IX International Course of Massive Data Analysis FOR GENOMICS

ciberer
CENTRO DE INVESTIGACIÓN BIOMÉDICA EN RED DE ENFERMEDADES RARAS

PRINCIPE FELIPE
CENTRO DE INVESTIGACION

INB

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Variant annotation

Where are we?

Sequence preprocessing

Mapping

Variant Calling

The haystack has been cleared away to reveal a large pile of needles

Variant prioritization

Functional annotation

GWAS Analysis

Gene-Set Analysis

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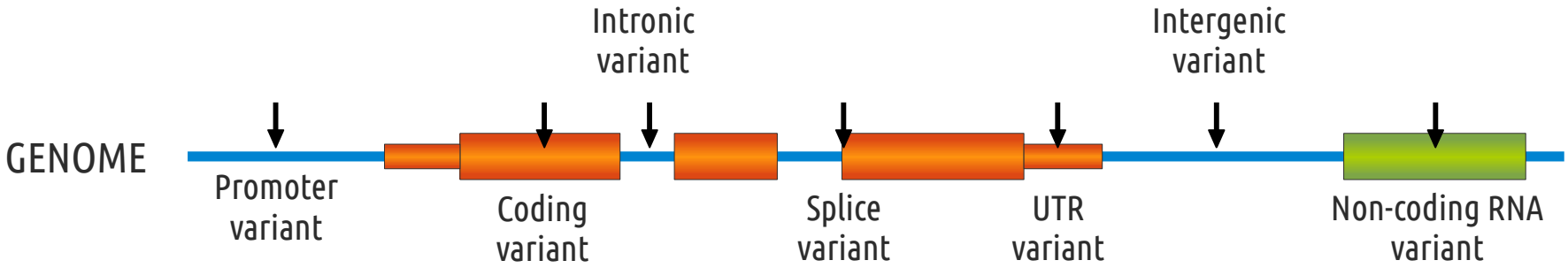
What is functional annotation?



Why we do that?

- Each individual exome carries ~25,000 variants → **PRIORITIZATION!**
- We want to identify a **small subset** of functionally important variants to pinpoint the putative disease causal variants
- We need strategies to **estimate the deleteriousness** of our variants to better identify disease-causal variants

CAUTION!

On average, each *normal* person is found to carry:

~11,000 synonymous variants

~11,000 non-synonymous variants

250 to 300 los-of-function variants in annotated genes

50 to 100 variants previously implicated in **inherited disorders**

1000 Genomes Project Consortium. *A map of human genome variation from population-scale sequencing.* **Nature**. 2010 Oct 28;467(7319):1061-73. PubMed PMID: 20981092

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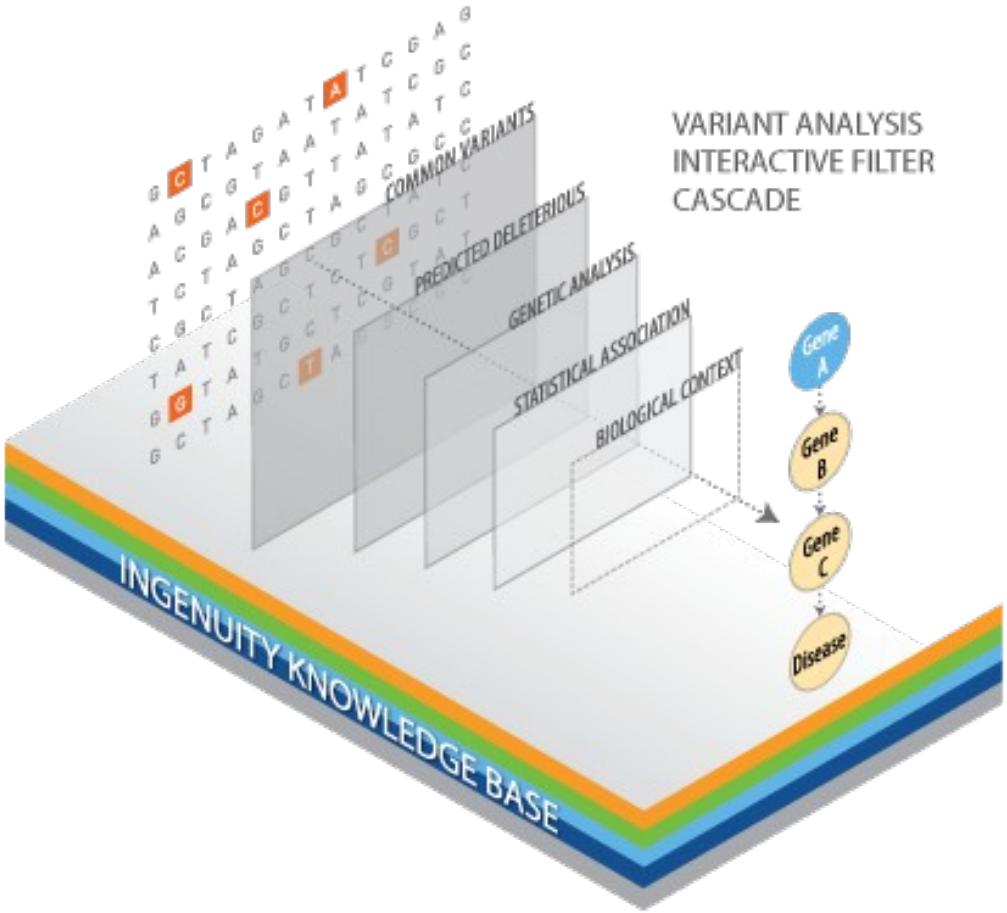
The objective



