

Introducción a la Genómica

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datos de SNPs

Cada programa tiene un formato diferente y es importante saber cambiar de formato

- ▶ PLINK: Es un programa compilado, corre por la linea de comandos y es muy rapido. Es particularmente util para manejar las bases de datos en si, exlcuir sujetos, seleccionar SNPs. No tiene la versatilidad de R para explorar graficos, crear nuevas funciones o hacer graficos, pero es muy utilizado y con experiencia en computacion facil de hacer pipelines.
- ▶ snpStats (bioconductor): Tiene varias funciones para ver la estructura de los datos (linakage-disequilibrium, pca, Fst), y hace analisis de asociacion en base de datos grandes, pero no prueba diferentes modelo de herencia. Usa un fromato especial (raw data).
- ▶ snpAssoc (r-cran): versatil para probar diferentes modelos de herencia, pero las funciones no estan optimizadas para manejar matrices muy grandes.
- ▶ tabix : un programa para gestionar datos en formato VCF usado por los 1000 genomas

Es un programa por linea de comandos desarrollado por Chrostopher Chang.

The screenshot shows the PLINK 1.9 website in a Mozilla Firefox browser. The page title is "PLINK 1.9 - Mozilla Firefox". The address bar shows "https://www.cog-genomics.org/plink2". The page has a navigation bar with links: "PLINK 1.9 home", "plink2-users", "GitHub", "File formats", "PLINK 1.9 index", and "PLINK 2.0".

The main content area is titled "PLINK 1.90 beta". It contains the following text:

This is a comprehensive update to Shaun Purcell's [PLINK](#) command-line program, developed by [Christopher Chang](#) with support from the [NIH-NIDDK's](#) Laboratory of Biological Modeling, the [Purcell Lab](#) at Mount Sinai School of Medicine, and others. ([What's new?](#)) ([Credits.](#)) ([Methods paper.](#))

Below this is a section titled "Binary downloads" with a table:

Operating system ¹	Build		
	Stable (beta 4.6, 15 Aug)	Development (6 Sep)	Old ² (v1.07)
Linux 64-bit	download	download	download
Linux 32-bit	download	download	download
OS X (64-bit)	download	download	download
Windows 64-bit	download	download	download
Windows 32-bit	download	download	download

Footnotes:

1: Solaris is no longer explicitly supported, but it should be able to run the Linux binaries.
 2: These are just mirrors of the binaries posted at <http://zzz.bwh.harvard.edu/plink/download.shtml>.

Source code, compilation instructions, and the like are on the [developer page](#).

The following documented PLINK 1.07 flags are not supported by 1.90 beta 4:

- `--qual-geno-scores`³
- `--segment`⁴
- `--dflam`
- `--tucc`

The left sidebar contains a list of links: Introduction, downloads, Recent version history, What's new?, Future development, Limitations, Note to testers, (Jump to search box), General usage, Citation instructions, Standard data input, PLINK 1 binary (.bed), Autosconversion behavior, PLINK text (.ped, .tped...), VCF (.vcf.gz), .bct, Oxford (.genl.gz), .bgem, 23andMe text, Generate random, Unusual chromosome IDs, Recombination map, Phenotypes, Covariates, Clusters of samples, Variant sets, Binary distance matrix, IBD report (.genome), Input filtering, Sample ID file, Variant ID file, Cluster membership, and Stat.manhattan.txt.

Tiene una documentación muy completa

PLINK

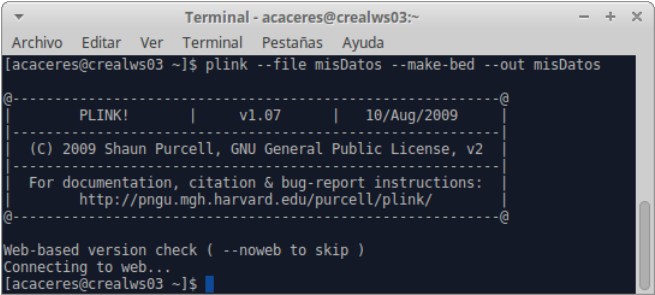
PLINK tiene dos formatos

- ▶ `.bed`, `.bim`, `.fam`: es el mas usado y separa la información en tres archivos genotipos (`.bed`), anotacion de SNPs (`.bim`), fenotipos (`.fam`)
- ▶ `.ped`, `.map`: `.ped` son los `.fam` en las primeras columnas y `.map` es una versión con menos info que `.bim`

