

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 *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, 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.

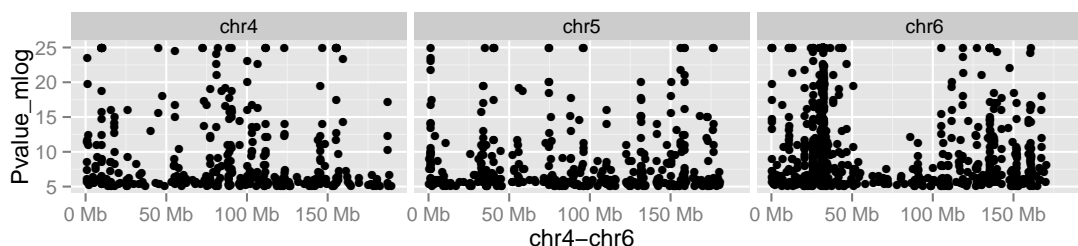
```
> gwtrunc = ebicat37
> requireNamespace("S4Vectors")
> mcols = S4Vectors::mcols
```

```

> 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. 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.

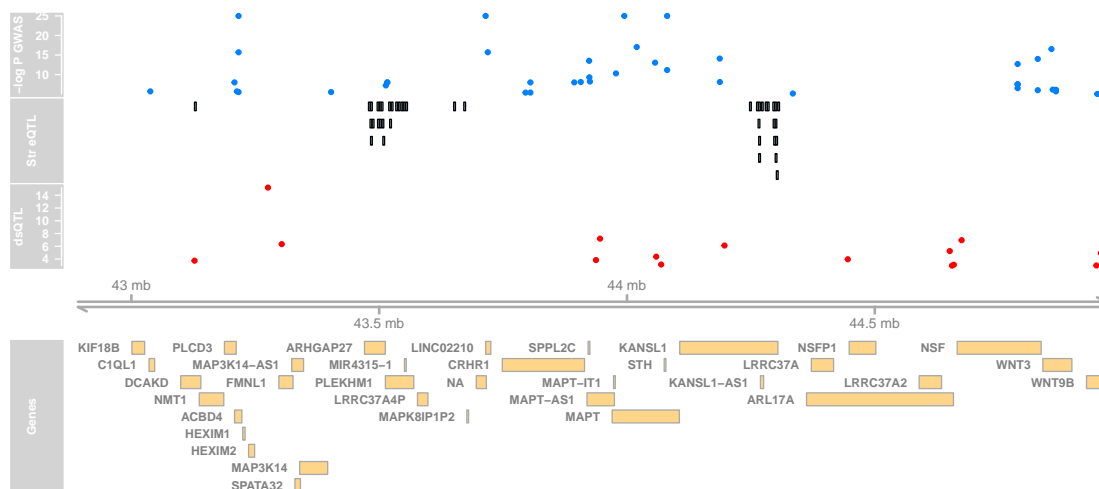
```
> g2 = GRanges(seqnames="chr17", IRanges(start=4.3e7, width=2e6))
> seqlevelsStyle(ebicat37) = "UCSC"
> basic = gwcex2gviz(basegr = ebicat37, contextGR=g2, plot.it=FALSE)
```

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
rs12951413 chr17:135237 rs9915773 chr17:135524 chr17:135981 rs11652478
rs11653478 rs12946667 chr17:136397 chr17:136464 rs34700119 rs36047229
chr17:138726 rs28705960 chr17:139250 rs9891792 rs9912566 chr17:139747
chr17:139853 chr17:139901 chr17:139984 rs9912795 rs9905901 chr17:140586
rs12950277 rs9913719 rs11650366 rs9675256 chr17:141286 rs57803378
chr17:143043 rs7502760 rs7212943 rs6565707 rs7501694 rs12450463
rs7213496 rs12940213 rs12452413 chr17:144037 rs34724309 rs34223743
chr17:146378 rs11867532 rs34927789 rs11869552 rs28583833 chr17:147237
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rs9897769 rs9909725 chr17:78654024 rs12937511 chr17:78654554
[ 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"

```

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

```

NA06985	00	03	03	01	03	02	03
	rs7213008	rs7212865	rs10153238	rs11654695	rs8072649	rs8072804	
NA06985	01	03	03	03	03	03	
	rs11649979	rs12938802	rs11650641	rs1138504	rs11150884	rs9907477	
NA06985	01	01	03	01	03	02	
	rs7226358	rs8066107	rs9915268	rs8078223	rs9896436	rs4890192	rs8078929
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	rs4890194	rs9674467	rs8075084	rs4890171	rs4890197	rs4890198	rs12941826
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	rs8073847	rs3923018	rs11651800	rs3923017	rs11654890	rs11652984	
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	rs7213702	rs12449638	rs7217872	rs12937656	rs9908467	rs9896350	rs7207284
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	rs7222853	rs12602957	rs7223759	rs7221298	rs12452527	rs11150870	
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	rs4074549	rs11656610	rs7502120	rs12941632	rs4073769	rs7212603	
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	rs7208299	rs11869174	rs6565714	rs3934764	rs6565715	rs7215343	rs12942009
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	rs2465803	rs8078047	rs6502870	rs11657525	rs3926687	rs4790781	rs2716945
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	rs12952184	rs16944437	rs9900828	rs9903630	rs9904109	rs11871700	
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	rs3744579	rs3744580	rs3826450	rs16945280	rs4792166	rs972947	rs9896157
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	rs2011094	rs7212419	rs4791475	rs4792176	rs4791476	rs9890025	rs7218761
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	rs16940757	rs11650055	rs2322052	rs2322053	rs2874669	rs7217598	rs9913751
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	rs726800	rs1005637	rs1005639	rs6502283	rs8074072	rs17663499	rs4513137
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	rs11867181	rs2079627	rs8080210	rs11078169	rs11078170	rs11078171	
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	rs4508458	rs12453186	rs11652847	rs11654550	rs10521233	rs17587876	
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	rs11651688	rs11651718	rs765475	rs765476	rs917388	rs7222364	rs7222105
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	rs12449826	rs2322939	rs9890735	rs12450186	rs11658332	rs9914411	
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	rs11078176	rs9900362	rs7216617	rs2218343	rs2120187	rs11868265	
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	rs9910557	rs16948423	rs9890442	rs12937820	rs1867232	rs16948430	
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	rs16948435	rs12601543	rs12941937	rs16948439	rs7216216	rs12948848	
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	rs17590660	rs16948456	rs4519361	rs4542695	rs2322968	rs997205	rs16948476
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	rs4792396	rs7207162	rs9915220	rs17667266	rs2322969	rs1530361	rs1530358
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	rs1530357	rs9902668	rs9909073	rs9909353	rs4792397	rs4792398	rs8064349
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	rs9303099	rs1029688	rs1029687	rs7210165	rs11078224	rs11652668	
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	rs11078225	rs8079640	rs12943936	rs12945821	rs16949067	rs722554	
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	rs8071165	rs11078226	rs11871117	rs12450626	rs4792438	rs17616525	
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	rs16949074	rs9891372	rs17616591	rs12452978	rs17678774	rs11652402	
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	rs8073382	rs9905776	rs11657441	rs16949080	rs6502337	rs8065848	rs3785681
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	rs3785680	rs11868899	rs9910671	rs7210500	rs12603348	rs2323093	rs2323094
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	rs8073984	rs12449610	rs12937279	rs12939377	rs2323095	rs2323096	

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	rs2323097	rs2874958	rs1990234	rs9303100	rs16949103	rs7212977	rs8070339
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	rs8075612	rs8079642	rs8081414	rs12936411	rs2530377	rs12453546	rs2856183
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	rs2530376	rs2530375	rs9913639	rs2530373	rs2530370	rs2530368	rs2259118
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	rs2856185	rs16949118	rs2856147	rs3020869	rs12941439	rs2158978	
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	rs16949234	rs12449595	rs2529629	rs12453877	rs2529627	rs2856177	
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	rs2023485	rs9901316	rs2529626	rs917309	rs2856178	rs10521264	rs8077231
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	rs2529625	rs3826366	rs917308	rs9901549	rs12452172	rs3785662	rs3785659
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	rs12601148	rs4792446	rs1050214	rs2230355	rs11078233	rs11078234	
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	rs7214082	rs1802618	rs2071245	rs1050216	rs1050223	rs11869719	rs11869759