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Sources of functional information

Table 1 Publicly available tools and databases for various tasks of genetic variant annotation and prioritization

Category	Database/tool/project	Description	URL
Genetic variant data sources	dbSNP[68]	Comprehensive, curated SNP and short indel database	http://www.ncbi.nlm.nih.gov/projects/SNP
	DbVar[69]	Comprehensive, curated database for structural variants	http://www.ncbi.nlm.nih.gov/dbvar
	DGV[70]	Human structural variants from samples with no phenotype	http://projects.tcag.ca/variation
Functional characterization of genomic elements	ENCODE[71]	High-throughput functional characterization of DNA elements, including noncoding regions	http://www.genome.gov/10005107
	SIFT[72], PolyPhen[73]	Prioritization of nonsynonymous SNPs	http://sift.jcvi.org, http://genetics.bwh.harvard.edu/pph2
Public gene–trait associations	dbGaP[34]	Comprehensive listing of genotype-to-phenotype mappings	http://www.ncbi.nlm.nih.gov/gap
	EGA[74]	Genotype–phenotype experiment archive	http://www.ebi.ac.uk/ega
Disease-associated mutations	HGMD[35]	Database for human disease mutations	http://www.hgmd.org
	OMIM[36]	Mendelian disease gene associations	http://www.ncbi.nlm.nih.gov/omim
	SwissVar[76]	Variant catalog of the UniProt knowledge bases	http://swissvar.expasy.org
	GAD[77]	NCBI source for genotype–disease associations	http://geneticassociationdb.nih.gov
	GWAS catalog from NHGRI[78]	SNP-phenotype associations found by GWAS	http://www.genome.gov/gwastudies
Whole-genome repositories	Complete genomics public genomes[79]	Complete genomics for 69 genomes from multiple ancestries (includes samples from the NHGRI and NIGMS repositories)	http://www.completegenomics.com/sequence-data/download-data
	1,000 Genomes[80]	Expanding resource currently housing three low-coverage whole genomes of multiple ancestries	http://www.1000genomes.org
Ancestry-focused variant data sources	HapMap[26]	Haplo-block mapping for diverse populations	http://www.hapmap.org
	HGDP[27]	SNP profiles of samples from several endogenous populations	http://hagsc.org/hgdp
Pharmacogenomic associations and data sources	PharmGKB[56]	Variant–pharmacokinetic/pharmacodynamic trait associations and gene–drug interactions	http://www.pharmgkb.org
	DrugBank[81]	Drug-target database with biochemical properties	http://drugbank.ca

Cordero P, Ashley EA. *Whole-genome sequencing in personalized therapeutics.* **Clin Pharmacol Ther**. 2012 Jun ;91(6):1001-9. PubMed PMID: 22549284

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Sources of functional information - ENCODE

ENCODE (The Encyclopedia of DNA Elements)

- Objective: Characterize all of the **functional elements encoded in the human genome**.
- The **80%** oh the human genome has a defined **biochemical function** in at least one cell type.
- Focus on **non-coding regions**: accessible DNA regions, DNA-binding motifs and RNA-coding.