PLINK

Para cambiar los formatos de misDatos.ped y misDatos.map a misDatos.bed, misDatos.bim y misDatos.fam

```
plink --file misDatos --make-bed --out misDatos
```



```
Terminal - acaceres@crealws03:~
Archivo  Editar  Ver    Terminal  Pestañas  Ayuda
[acaceres@crealws03 ~]$ plink --file misDatos --make-bed --out misDatos
@-----@
|          PLINK!          |          v1.07          |          10/Aug/2009          |
|-----|-----|-----|
| (C) 2009 Shaun Purcell, GNU General Public License, v2 |
|-----|-----|-----|
| For documentation, citation & bug-report instructions: |
| http://pngu.mgh.harvard.edu/purcell/plink/              |
|-----|-----|-----|
@-----@
Web-based version check ( --noweb to skip )
Connecting to web...
[acaceres@crealws03 ~]$
```

Datos de SNPs

Después del preprocesamiento de los datos, los datos que se obtienen es de un genotipo por individuo. Si tenemos 1 millón de SNPs y 1000 individuos, esto es típicamente una matriz de $10^3 \times 10^6$. Hay diferentes formas de organizar estos datos

	rs33	rs36	rs43	
NA090	A/C	G/G	T/A	...
NA091	A/A	G/G	T/A	...
NA092	A/A	G/C	T/A	...
NA093	A/C	C/C	A/A	...
...				

Datos de SNPs

Hay diferentes formas de organizar estos datos

	rs33	rs36	rs43	
NA090	A/C	G/G	T/A	...
NA091	A/A	G/G	T/A	...
NA092	A/A	G/C	T/A	...
NA093	A/C	C/C	A/A	...
...				

Una forma eficiente es llamar 0:homocigoto, 1:heterocigoto y 2:heterocigoto variante.

- ▶ para SNP=rs33 el alelo mas frecuente es A y el menos frecuente es C.

Entonces: A/A=0, A/C=1, CC=2

- ▶ para SNP=rs36 el alelo mas frecuente es G y el menos frecuente es C.

Entonces: G/G=0, G/C=1, CC=2

Datos típicos de SNPs (PLINK) formato bed

- Datos de los genotipos (datos.bed)

	rs33	rs36	rs43	
NA090	1	0	1	...
NA091	0	0	1	...
NA092	0	1	1	...
NA093	1	2	2	...
...				

Datos tipicos de SNPs (PLINK) formato bed

- Datos con la anotacion de SNPs (datos.bim)

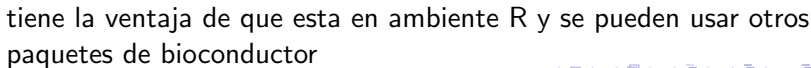
chr	snp	mor	pos	allele1	allele2
1	rs33	0	1034	A	C
1	rs36	0	2000	G	C
1	rs43	0	10056	T	A
...					

Datos típicos de SNPs (PLINK) formato bed

- Datos con los fenotipos (datos.fam)

ID	FAMID	sex	asthma	BMI-z
NA090	1	1	1	1.2
NA091	1	1	0	1.5
NA092	2	0	0	0.9
NA093	2	0	1	1

Es un programa en R (bioconductor)



SNPstats

se instalala como desde R por medio de los comandos

```
source("https://bioconductor.org/biocLite.R")  
biocLite("snpStats")
```

SNPstats

se carga con

```
library("snpStats")  
  
## Loading required package: survival  
## Loading required package: Matrix
```

puede leer datos de PLINK (formato .bed) mediante la función

```
snp<-read.plink(misDatos)
```

se pueden guardar como binarios de R snp.RData

```
save(snp, file="snp.RData")
```

también se pueden guardar datos de snpStats en PLINK con
`write.plink`

SNPstats

se pueden cargar los binarios snp.RData

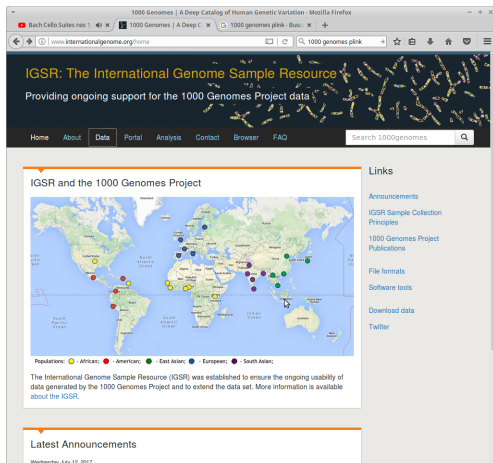
```
load("datos/snp.RData")
```

```
snp
```

```
## A SnpMatrix with 1500 rows and 439 columns  
## Row names: 1 ... 1500  
## Col names: 1 ... 439
```