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	rs11869709	rs4792447	rs7211577	rs7212116	rs12951559	rs12944270	
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	rs12945766	rs12150130	rs12150136	rs4792448	rs11871019	rs8080585	
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	rs16949277	rs11656595	rs8065030	rs4792449	rs11655445	rs12946884	
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	rs17617684	rs7218697	rs7223903	rs17679866	rs4792453	rs4792454	rs2323221
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	rs9903896	rs8067063	rs1859905	rs1859904	rs17680043	rs2874993	rs7503943
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	rs12453856	rs12453899	rs11078236	rs11078237	rs12450424	rs16949314	
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	rs11868525	rs16949319	rs7214616	rs4792461	rs9911711	rs960296	rs3815271
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	rs4284690	rs4303583	rs4303584	rs4303585	rs4303586	rs1465243	rs1465242

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	rs7220012	rs755732	rs755730	rs733769	rs12942020	rs7223714	rs2190626
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	rs886864	rs886863	rs719470	rs16949359	rs9896731	rs2190625	rs11870163
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	rs4792467	rs4791571	rs886862	rs9890556	rs4791573	rs16949371	rs4791574
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	rs2323174	rs9907589	rs9908363	rs3785658	rs9303102	rs1005322	rs1005321
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	rs740379	rs11078240	rs4792468	rs4792469	rs3826365	rs9890648	rs758049
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	rs7221273	rs11870395	rs12373159	rs12103925	rs7222205	rs4792471	
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	rs8080590	rs726942	rs7211702	rs2108461	rs9900779	rs1015663	rs2058044
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	rs9890916	rs9891555	rs740376	rs6502345	rs11870724	rs9909862	rs720873
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	rs7222164	rs1859906	rs917310	rs1871784	rs7217818	rs11552190	rs1053326
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	rs2291208	rs2086515	rs6502346	rs2199998	rs7225272	rs7226075	rs2127998
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	rs16949420	rs1994029	rs8069341	rs17619418	rs17619424	rs11078245	
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	rs16949426	rs8077326	rs17692591	rs11657444	rs17692633	rs17619645	
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	rs9914530	rs3912261	rs3912262	rs3912263	rs3912264	rs11651598	rs11651699
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	rs9303104	rs3848445	rs9972938	rs16949435	rs9909883	rs9916577	rs9898158
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	rs2109168	rs2109169	rs2109173	rs8081226	rs8081719	rs9892049	rs9892569
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	rs12953125	rs10521277	rs9895361	rs12947004	rs12945756	rs1019153	
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	rs1019155	rs17704478	rs16950020	rs7221028	rs9890809	rs16950022	
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	rs16950027	rs4424942	rs16950031	rs9900688	rs1465268	rs16950032	

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	rs16940920	rs8074303	rs8074490	rs8074531	rs9901465	rs8074969	rs16950033
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	rs12941773	rs12936630	rs9890349	rs12602267	rs12602281	rs9899112	
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	rs8078839	rs8078841	rs11653343	rs9909142	rs7218835	rs7217839	rs7218561
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	rs9915846	rs8075436	rs8080695	rs4597355	rs17646648	rs9897221	rs9897655
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	rs7216570	rs7208340	rs8182248	rs7208936	rs7210007	rs8182247	rs8065954
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	rs4791613	rs8075196	rs17647512	rs11869796	rs8079915	rs8080696	
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	rs17770949	rs16950980	rs8065619	rs2323556	rs16950991	rs9889878
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	rs9891067	rs230956	rs230960	rs230961	rs170745	rs7213079	rs230963	
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	rs9905479	rs7503412	rs28392580	rs7502225	rs11653100	rs11653209	
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	rs11078366	rs6502556	rs8068587	rs4985714	rs8066877	rs8070944	rs16961288
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	rs2670550	rs2670549	rs11653655	rs7215588	rs12450213	rs8064296	rs8065260
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	rs9903294	rs2472689	rs1630656	rs11867522	rs8072407	rs3182911	rs7219012
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	rs12944514	rs11658544	rs16960167	rs7214134	rs2428589	rs2428588	
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	rs12451469	rs2428580	rs2453614	rs16960177	rs9906930	rs7225055	rs7225894
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	rs2240097	rs2240096	rs7213572	rs8068853	rs7214851	rs8078268	rs4924996
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	rs8076975	rs2453603	rs8072992	rs7211758	rs7222869	rs8067420	rs1470318

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	rs11871259	rs2440153	rs2453580	rs751259	rs894680	rs12943918	rs8080953
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	rs2018675	rs2453583	rs735579	rs2453584	rs9905246	rs2440154	rs12451696
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	rs2440155	rs2453585	rs2453576	rs1808941	rs2014082	rs2453574	rs2453573
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	rs7219149	rs11650156	rs2247518	rs2289668	rs8076893	rs9909350	rs16960201
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	rs2453569	rs2453568	rs720252	rs16960202	rs16960203	rs2244280	rs2440150
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	rs1443460	rs2289669	rs16960206	rs2289670	rs8081204	rs9900821	rs8076891
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	rs8065082	rs11657807	rs2289667	rs2289666	rs11871177	rs716126	rs1961669
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	rs2253611	rs2250486	rs2453599	rs10735	rs3803838	rs2453594	rs2120273
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	rs2453589	rs2165894	rs7222948	rs2245724	rs2245639	rs2453586	rs2165895
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	rs7216938	rs9674673	rs2440161	rs11656199	rs12949521	rs2440162	rs2440163