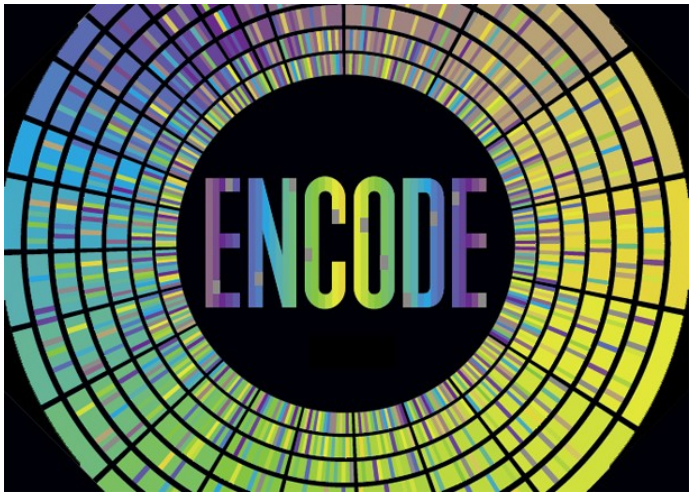
ARTICLE

doi:10.1038/nature11247

An integrated encyclopedia of DNA elements in the human genome

The ENCODE Project Consortium*

The human genome encodes the blueprint of life, but the function of the vast majority of its nearly three billion bases is unknown. The Encyclopedia of DNA Elements (ENCODE) project has systematically mapped regions of transcription, transcription factor association, chromatin structure and histone modification. These data enabled us to assign biochemical functions for 80% of the genome, in particular outside of the well-studied protein-coding regions. Many discovered candidate regulatory elements are physically associated with one another and with expressed genes, providing new insights into the mechanisms of gene regulation. The newly identified elements also show a statistical correspondence to sequence variants linked to human disease, and can thereby guide interpretation of this variation. Overall, the project provides new insights into the organization and regulation of our genes and genome, and is an expansive resource of functional annotations for biomedical research.



The ENCODE Project Consortium. *An integrated encyclopedia of DNA elements in the human genome.* **Nature**. 2012 Sep 6;489(7414):57-74. Pubmed PMID: 22955616

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Computational methods and tools

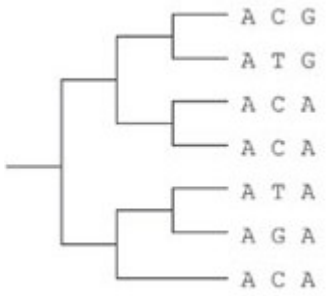
- **Annotated information** is sometimes **limited**, particularly for rare and complex traits
- Computational methods can measure deleteriousness by using **comparative genomics** and knowledge of **protein biochemistry and structure**

Comparative Genomics

Focus on sequences that have not been remove by **natural selection**.

Quantify evolutionary changes in genes or genomes and define conserved and neutral regions.

Variants observed in conserved sites are highly likely to be **deleterious**.



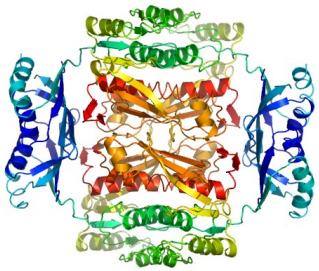
Effects in protein-coding variants

Can combine **evolutionary** and **biochemical** information.

Two types of approaches: first **principles** approaches and **trained** approaches.

Use **alignments of homologous proteins** to estimate mutational deleteriousness.

Use **biochemical data** such as amino acid properties, binding information and structural information to estimate the impact.



Effects in non-coding variants

The majority of the human genetic variation is in non-coding regions.

No detectable conservation outside vertebrates.

Main strategy for estimation is testing the **mammalian conservation** of the non-coding variants.