1000 Genomes

Repositorio de datos de los 1000 genomas donde se pueden descargar los datos de 2504 individuos



The screenshot shows the IGSR website in a Mozilla Firefox browser. The page title is "IGSR: The International Genome Sample Resource". The main heading is "IGSR: The International Genome Sample Resource" with the subtitle "Providing ongoing support for the 1000 Genomes Project data". The navigation bar includes links for Home, About, Data, Portal, Analysis, Contact, Browser, and FAQ. A search bar is located on the right. The main content area features a world map titled "IGSR and the 1000 Genomes Project" showing the distribution of the 2504 individuals. The map is color-coded by population group: Africans (yellow), Americans (red), East Asians (green), Europeans (blue), and South Asians (purple). A legend below the map identifies these groups. To the right of the map is a "Links" section with categories: Announcements, IGSR Sample Collection Principles, 1000 Genomes Project Publications, File formats, Software tools, Download data, and Twitter. Below the map is a "Latest Announcements" section with the date "Wednesday, July 12, 2017".

IGSR: The International Genome Sample Resource

Providing ongoing support for the 1000 Genomes Project data

Home About **Data** Portal Analysis Contact Browser FAQ

Search 1000genomes

IGSR and the 1000 Genomes Project

Populations: ● - Africans; ● - Americans; ● - East Asians; ● - Europeans; ● - South Asians

The International Genome Sample Resource (IGSR) was established to ensure the ongoing usability of data generated by the 1000 Genomes Project and to extend the data set. More information is available about the IGSR.

Links

- Announcements
- IGSR Sample Collection Principles
- 1000 Genomes Project Publications
- File formats
- Software tools
- Download data
- Twitter

Latest Announcements

Wednesday, July 12, 2017

Hay un servidor ftp para descargar datos Los archivos son enormes, pero se pueden leer por regiones con Tabix

1000 Genomes

También hay un browser para bajar datos de regiones

Mozilla Firefox

http://phase3browser.1000genomes.org/index.html

This website has been archived. The preferred way to access 1000 Genomes data is via the [Ensembl GRCh37](#) genome browser.

1000 Genomes


A Deep Catalog of Human Genetic Variation

Tools | Help

Search 1000 Genomes

e.g. gene BRCA2 or Chromosome 6:133090746-133108748

Start Browsing 1000 Genomes data

 [Browse Human](#) -- GRCh37

[Protein variations](#) -- View the consequences of sequence variation at the level of each protein in the genome.

[Individual genotypes](#) -- Show different individual's genotype, for a variant.

Browser update October 2014

This release is based on [Ensembl 80](#) and contains the phase 3 integrated release for 2504 individuals. The data can be found on [the ftp site](#).

Please see [www.1000genomes.org](#) for more information about the data presented here and instructions for downloading the complete data set.

- [View sample data](#)


The 1000 Genomes Browser


1000 Genomes Browser based on [Ensembl v80 GRCh37](#)


As the Phase 3 1000 Genomes variants are in the process of being archived at dbSNP and DGVs, we have created a version of the Ensembl databases which contain the phase3 autosomal variants. This is presented here alongside the v80 GRCh37 Ensembl core and regulatory databases. This release represents more than 80M short variants with genotypes for 2504 individuals across 26 populations.

[Read more about this browser's features.](#)

Links

 [1000 Genomes](#) -- More information about the 1000 Genomes Project on the 1000 genomes main site.


 [Phase1 browser](#) -- This browser is based on Ensembl release 73 and represents the variant set analysed as part of [An integrated map of genetic variation from 1,092 human genomes](#), Nature 491, 56-65.

 [Tutorial](#) -- The 1000 Genomes Browser Tutorial.

The 1000 Genomes Project is an international collaborative project described at [www.1000genomes.org](#).

The 1000 Genomes Browser is based on Ensembl web code.

[Ensembl](#) is a joint project of [EMBL-EBI](#) and the [Wellcome Trust](#)

[Sanger Institute](#) 

www.1000genomes.org

1000 Genomes

obtemos datos para *MAF*

The screenshot shows the 1000 Genomes browser interface in a Mozilla Firefox browser. The address bar shows the URL: `phase3browser:1000genomes.org/Homo_sapiens/Location/ViewHdb-core.g-ENSGG0C`. The page title is "A Deep Catalog of Human Genetic Variation".