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	rs2453602	rs17684040	rs4598966	rs2012843	rs2453604	rs1806922	rs11654072
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	rs7342960	rs11650399	rs12604069	rs12946324	rs8080984	rs2120274	
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	rs16960251	rs4273101	rs2453608	rs7405862	rs7502992	rs12941194	rs7215257
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	rs9914765	rs8079648	rs7225451	rs7210433	rs1470317	rs11871420	rs9889632
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	rs8064748	rs8074500	rs4925026	rs8065688	rs11871642	rs4621031	rs3888642
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	rs11204407	rs9901895	rs4925036	rs1004490	rs1004491	rs4646794	rs4646795
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	rs962801	rs962800	rs2072332	rs4646798	rs1034897	rs2386145	rs16960280
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	rs1800869	rs4646801	rs4646802	rs2108971	rs8073767	rs4646804	rs4244600
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	rs7216	rs7215	rs3760489	rs11868363	rs4646807	rs8074204	rs12937179

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	rs12453474	rs11658227	rs8081130	rs16960349	rs8064572	rs8079625	
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	rs4925044	rs16960360	rs12325921	rs7222445	rs9900497	rs4925045	rs758427
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	rs2891935	rs7213388	rs11656096	rs7206967	rs11657205	rs9910370	rs2010744
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	rs7214841	rs4924793	rs1006553	rs12948881	rs11650088	rs2108967	rs1006556
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	rs4319825	rs1042183	rs917520	rs2228100	rs3744695	rs3744694	rs3744693
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	rs3744692	rs3786036	rs2072330	rs2072329	rs9895030	rs4646790	rs2072328
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	rs887241	rs887240	rs887239	rs4646789	rs4646788	rs4646787	rs12951039
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	rs2072327	rs4646786	rs4646785	rs4646784	rs4646783	rs3760487	rs7221211
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	rs9905570	rs205094	rs1662214	rs1638522	rs205093	rs205090	rs176098
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	rs9897295	rs184006	rs205088	rs169512	rs9915902	rs11656704	rs9894723
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	rs157397	rs157398	rs169513	rs205103	rs205104	rs9905538	rs8064549
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	rs6587207	rs8080190	rs7224567	rs7224875	rs9915039	rs4925067	rs8079093
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	rs9901862	rs10459970	rs8082671	rs6587208	rs6587209	rs4577147	rs7210751
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	rs9914328	rs7221669	rs3909257	rs1182231	rs12946508	rs7219688	rs16960644
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	rs8072517	rs3930821	rs11656284	rs9908154	rs9907149	rs9916049	rs2958478
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	rs7223285	rs11657497	rs1564296	rs17052362	rs11656087	rs1985718	
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	rs7214074	rs2342184	rs7216763	rs9912295	rs17052370	rs2342183	rs12948022
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	rs4889746	rs8081093	rs8069215	rs11867688	rs899418	rs2880273	rs2880272
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	rs8076832	rs7359574	rs1121327	rs2169915	rs7502023	rs8079247	rs1842110
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	rs899414	rs11871520	rs755583	rs755584	rs2199698	rs4993505	rs12949684
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	rs4993506	rs4993507	rs4993511	rs981637	rs12051613	rs12601480	rs8069077
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	rs8066323	rs7215861	rs7215892	rs1871323	rs6565377	rs12943366	rs1159589
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	rs1842109	rs12450492	rs4393617	rs4889721	rs9989453	rs2169914	rs2169913
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	rs6565378	rs1985878	rs1985877	rs7218015	rs11651208	rs17052396	rs2061853
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	rs7225244	rs6565381	rs8068034	rs11150718	rs7350915	rs12940235	
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	rs12948134	rs2880292	rs12103516	rs11658486	rs8075964	rs7218889	
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	rs2169916	rs1877500	rs1817415	rs1382623	rs12950467	rs2219805	rs9897562
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	rs12937394	rs6565386	rs8072844	rs402052	rs3751916	rs2019216	rs8073228
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	rs907708	rs907707	rs9896042	rs2342216	rs12450390	rs1850565	rs8065425
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	rs8066357	rs1512846	rs12452224	rs12450074	rs907704	rs17052434	rs1518049
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	rs7215275	rs12940712	rs4889733	rs17808614	rs11150722	rs9891438	
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	rs8079620	rs12937428	rs7220319	rs12449520	rs4889742	rs1040269	rs932219
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	rs7212653	rs1915048	rs11150728	rs2002203	rs8076748	rs2077219	rs1829489
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	rs7213631	rs1818692	rs4889744	rs11868088	rs9908622	rs11869580	rs1829491
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	rs11868335	rs2203931	rs7222514	rs8070275	rs8066332	rs11658968	
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	rs8080725	rs7225129	rs12942556	rs11868559	rs12150105	rs12944067	
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	rs1850005	rs1515750	rs1973661	rs2292697	rs2292698	rs9807046	rs12453646
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	rs11080119	rs8079454	rs7503713	rs3930206	rs9748137	rs9748024	rs9893017
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	rs4302084	rs7213094	rs1976838	rs5015403	rs4795878	rs11868485	rs11653494
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	rs9910343	rs16966494	rs11867343	rs7218531	rs11656707	rs11871417	
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	rs2313050	rs4795077	rs7215009	rs4796099	rs1851271	rs7226210	rs7221571
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	rs12600900	rs12600912	rs2139942	rs11080048	rs11658274	rs9912637	
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	rs1969373	rs1521563	rs12103473	rs11657456	rs7225143	rs12453728	