Cooper GM, Shendure J. *Needles in stacks of needles: finding disease-causal variants in a wealth of genomic data.* **Nature Reviews Genetics**. 2011 Aug 18;12(9):628-40. Pubmed PMID: 21850043

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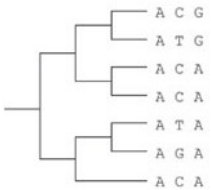
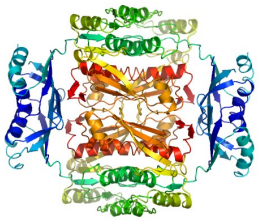
Computational methods and tools

Prediction scores for non-synonymous variants





Cooper GM, Shendure J. *Needles in stacks of needles: finding disease-causal variants in a wealth of genomic data.* **Nature Reviews Genetics**. 2011 Aug 18;12(9):628-40. Pubmed PMID: 21850043

Table 1 | **Tools for protein-sequence-based prediction of deleteriousness**

Name	Type	Information	URL	Refs
MAPP	Constraint-based predictor	Evolutionary and biochemical	http://mendel.stanford.edu/SidowLab/downloads/MAPP/index.html	27
SIFT	Constraint-based predictor	Evolutionary and biochemical (indirect)	http://sift.bii.a-star.edu.sg/	39
PANTHER	Constraint-based predictor	Evolutionary and biochemical (indirect)	http://www.pantherdb.org/	41
MutationTaster*	Trained classifier	Evolutionary, biochemical and structural	http://www.mutationtaster.org/	40
nsSNP Analyzer	Trained classifier	Evolutionary, biochemical and structural	http://snpanalyzer.uthsc.edu/	44
PMUT	Trained classifier	Evolutionary, biochemical and structural	http://mmb2.pcb.ub.es:8080/PMut/	38
polyPhen	Trained classifier	Evolutionary, biochemical and structural	http://genetics.bwh.harvard.edu/pph2/	35
SAPRED	Trained classifier	Evolutionary, biochemical and structural	http://sapred.cbi.pku.edu.cn/	42
SNAP	Trained classifier	Evolutionary, biochemical and structural	http://www.rostlab.org/services/SNAP/	36
SNPs3D	Trained classifier	Evolutionary, biochemical and structural	http://www.snps3d.org/	51
PhD-SNP	Trained classifier	Evolutionary and biochemical (indirect)	http://gpcr2.biocomp.unibo.it/~emidio/PhD-SNP/PhD-SNP_Help.html	37

*Also makes predictions for synonymous and non-coding variant effects: for example, splicing. MAPP, Multivariate Analysis of Protein Polymorphism; polyPhen, polymorphism phenotyping.

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Computational methods

Prediction scores for non-coding variation

Table 2 | **Tools for nucleotide-sequence-based prediction of deleteriousness**

Name	Type	Information	URL	Refs
phastCons	Phylogenetic HMM	Evolutionary	http://compgen.bscb.cornell.edu/phast/	60
GERP	Single-site scoring	Evolutionary	http://mendel.stanford.edu/SidowLab/downloads/gerp/index.html	67
Gumby	Single-site scoring	Evolutionary	http://pga.jgi-psf.org/gumby/	21
phyloP	Single-site scoring	Evolutionary	http://compgen.bscb.cornell.edu/phast/	66
SCONE	Single-site scoring	Evolutionary	http://genetics.bwh.harvard.edu/scone/	68
binCons	Sliding-window scoring	Evolutionary	http://zoo.nhgri.nih.gov/binCons/index.cgi	69
Chai Cons	Sliding-window scoring	Evolutionary and structural	http://research.nhgri.nih.gov/software/chai	71
VISTA	Visualization tool (various scores)	Evolutionary	http://genome.lbl.gov/vista/index.shtml	70

GERP, Genomic Evolutionary Rate Profiling; HMM, hidden Markov model; SCONE, Sequence Conservation Evaluation.