The interface has a sidebar on the left with a "Location" menu. The main content area is titled "Data Slicer" and contains the following information:

Data Slicer:

When slicing a VCF or BAM file, both the data file and its index file should be present on the web server and named correctly.
The VCF file should have a ".vcf.gz" extension, and the index file should have a ".vcf.gz.tbi" extension.
E.g: MyData.vcf.gz, MyData.vcf.gz.tbi
The BAM file should have a ".bam" extension, and the index file should have a ".bam.bai" extension.
E.g: MyData.bam, MyData.bam.bai

Click [here](#) for more extensive documentation.

Upload files

VCF File URL: `ftp://ftp.1000genomes.ebi.ac.uk/vol1/ftp/release/20130502/ALL.chr17.phase3_shapeit2_mvncall_integrated_v5a.20130502.genotypes.vcf.gz`

[Clear box](#)

e.g. `ftp://ftp.1000genomes.ebi.ac.uk/vol1/ftp/release/20130502/ALL.chr17.phase3_shapeit2_mvncall_integrated_v5a.20130502.genotypes.vcf.gz`

Region: `17:43921017-43972966`

e.g. `1:1-50000`

BAM options (this doesn't apply to VCF files): ☐

Generate .bai file *

*(please note that the generation of .bai file may take approximately 30 seconds)

VCF filters (this doesn't apply to BAM files): ☐ No filtering ☐ By individual

The bottom of the page shows a chromosome browser view with a track labeled "Assembly exceptions, Chromosome bands" and a scale from 43,921,017 to 43,972,966.

1000 Genomes

Formato VCF

1000 Genomes browser: Homo sapiens - Region in detail - Chromosome 17:43,921,017-43,972,966 - Mozilla Firefox

Bach Cello Suites nos 1 | 1000 Genomes browser: H | Haploview | Broad Institute

phase3browser: 1000genomes.org/homo_sapiens/location/View?db=core;g=ENSG0C haploview

This website has been archived. The preferred way to access 1000 Genomes data is via the [Ensembl GRCh37](#) genome browser.

Configure Region Image | Configure Overview Image | Configure Chromosome Image | Personal Data

20
A De

Custom Data
Add your data
Attach DAG
Manage Data
Features on Karyotype

Manage Configurations
Configurations for this page
All configurations
Configuration sets

Online Tools
Variant Effect Predictor
Assembly Converter
ID History Converter
Data Slicer
Variation Pattern Finder
VCF to PED converter
Forge Analysis (v1.0)
Allele Frequency

Location: 17:43921017-43972966
Gene:

Thank you - your VCF file
[17:43921017-43972966.ALL.chr17.phase3_shapeit2_mvncall_integrated_v5a.20130502.genotypes.vcf.gz](#) [Size: 367480] has been generated.
Right click on the file name and choose "Save link as ..." from the menu

Preview

#CHROM	POS	ID	REF	ALT	QUAL	FILTER	INFO	FORMAT	H000096
17	43921068		rs555347111	C	T	100	PASS	AC=2;AF=	
17	43921106		rs573543994	C	G	100	PASS	AC=1;AF=	
17	43921126		rs542617372	C	A	100	PASS	AC=1;AF=	
17	43921130		rs562398147	C	T	100	PASS	AC=1;AF=	
17	43921131		rs576107214	G	A	100	PASS	AC=1;AF=	

Location: 17:43921017-43972966 Go

Gene: Go

1000 Genomes

Formato VCF

1000 Genomes browser: Homo sapiens - Region in detail - Chromosome 17:43,921,017-43,972,966 - Mozilla Firefox

1000 Genomes browser: Haplotype | Broad Institute

phase3 browser: 1000genomes.org/homo_sapiens/location/View?db=core;g=ENSG00000177972

This website has been archived. The preferred way to access 1000 Genomes data is via the [Ensembl Genomes](#) genome browser.