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	rs7212623	rs11871008	rs2948534	rs2948533	rs2945384	rs2948532	rs10775412
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	rs4795816	rs4267373	rs9303666	rs9898153	rs9912493	rs2241906	rs1075952
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	rs9905566	rs3094272	rs4795835	rs4794975	rs12949932	rs3094274	rs732222
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	rs4239242	rs361499	rs4794976	rs16966434	rs3107064	rs8368	rs9899312

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	rs8075943	rs11080261	rs9899871	rs11080266	rs9896280	rs4523974	
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	rs9907600	rs9891469	rs12952498	rs4538061	rs4239246	rs9890882	rs4794996
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	rs11868072	rs6505406	rs4795911	rs7209966	rs10454091	rs10454092	
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	rs11080289	rs12948602	rs7218693	rs9901359	rs9908208	rs9897012	rs9897029
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	rs9901551	rs7208810	rs12952168	rs917631	rs16965715	rs11080124	
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	rs17803815	rs2058284	rs3764417	rs717663	rs7220213	rs9913111	rs4795549

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	rs216451	rs216452	rs186262	rs2874671	rs216455	rs216457	rs170053
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	rs315439	rs4795630	rs315440	rs1126172	rs1126173	rs12452086	rs1421131
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	rs385535	rs373531	rs17246595	rs9896472	rs9915783	rs952581	rs7223114
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	rs1948606	rs11657231	rs9303662	rs8081544	rs1908958	rs10432046	
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	rs10432047	rs10432048	rs12103815	rs8078963	rs6505334	rs4499288	
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	rs1391077	rs11651260	rs11651326	rs9914417	rs8081703	rs8080646	rs9916185
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	rs10459963	rs320643	rs9911125	rs9905033	rs12449358	rs320645	rs8081861
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	rs7207679	rs35024811	rs320628	rs320629	rs1504575	rs63953	rs63954
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	rs320631	rs7223147	rs963048	rs320633	rs320637	rs320638	rs320641

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	rs400843	rs445907	rs1875873	rs424892	rs447040	rs17836780	rs1874604
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	rs12449721	rs17249146	rs320642	rs2036537	rs9674859	rs3104299	rs7217704
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	rs2174341	rs12449923	rs17184727	rs12943787	rs12937449	rs12937459	
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	rs377066	rs412602	rs374430	rs431564	rs2645983	rs2656087	rs16963766
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	rs4795768	rs17836785	rs733136	rs452439	rs439783	rs9915690	rs4795769
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	rs12946336	rs2014285	rs2014268	rs17249181	rs11653379	rs7224450	rs950537
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	rs6505336	rs7501738	rs1504573	rs1394388	rs12449795	rs9901182	rs7503350
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	rs959338	rs12450971	rs11868983	rs11868989	rs10512443	rs7213724	
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	rs1394387	rs1394386	rs1394385	rs7223760	rs11080213	rs7219978	rs7224859
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	rs1504582	rs16968252	rs924846	rs924847	rs1007034	rs1007035	rs16968253
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	rs1007033	rs17184825	rs1039578	rs1979909	rs4795770	rs1394393	rs1394394
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	rs1394395	rs6505337	rs7220131	rs11652103	rs11656759	rs7215745	rs8074678
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	rs6505338	rs9896958	rs2347154	rs905754	rs871764	rs17782182	rs1394392
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	rs1394391	rs931796	rs1995526	rs1995525	rs1504581	rs17184873	rs8072171
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	rs1875875	rs931795	rs1504580	rs11080214	rs7224966	rs7226138	rs7207448
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	rs12150421	rs7207801	rs11867162	rs1021892	rs12946750	rs1021891	
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	rs2089164	rs12941575	rs7225320	rs7220791	rs8074495	rs11652948	rs1504577
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	rs1394389	rs12946200	rs11652495	rs1394390	rs11658120	rs12951547	
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	rs4353517	rs9895229	rs7207476	rs11080216	rs4794947	rs11657729	
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	rs17184908	rs10853155	rs9898140	rs11080217	rs4795778	rs9914451	
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	rs11080218	rs12950864	rs11655499	rs12601602	rs8073613	rs7207391	

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	rs1504579	rs8078262	rs17185000	rs8076691	rs8082353	rs8076841	rs16968314
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	rs4794949	rs4795781	rs16968318	rs17782332	rs1827650	rs17782343	
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	rs17185036	rs16963769	rs9901960	rs9902936	rs17185057	rs16968321	
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	rs17185084	rs9904433	rs7213646	rs8075266	rs4572456	rs17836803	rs2036535
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	rs9915725	rs4795783	rs4795784	rs4795785	rs1472742	rs12953219	rs1504576
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	rs9709314	rs9709422	rs9894658	rs4795791	rs7502868	rs11656800	rs11656544
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	rs9913678	rs12940736	rs1354489	rs972860	rs12162163	rs2347151	rs4286149
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	rs13341020	rs7221119	rs12602581	rs2347155	rs905752	rs9903070	rs11656936
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	rs11657983	rs12450871	rs1123025	rs1123024	rs12451584	rs7210023	
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	rs17836818	rs12450545	rs9898160	rs4510072	rs4794950	rs9892208	
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	rs9914228	rs9908799	rs7219482	rs12603550	rs7221002	rs12601996	rs1995523
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	rs12952607	rs952541	rs1394384	rs952540	rs12601163	rs869097	rs2881565
