547
NA06985      01      03      03      01      03      01      01
      rs9893153 rs4073038 rs9911217 rs12602181 rs8072482 rs11652770 rs9896583
NA06985      03      00      02      02      02      02      03
      rs8072895 rs6416856 rs7501672 rs9675039 rs6502043 rs10432005 rs12449903
NA06985      02      03      03      02      02      01      03
      rs7406561 rs8077967 rs7502145 rs4986109
NA06985      01      02      01      02
[ reached getOption("max.print") -- omitted 89 rows ]

```

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 = 
chr17:2220 ~ rs4790867+rs10454094+rs2586238+rs7207284 (MAF = 0.125, R-squared = 0.706
chr17:6689 ~ rs4424950+rs4790867+rs7225087+rs11658347 (MAF = 0.125, R-squared = 0.592
rs34663111 ~ rs11658079+rs1609550+rs4985594+rs9788983 (MAF = 0.1166667, R-squared = 0
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)
```

	SNPs used				
R-squared	1 tags	2 tags	3 tags	4 tags	<NA>
[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), mcols(ebicat37)$SNPS))
```

```
[1] 184
```

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), mcols(ebicat37)$SNPS))
```

```
[1] 295
```

## 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 6569 mapped keys (of 6570 keys)
DOCHILDREN has 1811 mapped keys (of 6570 keys)
```



```

DOOBSOLETE has 2374 mapped keys (of 2374 keys)
DOOFFSPRING has 1811 mapped keys (of 6570 keys)
DOPARENTS has 6569 mapped keys (of 6570 keys)
DOTERM has 6570 mapped keys (of 6570 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:0001816                DOID:0002116
            "angiosarcoma"                "pterygium"
                DOID:0014667                DOID:0050004
    "disease of metabolism" "seminal vesicle acute gonorrhea"
                DOID:0050012
            "chikungunya"

```

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

```

> cattra = mcols(ebicat37)$Disease.Trait
> mat = match(tolower(cattra), tolower(allt))
> catDO = names(allt)[mat]
> na.omit(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
[26] 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] NaN

```

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(cattra[is.na(catDO)])[1:20]

```

NULL

```
> nomatch = cattra[is.na(catDO)]  
> unique(nomatch)[1:5]
```

NULL

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="gwascats"), pattern="hpo", full=TRUE)  
> HPOgraph = obo2graphNEL(hpobo)  
> close(hpobo)
```

The phenotypic terms are obtained via:

```
> requireNamespace("graph")  
> hpoterms = unlist(graph::nodeData(HPOgraph, graph::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))

character(0)
```

More work on formalization of trait terms is underway.

## 7 CADD scores

Kircher et al. (Kircher et al., 2014) define combined annotation-dependent depletion scores measuring variant pathogenicity in an integrative way. Small requests to bind scores for SNV to GRanges can be resolved through HTTP; large requests can be carried out on a local tabix-indexed selection from their archive.

```
> g3 = as(ebicat37, "GRanges")
> bg3 = bindcadd_snv( g3[which(seqnames(g3)=="chr3")][1:20] )
> inds = ncol(mcols(bg3))
> bg3[, (inds-3):inds]
```

This requires cooperation of network interface and server, so we don't evaluate in vignette build but on 1 Apr 2014 the response was:

GRanges with 20 ranges and 4 metadata columns:

	seqnames	ranges	strand		Ref	Alt
	<Rle>	<IRanges>	<Rle>		<character>	<character>
[1]	3	[109789570, 109789570]	*		A	G
[2]	3	[ 25922285, 25922285]	*		G	A
[3]	3	[109529550, 109529550]	*		T	C
[4]	3	[175055759, 175055759]	*		T	G
[5]	3	[191912870, 191912870]	*		C	T
...	...	...	...	...	...	...
[16]	3	[187716886, 187716886]	*		A	G
[17]	3	[160820524, 160820524]	*		G	C
[18]	3	[169518455, 169518455]	*		T	C
[19]	3	[179172979, 179172979]	*		G	T
[20]	3	[171785168, 171785168]	*		G	C
	CScore	PHRED				
	<numeric>	<numeric>				
[1]	-0.182763	3.110				
[2]	-0.289708	2.616				
[3]	0.225373	5.216				
[4]	-0.205689	3.003				

```

[5] -0.172189      3.161
...      ...      ...
[16] -0.019710      3.913
[17] -0.375183      2.235
[18] -0.695270      0.987
[19] -0.441673      1.949
[20]  0.231972      5.252
---
seqlengths:
      1          2          3          4 ...          21          22          X
249250621 243199373 198022430 191154276 ... 48129895 51304566 155270560

```

## 8 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.dbSNP144.GRCh37" %in% installed.packages()[,1]) {
+   library(SNPlocs.Hsapiens.dbSNP144.GRCh37)
+   chklocs("20", ebicat37)
+ }

[1] TRUE

```

This is not a fast procedure. As of March 2017, small numbers of catalog locations are found discrepant with dbSNP for GRCh37.

## References

- Martin Kircher, Daniela M Witten, Preti Jain, Brian J O’Roak, Gregory M Cooper, and Jay Shendure. A general framework for estimating the relative pathogenicity of human genetic variants. *Nat Genet*, Feb 2014. doi: 10.1038/ng.2892.
- John D Osborne, Jared Flatow, Michelle Holko, Simon M Lin, Warren A Kibbe, Li-hua 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>.