Cooper GM, Shendure J. *Needles in stacks of needles: finding disease-causal variants in a wealth of genomic data.* **Nature Reviews Genetics**. 2011 Aug 18;12(9):628-40. Pubmed PMID: 21850043

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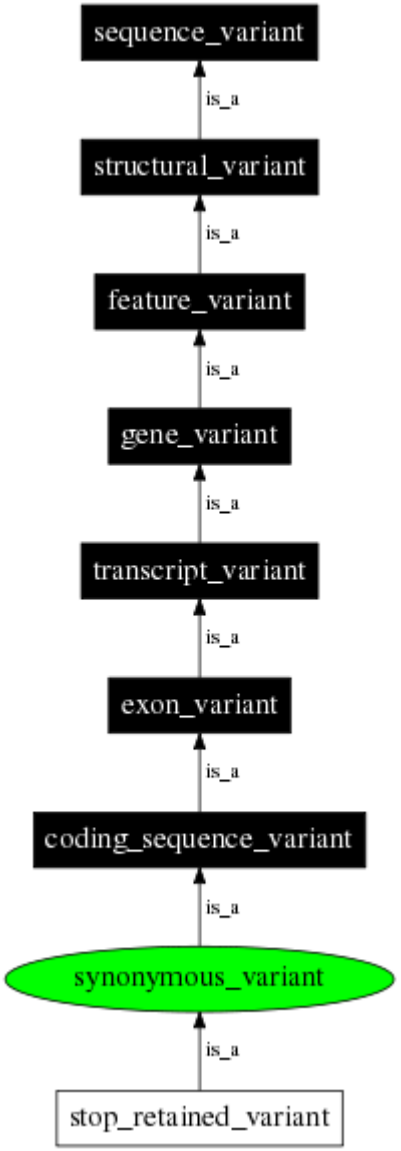
Consequence types

The standard: SO The Sequence Ontology Project

Common vocabulary

Label	SO accession	Description
Coding sequence	SO:0001580	In coding sequence with in determinate effect
Synonymous codon	SO:0001588	In coding sequence, not resulting in an amino acid change (silent mutation)
Non-synonymous codon	SO:0001583	In coding sequence and results in an amino acid change in the encoded peptide sequence
Stop gained	SO:0001587	In coding sequence, resulting in the gain of a stop codon
Stop lost	SO:0001587	In coding sequence, resulting in the gain of a stop codon
Splice site	SO:0001630	1-3bps in to an exon or 3-8bps into an intron
Splice acceptor	SO:0001574	A splice variant that changes the 2 base region at the 3' end of an intron
Splice donor	SO:0001575	A splice variant that changes the 2 base region at the 5' end of an intron
5' UTR	SO:0001623	In 5 prime untranslated region
3' UTR	SO:0001624	In 3 prime untranslated region
Upstream	SO:0001635	Within 5kb upstream of the 5 prime end of a transcript
Downstream	SO:0001633	Within 5kb downstream of the 3 prime end of a transcript
TFBS	SO:0001782	A sequence variant located with in a transcription factor binding site
miRNA target	SO:0000934	A binding site where the molecule is a microRNA
Intergenic	SO:0001628	More than 5 kb either upstream or downstream of a transcript