Configure Region Image | Configure Overview Image | Configure Chromosome Image | Personal Data

Custom Data
Add your data
Attach DAG
Manage Data
Features on Karyotype

Manage Configurations
Configurations for this page
All configurations
Configuration sets

Online Tools
Variant Effect Predictor
Assembly Converter
ID History Converter
Data Slicer
Variation Pattern Finder
VCF to PED converter
Forge Analysis (v1.0)
Allele Frequency

Thank you - your VCF file
[17:43921017-43972966.ALL.chr17.phase3_shapeit2_mvncall_integrated_v5a.20130502.genotypes.vcf.gz](#) [Size: 3674602] has been generated.
Right click on the file name and choose "Save link as ..." from the menu

Preview

HG00119	HG00120	HG00121	HG00122	HG00123	HG00125	HG00126	HG00127	HG00128	HG00129
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0

Location: 17:43921017-43972966 Go

Gene: Go

Paquete Variant Annotation para leer datos VCF

The screenshot shows the Bioconductor website for the VariantAnnotation package. The browser is Mozilla Firefox. The address bar shows the URL: bioconductor.org/packages/release/bioc/html/VariantAnnotation.html. The search bar contains the text "vcf bioconductor".

The page header includes the Bioconductor logo and navigation links: Home, Install, Help, Developers, and About.

The main content area is titled "VariantAnnotation" and includes a summary of the package's popularity and stability:

- platforms: all
- downloads: top 5%
- posts: 15 / 17274
- in Bioc: 6 years
- build: ok
- currents: 2.67
- test coverage: 73%

The DOI is [10.18129/B3.bioc.VariantAnnotation](https://doi.org/10.18129/B3.bioc.VariantAnnotation).

The section "Annotation of Genetic Variants" describes the package's purpose: "Bioconductor version: Release (3.5). Annotate variants, compute amino acid coding changes, predict coding outcomes. Author: Valerie Obenchain [aut], Michael Lawrence [aut], Stephanie Gogarten [ctb]. Maintainer: Valerie Obenchain <maintainer at bioconductor.org>".

The "Citation" section provides a citation for the package: "Obenchain V, Lawrence M, Carey V, Gogarten S, Shannon P and Morgan M (2014). 'VariantAnnotation: a Bioconductor package for exploration and annotation of genetic variants.' *Bioinformatics*, 30(14), pp. 2076-2078. doi: [10.1093/bioinformatics/btu116](https://doi.org/10.1093/bioinformatics/btu116)".

The "Installation" section provides instructions for installing the package in R: "To install this package, start R and enter:

```
## try http:// if https:// URLs are not supported
source("https://bioconductor.org/biocLite.R")
biocLite("VariantAnnotation")
```

".

The "Documentation" section provides instructions for viewing the documentation: "To view documentation for the version of this package installed in your system, start R and enter:

```
browseVignettes("VariantAnnotation")
```

".

The right sidebar contains two sections: "Documentation" and "Support". The "Documentation" section lists links to the package vignettes, manuals, and other resources. The "Support" section provides information on how to get help, including a link to the support site and a link to the mailing list.

VCF in R

se pueden cargar los binarios snp.RData

```
source("http://bioconductor.org/biocLite.R")  
biocLite("VariantAnnotation")
```

The screenshot shows a Mozilla Firefox browser window with the address bar displaying the URL: `bioconductor.org/packages/release/bioc/vignettes/VariantAnnotation/inst/doc/VariantAnnotation.pdf`. The search bar contains the text "vcf bioconductor". The main content area displays the title "1. Introduction to VariantAnnotation" in blue, followed by the author "Valerie Obenchain" and the date "June 23, 2017". Below this is a "Contents" section with a table of contents listing chapters and page numbers. The bottom of the browser window shows a search bar with the text "Buscar en la página" and a dropdown menu with options: "Resaltar todo", "Coincidencia de mayúsculas/minúsculas", and "Palabras completas".

1. Introduction to *VariantAnnotation*

Valerie Obenchain

June 23, 2017

Contents

1	Introduction	1
2	Variant Call Format (VCF) files	2
2.1	Data import and exploration	2
2.1.1	Header information	3
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2.2	Import data subsets	8
2.2.1	Select genomic coordinates	8
2.2.2	Select VCF fields	9
3	Locating variants in and around genes	10
4	Amino acid coding changes	11
5	SIFT and PolyPhen Databases	13
6	Other operations	15
6.1	Create a SnpMatrix	15

Buscar en la página

Resaltar todo Coincidencia de mayúsculas/minúsculas Palabras completas

VCF in R

```
library(VariantAnnotation)
fl<-"17.43921017-43972966.ALL.chr17.phase3_shapeit2_mvncall_integrated_
vcf <- readVcf(fl, "hg19")
genos<-geno(vcf)
names(genos)
dim(genos$GT)
genos$GT[1:5,1:5]
```

Si el archivo es grande readVcf permite leer sólo regiones de interes

VCF in R

Los genotipos en formato 0,1,2 pueden ser encontrados en *genos\$DS*.