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	rs9635766	rs12944010	rs17836824	rs1472740	rs1472741	rs12937545	
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	rs4513141	rs7208436	rs7209964	rs1504570	rs1875872	rs1857737	rs17249479
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	rs9915618	rs7222281	rs7207388	rs1504571	rs1553495	rs9894197	rs1553496
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	rs4795795	rs4795797	rs17249521	rs12602517	rs12600630	rs12600538	
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	rs10512445	rs17249577	rs1347351	rs17249591	rs12103532	rs1865392	
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	rs12185231	rs12185267	rs9909130	rs4794966	rs977296	rs977295	rs7502177
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	rs16968774	rs11869137	rs12938529	rs2046898	rs2046899	rs4474738	
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	rs2347558	rs2347559	rs16968785	rs4795826	rs6505373	rs7207102	rs989956
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	rs989957	rs9897152	rs6505374	rs2029531	rs12938719	rs989353	rs7223612
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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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	rs4795904	rs8081356	rs1860180	rs8073784	rs17809115	rs3919504	rs7504095

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	rs11656007	rs11656109	rs11652256	rs8075846	rs9905791	rs2215185	
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	rs12451323	rs2041190	rs2215184	rs16969449	rs4795908	rs16969454	
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	rs12453746	rs16969457	rs12449657	rs12452741	rs4100073	rs1233653	
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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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	rs1431991	rs3136674	rs3136675	rs3136676	rs3136677	rs159313	rs2072069
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	rs2072070	rs159314	rs159315	rs159316	rs11575025	rs159317	rs159318
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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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	rs212462	rs212463	rs212464	rs212465	rs212466	rs169862	rs167171
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	rs159247	rs150509	rs150511	rs150512	rs150514	rs2118232	rs150516
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	rs159245	rs150521	rs4795917	rs7217062	rs159244	rs16969797	rs17577327
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	rs159236	rs210812	rs159237	rs1036494	rs1036492	rs11080273	rs159240
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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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	rs210832	rs210833	rs210834	rs1030603	rs12950822	rs212448	rs191931
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	rs176931	rs8065093	rs295066	rs295067	rs8076080	rs12602394	rs12951119
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	rs17614930	rs12947419	rs1431993	rs295094	rs7214235	rs11651716	rs7216203
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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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	rs213141	rs213142	rs7214683	rs4795929	rs9898608	rs4795004	rs9899090
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	rs887229	rs887228	rs4996565	rs16970084	rs11654085	rs11080285	rs7215934
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	rs12938657	rs12950814	rs968891	rs9916771	rs16970282	rs9896407	rs8074211
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	rs17666879	rs4795998	rs8067477	rs4795999	rs12451550	rs11080297	rs723704

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	rs2159223	rs9898213	rs9899592	rs887081	rs12453075	rs4795044	rs12951090
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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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	rs9892982	rs2339211	rs9898801	rs11652524	rs9674621	rs11652046	rs9894585
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	rs730547	rs12051815	rs2009052	rs11080301	rs1008094	rs7222275	rs4616327
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	rs10853173	rs8066240	rs11080302	rs6505432	rs6505433	rs7213106	
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	rs11080303	rs10512465	rs4796004	rs11080304	rs17544779	rs11656880	
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	rs11653855	rs8072551	rs715111	rs11654328	rs7208329	rs11655777	
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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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	rs4796010	rs9895219	rs12150271	rs12150241	rs234824	rs17627806	
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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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	rs11651360	rs7359659	rs7359660	rs12942949	rs17545366	rs234828	
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	rs10445389	rs12601965	rs12600682	rs234829	rs8067780	rs4796011	rs170923
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	rs12945685	rs12945921	rs234831	rs11652590	rs17545471	rs9893892	

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	rs234835	rs11658261	rs11871805	rs17146	rs16970422	rs4796012	rs11080311
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	rs234818	rs234819	rs17545903	rs2339116	rs11658047	rs4796013	rs7223630
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	rs7211280	rs7210677	rs900206	rs11080312	rs900207	rs754791	rs12601180
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	rs12953044	rs12452723	rs7213591	rs7211660	rs7213451	rs11651066	
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	rs12449962	rs7220083	rs7213132	rs975126	rs6505435	rs11653582	rs12451451
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	rs4796014	rs12945282	rs1482104	rs9910965	rs4280300	rs7209401	rs11655339
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	rs4796020	rs16970461	rs11868737	rs12937810	rs11868554	rs2062101	
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	rs8249	rs7208342	rs8075549	rs8076878	rs4041564	rs2339120	rs1351554
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	rs3135991	rs3135992	rs3135993	rs3135996	rs3135997	rs3135998	rs3136000
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	rs3136021	rs3136022	rs3136023	rs3136025	rs3136026	rs4986974	rs3136028