More information: http://www.ensembl.org/info/docs/variation/predicted_data.html

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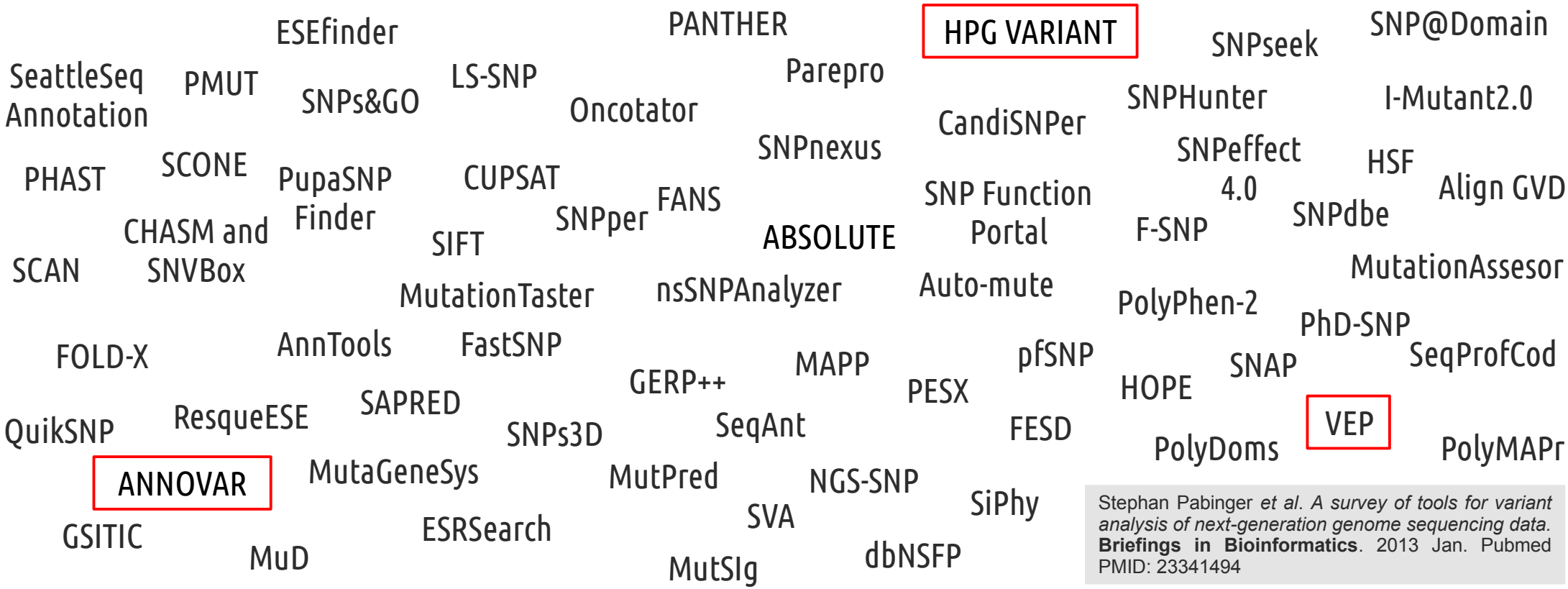
Tools for functional annotation

- We need to measure the **impact** of each variant in the genome
- We **cannot** annotate 25,000 variants **manually** checking more than 20 databases
- **Tools integrate** biological information and **ease** the functional annotation of hundreds of thousand variants



Stephan Pabinger *et al. A survey of tools for variant analysis of next-generation genome sequencing data.* **Briefings in Bioinformatics**. 2013 Jan. Pubmed PMID: 23341494

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ANNOVAR

ANNOVAR web site: http://www.openbioinformatics.org/annovar/

- Free and open source
- Can annotate SNV, insertions and deletions
- **Regulatory information**: Conserved genomic regions, TFBSs, miRNA targets and predicted miRNA secondary structures. ENCODE DNAse I hypersensitive sites, Histone methylations, ChIP and RNA-Seq peaks
- DbSNP, 1000 genomes SIFT and GERP filtering
- **Predictions**: Polyphen, LRT, MutationTaster, PhyloP
- Can handle **custom annotations** in GFF3
- Can handle 1 o 0-based coordinates
- **5 Species** (human, mouse, worm, fly, yeast)

- Accepts VCF4, GFF3-SOLiD and CSV BUT after conversion to their **particular input file**:

Chr	Start	End	Ref	Obs	Comments
1	161003	161003	C	T	comments: rs1000050

- **Perl** written program
- **Installation** required
- Users need to **download** every annotation database and save them locally (**~35GB** per assembly)
- Need to be **run several times**
- **Output**: several files depending on the query
- Does not use **Sequence Ontology** terms

Wang K, Li M, Hakonarson H. *ANNOVAR: Functional annotation of genetic variants from next-generation sequencing data.* **Nucleic Acids Research**. Sep;38(16):e164 Pubmed PMID: 20601685

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ANNOVAR

EXAMPLE of ANNOVAR usage

```
DOWNLOADING BIOLOGICAL DATA:

 user@computer:~$ annotate_variation.pl -buildver hg19 -downdb refgene humandb/

 user@computer:~$ annotate_variation.pl -buildver hg19 -downdb snp135 -webfrom annovar humandb/

 user@computer:~$ annotate_variation.pl -buildver hg19 -downdb phastConsElements46way humandb/

 user@computer:~$ annotate_variation.pl -buildver hg19 -downdb 1000g2012apr -webfrom annovar
humandb/

 user@computer:~$ annotate_variation.pl -buildver hg19 -downdb cytoBand humandb/



EXTRACTING THE EFFECT:

 user@computer:~$ annotate_variation.pl -geneanno example/ex1.human humandb/

 user@computer:~$ annotate_variation.pl -regionanno -dbtype band example/ex1.human humandb/

 user@computer:~$ annotate_variation.pl -filter -dbtype 1000g2012apr_eur example/ex1.human
humandb/
```