Si no se puede entonces se puede calcular así

```
snps<-genos$GT
snps[snps=="0|0"]<-0
snps[snps=="1|1"]<-2
snps[snps!="0" & snps!="2"]<-1
snps[1:5,1:5]
save(snps, file="snpsMAPT.RData")
```


VCF in snpStats

snpStats usa formato 1,2,3 para genotipos y el 0 para missing

```
library(snpStats)
snpsnew<-t(snps)
snpsnew[snps=="0"] <- 1
snpsnew[snps=="1"] <- 2
snpsnew[snps=="2"] <- 3

snpsSNPstats <- new("SnpMatrix", snpsnew)
print(as(snpsSNPstats[1:5,1:5], 'character'))
save(snpsSNPstats, file="snpsSNPstats.RData")
```

1000 Genomes

Los datos de los 1000 genomas (y HapMap) también están en formato PLINK por cromosomas

Resources - PLINK 1.9 - Mozilla Firefox

Chopin - Complete Noci x Resources - PLINK 1.9 x +

https://www.cog-genomics.org/plink/1.9/resources

PLINK 1000 genomes

Limitations
Note to testers
[Jump to search box]
Citation instructions

General usage

Standard data input
PLINK 1 binary (.bed)
Autocorrelation behavior
PLINK test (.pos, .bed...) VCF (.vcf.gz), .bed
Oxford (.gen(.gz), .igen)
23andMe test
Generate random
Unusual chromosome IDs
Recombination map
Phenotypes
Covariates
Clusters of samples
Variant sets
Binary distance matrix
IBD report (.genome)

Input filtering
Sample ID file
Variant ID file
Cluster membership
Set membership
Attribute-based
Chromosomes
SNPs only
Simple variant window
Multiple variant ranges
Sample/variant thinning
Covariates (-filter)
Missing genotypes
Missing phenotypes
Minor allele frequencies
Hardy-Weinberg
Mendel errors
Quality scores
Relationships

Main functions
Data management
--make-bed
--recode
--output chr
--zero-cluster
--split a--merge a
--set-missing
--fix missing a2
--set-missing var-ids
--update map...
--update ids...
--rpl
--rpl-ican
--use-allele-freqs

Genotype data

1000 Genomes phase 1 (hosted by [GigaDB](#), Aspera download available there)

- Entire dataset as a single .tar.gz (1.11 GB)
- Split by chromosome:
 - chr1 (93.1 MB)
 - chr2 (102 MB)
 - chr3 (83.8 MB)
 - chr4 (84.2 MB)
 - chr5 (77.2 MB)
 - chr6 (76.1 MB)
 - chr7 (70.9 MB)
 - chr8 (66.7 MB)
 - chr9 (53.5 MB)
 - chr10 (59.6 MB)
 - chr11 (59.9 MB)
 - chr12 (57.6 MB)
 - chr13 (43.1 MB)
 - chr14 (39.9 MB)
 - chr15 (37.4 MB)
 - chr16 (40.0 MB)
 - chr17 (35.0 MB)
 - chr18 (34.9 MB)
 - chr19 (28.9 MB)
 - chr20 (27.4 MB)
 - chr21 (17.2 MB)
 - chr22 (17.4 MB)
 - chrX, not including pseudoautosomal region (38.6 MB)
 - chrY (802 KB)
 - Pseudoautosomal region (2.7 MB)
 - chrMT (45.8 KB)

Refer to the 1000 Genomes website for [additional sample information](#), [data usage rules](#), and [citation instructions](#).

HapMap phase 2
See the [PLINK 1.07 resources page](#).

Teaching materials and example dataset

ds

Buscar todo Coincidencia de mayúsculas/minúsculas Palabras completas 2 de 11 aciertos

PLINK a VCF

- ▶ los comandos PLINK pueden usar formato VCF
- ▶ también se puede convertir .bed .bim .fam a formato a VCF y vice-versa

```
$ plink --bfile [filename prefix] --recode vcf --out [VCF prefix]
```

```
$ plink --vcf [VCF filename] --out [.bed/.bim/.fam prefix]
```

Ejercicio

- ▶ Descargar datos de los 1000 Genomas en PLINK
- ▶ leerlos en snpStats
- ▶ si PLINK está instalado convertirlos en VCF
- ▶ leerlos en snpStats