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	rs9913773	rs9892424	rs6505438	rs8067493	rs2240074	rs10853174	rs3926358
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	rs9914089	rs16970607	rs10491117	rs16970611	rs3937429	rs11868399	
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	rs11080320	rs9891230	rs11650161	rs12947947	rs9914109	rs4796032	
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	rs2622524	rs9893542	rs16970808	rs2671822	rs2622525	rs2671820	rs11080335
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	rs17550632	rs12452797	rs17637907	rs2840044	rs321601	rs9891887	
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	rs17550716	rs11653310	rs16971128	rs11655098	rs9891563	rs12600662	
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	rs183435	rs2604845	rs16971207	rs2604844	rs225249	rs17669281	rs17606150
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	rs8065607	rs8069816	rs4794762	rs4794763	rs7212656	rs4794764	rs9904684
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	rs11653037	rs17138919	rs2176395	rs4794766	rs2138733	rs8080584	rs1914365
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	rs7222985	rs8068600	rs11867558	rs8070847	rs9900623	rs9895316	rs8074124
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	rs3803749	rs2471623	rs3902482	rs2471624	rs3884068	rs8070036	rs2429994
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	rs11079059	rs7219106	rs12450778	rs12949337	rs12942093	rs7221033	
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	rs228274	rs4907	rs228275	rs668461	rs9903126	rs11656344	rs2306882
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	rs228286	rs3744070	rs2241014	rs228287	rs228288	rs228289	rs228290
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	rs16531	rs16534	rs2240083	rs16537	rs521633	rs16530	rs3025213	rs559502
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	rs9908131	rs8069194	rs7223438	rs6503507	rs4511574	rs11078898	rs7221875
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	rs7208487	rs8065896	rs7215002	rs8073144	rs9906612	rs8077629	rs8077259
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	rs10491128	rs12600751	rs8076546	rs9904919	rs6503512	rs3814885	rs6503513
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	rs7211837	rs1139825	rs4795357	rs4795358	rs11656614	rs7501488	rs7226222
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	rs4795369	rs11655550	rs4533315	rs12938099	rs4611492	rs9896487	
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	rs11654535	rs4390625	rs12940881	rs11078901	rs11078902	rs11078903	
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	rs12449852	rs4426376	rs9893757	rs9894037	rs12948906	rs11870631	
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	rs8077658	rs2018026	rs6503518	rs12943456	rs11078907	rs7225096	
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	rs12936996	rs12937013	rs8069155	rs11868837	rs7503705	rs11078912	
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	rs11078913	rs2303315	rs4795379	rs9916852	rs11658678	rs8065963	rs4404103
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	rs7226073	rs4795380	rs8069074	rs12450559	rs4239222	rs7503069	rs16965156
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	rs11657058	rs11657153	rs11654018	rs2303316	rs12947506	rs7503377	
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	rs7216086	rs7342947	rs9972899	rs17604809	rs11078915	rs6503521	
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	rs12938115	rs4795384	rs4488484	rs12602067	rs12944298	rs7503195	
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	rs8081144	rs7218361	rs903507	rs8182252	rs7224759	rs1874226	rs11653404
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	rs4795385	rs11657812	rs9909879	rs412430	rs1619021	rs1877030	rs388548
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	rs3907837	rs998480	rs9916503	rs9889354	rs380373	rs12453736	rs12453682
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	rs14050	rs2952151	rs2941503	rs907087	rs2247862	rs903502	rs2941504
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	rs1565922	rs2934955	rs2934954	rs2934953	rs2934952	rs2941505	rs2941506
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	rs9892376	rs2517954	rs2517955	rs2517956	rs2517961	rs12601489	rs8182267
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	rs9911069	rs9908983	rs8076347	rs12942660	rs2060941	rs9910852	rs9911017
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	rs12946188	rs12946792	rs16965360	rs3816470	rs9913769	rs12945253	
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	rs3169572	rs2278894	rs7942	rs4378650	rs8076131	rs9910635	rs12603332
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	rs9916279	rs17855429	rs8066582	rs8080546	rs11652139	rs11658328	
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	rs25645	rs2227331	rs12602956	rs2827	rs1042657	rs2227332	rs1042658
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	rs2227334	rs1045929	rs12309	rs709592	rs709591	rs16965540	rs2270401
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	rs9915684	rs7503939	rs9916158	rs2302775	rs2302774	rs8071421	rs9709063
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	rs16965916	rs9902392	rs3136695	rs3136694	rs2229095	rs2023906	rs3136689
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	rs588019	rs2290065	rs3136688	rs16965949	rs3136687	rs11574664	rs11574663
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	rs11078949	rs1018953	rs3136686	rs3136685	rs7218603	rs12453886	
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	rs12603336	rs7221109	rs8074179	rs803129	rs9895632	rs9894823	rs757411
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	rs2429549	rs16966134	rs2462961	rs12946793	rs12945784	rs8068810	
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	rs17574228	rs7521	rs10445372	rs7502673	rs11870461	rs7350928	rs17574361
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	rs17652961	rs17574425	rs7220988	rs1076222	rs1078997	rs7212164	rs7350980
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	rs4597358	rs17574604	rs17653162	rs16940834	rs17653193	rs17653211	
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	rs12185243	rs8077487	rs11079729	rs12150542	rs12150090	rs7221390	
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	rs1102461	rs858677	rs701982	rs11570480	rs221605	rs11570475	rs11570466