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Variant Effect Predictor (VEP)

VEP documentation site: http://www.ensembl.org/info/docs/variation/vep/index.html

- Backed by **Ensembl**
- Free and open source
- **3 ways of functionality**: web interface, standalone Perl script and Ensembl's Perl API
- **Input** formats: CSV, VCF, Pileup and HGVS
- **Regulatory information**: TFBSs
- **Filtering** by coding regions and MAF
- **Predictions**: SIPF, PolyPhen
- 1000 genomes and dbSNP information
- Uses **Sequence Ontology**
- **Many species**

- Regulatory information does **not include miRNA targets**
- Web interface limit: **750 variants**
- The **standalone Perl script** needs:
  - **Perl** and **MySQL** support (more than 100GB of data)
  - **Download**, **install** and **update** every ~ 2 months
- Perl **API** requires:
  - **Installation** (Really, really hard!)
  - **Downloads** and **update**
  - API documentation → **Hard to understand**

McLaren W, Pritchard B, Rios D, Chen Y, Flicek P, Cunningham F. *Deriving the consequences of genomic variants with the Ensembl API and SNP Effect Predictor.* **BMC Bioinformatics** 26(16):2069-70(2010) Pubmed PMID: 20562413

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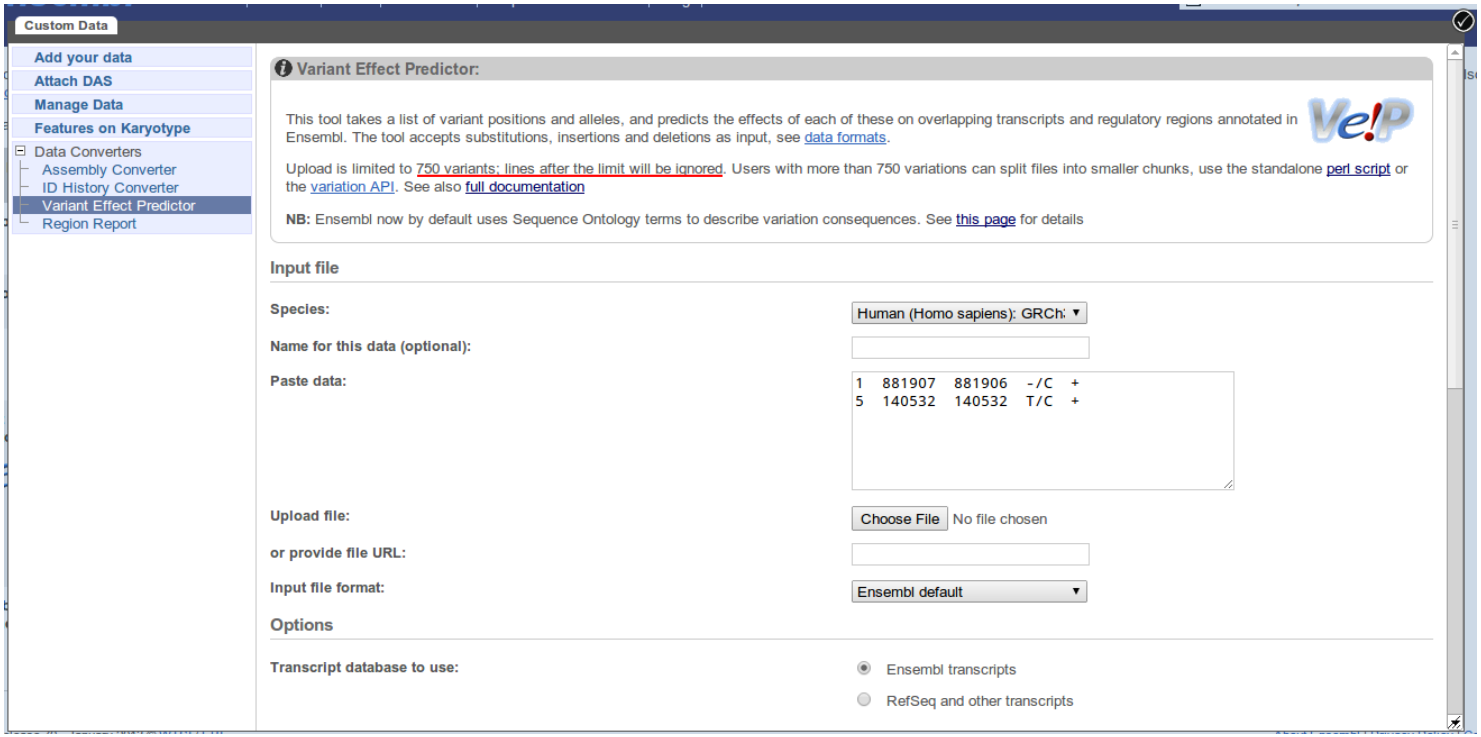
Variant Effect Predictor (VEP)