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	rs2734274	rs2277633	rs2696245	rs2277634	rs2586488	rs1800215	rs2075559
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	rs2696298	rs11652870	rs12150329	rs7223741	rs11079902	rs9903154	
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	rs202122	rs8082027	rs17590785	rs202121	rs202120	rs202119	rs202118
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	rs1106350	rs4147523	rs3764389	rs7214475	rs7225739	rs4239191	rs4627424
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	rs17817797	rs11871712	rs1344547	rs10515093	rs12450116	rs1477143	
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	rs1114603	rs7223639	rs11656169	rs11656277	rs6504958	rs10852974	
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	rs7211945	rs7213385	rs2287222	rs2287223	rs1465353	rs4316816	rs9906846
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	rs9892566	rs2024498	rs12450222	rs17210733	rs1123937	rs12942558	
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	rs9905382	rs9893283	rs3744086	rs12943166	rs11649815	rs8071182	rs8071058
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	rs9890485	rs8072613	rs11079483	rs11079484	rs9901682	rs6504123	rs8067559
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	rs8067172	rs8066771	rs917560	rs1558239	rs1974598	rs17746711	rs8064732
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	rs4644910	rs2041279	rs17684593	rs11655826	rs4968629	rs8080560	rs7226286

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	rs1860339	rs9910639	rs16946471	rs1860336	rs3901444	rs6504124	rs7504097
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	rs17747354	rs4968743	rs11867290	rs9893305	rs11870240	rs9896726	
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	rs9907967	rs8078012	rs8067624	rs9901698	rs17758538	rs9903162	rs9906152
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	rs12950220	rs7220224	rs11659015	rs8081885	rs1125406	rs4380108	rs4591205
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	rs8077625	rs4422037	rs4630614	rs4578727	rs9908887	rs12948372	rs11868614
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	rs8081977	rs12451929	rs11871421	rs8071111	rs8182298	rs8077260	rs8182324
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	rs6504130	rs8064710	rs8082613	rs8067960	rs7226368	rs12603939	rs1476811
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	rs1476812	rs12943559	rs9903891	rs12952864	rs2109263	rs12103554	
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	rs12051594	rs9915826	rs9303464	rs8081770	rs9912821	rs12601553	rs8075749
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	rs8081798	rs6504132	rs9909378	rs887400	rs9914779	rs7208765	rs8070469
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	rs7216408	rs3999623	rs4968744	rs6504134	rs9903993	rs7224903	rs7226117
NA06985	03	01	01	03	01	03	03
	rs9807025	rs9807045	rs9807049	rs9912023	rs16946586	rs16946590	rs7223963
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	rs7225167	rs9913598	rs11655365	rs7217322	rs9906948	rs7220785	rs7212412
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	rs9907758	rs9892218	rs7224038	rs16946625	rs9903532	rs17686192	
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	rs17759579	rs17759603	rs17686364	rs1548739	rs1548740	rs16946650	
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	rs9911127	rs8068079	rs7207214	rs9907865	rs16946732	rs239365	rs239364
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	rs1319247	rs7212556	rs17745114	rs7209974	rs2109653	rs17745138	rs9906570
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	rs4290	rs4293	rs760281	rs4295	rs4297	rs3730021	rs4299
	rs4301	rs3730025					
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	rs4303	rs4305	rs13306085	rs4309	rs4311	rs12720746	rs4314
	rs12709426						
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	rs4316	rs4317	rs4318	rs4324	rs4325	rs4329	rs4333
	rs12709430	rs1987693					
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	rs4343	rs13306091	rs3730036	rs4344	rs4345	rs12709434	rs4349
	rs12720727						
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	rs12720728	rs12720724	rs4351	rs12936400	rs4353	rs4976	rs13306084
	rs4357						
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	rs7220646	rs12450683	rs2854152	rs2246323	rs3020607	rs2070680	rs2727308
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	rs3020619	rs4080076	rs5388	rs6174	rs3744287	rs4341800	rs2001344
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	rs7219235	rs2854184	rs7209608	rs2532114	rs2532115	rs2907396	rs11657170
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	rs2005132	rs2320125	rs2003549	rs2286565	rs16947270	rs9911257	rs1860334
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	rs1395826	rs1395825	rs17713225	rs11870521	rs9899635	rs7221351	rs740804
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	rs12950044	rs7222835	rs7406143	rs6416955	rs6416958	rs6504563	rs12944942
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	rs2947862	rs10445226	rs10445206	rs10445207	rs9903306	rs2947887	
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	rs16974253	rs2905439	rs1121381	rs2428347	rs7214397	rs17762511	rs7224395

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	rs6501341	rs16974265	rs4381637	rs4381638	rs12937601	rs17762595	
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	rs8064791	rs2905370	rs543279	rs2214207	rs2188783	rs4506945	rs471194
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	rs2188698	rs12949316	rs2947879	rs1157845	rs12942463	rs16974282	
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	rs16974286	rs7208359	rs7208086	rs7226266	rs16974294	rs2905364	rs8070789
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	rs2157988	rs2051734	rs2285572	rs10512528	rs2947872	rs16974315	
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	rs12951576	rs9895917	rs8182257	rs2947871	rs2947870	rs1858969	rs2947869
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	rs1119753	rs1119752	rs16966924	rs2947868	rs2012628	rs2012061	rs2947883
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	rs12601748	rs1967299	rs1859426	rs12947839	rs8078070	rs11077460	rs956255
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	rs4488494	rs12939860	rs7222686	rs16974335	rs16974337	rs10445208	
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	rs8071754	rs8070733	rs2189755	rs4141190	rs4141192	rs8077406	rs2107606
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	rs4968863	rs1473120	rs2057823	rs2057822	rs16974356	rs12452498	
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	rs11868063	rs757531	rs757530	rs11652982	rs11654389	rs8066785	rs8066367
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	rs1987598	rs970561	rs12602917	rs16974392	rs7212316	rs7213660	rs6501346
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	rs3744488	rs747886	rs739549	rs739548	rs9899484	rs2106607	rs10512532
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	rs180142	rs180139	rs180138	rs180135	rs8067741	rs8077328	rs180134
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	rs16974662	rs13342669	rs13342680	rs8066354	rs7222428	rs2106611	rs180100
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	rs9891420	rs180076	rs9895362	rs180074	rs9896571	rs180073	rs9904930
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	rs9907896	rs180052	rs12453357	rs8080450	rs9895890	rs8079591	rs17699266
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	rs4519370	rs1013996	rs7223525	rs1013995	rs7209397	rs2190605	rs917299
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	rs1024574	rs968231	rs968232	rs7210827	rs8068029	rs7216332	rs4436822
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	rs9895144	rs9914814	rs236533	rs657282	rs656918	rs656367	rs9913208
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	rs236550	rs4538053	rs236551	rs236552	rs236553	rs236554	rs236555
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	rs236556	rs9896235	rs236557	rs236558	rs236559	rs9891872	rs7213181
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	rs312718	rs7223241	rs312719	rs4968890	rs312721	rs7214819	rs312723
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	rs17715333	rs312725	rs312726	rs312727	rs11077488	rs6501384	rs411079
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	rs432241	rs236577	rs427309	rs427986	rs431930	rs683896	rs17715538
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	rs12945349	rs12948615	rs8078592	rs188744	rs312699	rs236575	rs192853
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	rs312702	rs7217963	rs12951087	rs312703	rs312705	rs236576	rs7222503
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	rs16975529	rs9901891	rs7208007	rs312707	rs8080802	rs7225313	rs7224535
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	rs7207089	rs312740	rs312741	rs17716015	rs312742	rs17716021	rs312743
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	rs7209774	rs16975575	rs8072128	rs312688	rs11653931	rs312690	rs10775360
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	rs17763583	rs312691	rs16975583	rs4462644	rs312677	rs12947451	rs11654895
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	rs17175927	rs8064240	rs312747	rs16975594	rs16975596	rs312749	rs12603464
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	rs312762	rs312763	rs312764	rs312768	rs3915641	rs312770	rs9911531
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	rs421333	rs413073	rs16975961	rs532348	rs9904090	rs16975968	rs9911708
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	rs11657522	rs4793507	rs17823681	rs1468456	rs10512553	rs982985	rs982986
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	rs8065654	rs17823861	rs12453255	rs9909682	rs12944804	rs2041054	
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	rs9893719	rs9902135	rs4793354	rs2051978	rs7216083	rs7216099
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	rs7208178	rs11077568	rs7226156	rs9902420	rs9302937	rs2190712
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	rs9907236	rs2215059	rs4793355	rs8076723	rs17179656	rs16976696
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	rs10512569	rs10512570	rs10512571	rs11654195	rs12945199	rs12943436
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	rs11655127	rs8069860	rs9901464	rs12935876	rs16976701	rs11653238
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	rs12325887	rs11656077	rs12948809	rs12945824	rs12947902	rs12947941
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	rs8068580	rs1859929	rs1859928	rs4793276	rs7220150	rs4793277	rs12451603
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	rs12942980	rs12450445	rs11077634	rs2567524	rs2060097	rs9907286	
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	rs11650965	rs12937112	rs16970220	rs7219060	rs12947286	rs11871706	
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	rs2411124	rs4294874	rs4296316	rs4586516	rs8076139	rs16970238	rs11650295
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	rs7219083	rs4789464	rs12103923	rs9915353	rs9913695	rs8082294	rs9892692
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	rs16970252	rs3826290	rs3826291	rs2410426	rs2410427	rs3916018	rs9891343
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	rs11655530	rs1508146	rs1508147	rs7226253	rs906559	rs906560	rs11868709
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	rs4789573	rs4789574	rs16971017	rs11871694	rs8067105	rs12938580	
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	rs9898952	rs12948040	rs11150739	rs12939413	rs9900445	rs8081444	
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	rs7503911	rs2315922	rs9913162	rs7359591	rs8072229	rs8072355	rs7359577
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	rs8072836	rs9899843	rs12941958	rs8069295	rs12951944	rs12941790	
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	rs9902376	rs9896771	rs12946115	rs12603074	rs10401045	rs2315921	
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	rs9915378	rs9891160	rs12940631	rs7503394	rs6565479	rs7406799	rs4889786
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	rs9674559	rs12941240	rs3764371	rs7213696	rs4602089	rs12942526	
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	rs3829572	rs3751945	rs2589156	rs2333988	rs7217580	rs2248502	rs2589155
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	rs12449697	rs12449703	rs9319620	rs9674879	rs9709386	rs1799919	rs2070871
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	rs4077074	rs4969468	rs4969467	rs4969461	rs4969477	rs9903371	rs9894004
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	rs12949488	rs15324	rs4246444	rs4246445	rs1140616	rs4547403	rs4502283
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	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="gwascat"), 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>.