VEP web interface: http://www.ensembl.org/tools.html



*The web interface to the VEP has a hard **limit of 750 variants** in your uploaded file. However, it is possible that the tool will not work with fewer variants than this, depending on the content of your data and the features you switch on. For example, a relatively small file (e.g. 100 variants) **may fail to return results if every variant in the file falls in a different gene and those genes are spread across many chromosomes**. Contrastingly, a file containing 500 variants may return results quickly if those variants all fall in just a few genes.*

*To mitigate this issue, users should consider **splitting up their input by chromosome** and uploading each chromosome's variants as a separate file. The problem can also be solved by using the VEP script - it is a command line tool, but not as hard to use as you might think! It also offers many more features than the web interface and is a generally much more powerful tool.*

http://www.ensembl.org/info/docs/variation/vep/index.html

McLaren W, Pritchard B, Rios D, Chen Y, Flicek P, Cunningham F. *Deriving the consequences of genomic variants with the Ensembl API and SNP Effect Predictor.* **BMC Bioinformatics** 26(16):2069-70(2010) Pubmed PMID: 20562413

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Variant Effect Predictor (VEP)

EXAMPLE of API usage: Getting all variations in a particular human transcript and see what is the effect of that variation in the transcript

```perl
use strict;
use warnings;
use Bio::EnsEMBL::Registry;

my $registry = 'Bio::EnsEMBL::Registry';

$registry->load_registry_from_db(
    -host => 'ensembldb.ensembl.org',
    -user => 'anonymous'
);

my $stable_id = 'ENST00000393489'; #this is the stable_id of a human transcript
my $transcript_adaptor = $registry->get_adaptor('homo_sapiens', 'core', 'transcript'); #get the adaptor to get the Transcript from the database
my $transcript = $transcript_adaptor->fetch_by_stable_id($stable_id); #get the Transcript object

my $trv_adaptor = $registry->get_adaptor('homo_sapiens', 'variation', 'transcriptvariation'); #get the adaptor to get TranscriptVariation objects
my $trvs = $trv_adaptor->fetch_all_by_Transcripts([$transcript]); #get ALL effects of Variations in the Transcript

foreach my $tv (@{$trvs}) {
        my $tvas = $tv->get_all_alternate_TranscriptVariationAlleles();

        foreach my $tva(@{$tvas}) {
                my @ensembl_consequences;
                my @so_consequences;

                my $ocs = $tva->get_all_OverlapConsequences();

                foreach my $oc(@{$ocs}) {
                        push @ensembl_consequences, $oc->display_term;
                        push @so_consequences, $oc->SO_term;
                }

                my $sift = $tva->sift_prediction;
                my $polyphen = $tva->polyphen_prediction;

                print
                        "Variation ", $tv->variation_feature->variation_name,
                         " allele ", $tva->variation_feature_seq,
                         " has consequence ", join(",", @ensembl_consequences),
                         " (SO ", join(",", @so_consequences), ").";

                if(defined($sift)) {
                        print " SIFT=$sift";
                }
                if(defined($polyphen)) {
                        print " PolyPhen=$polyphen";
                }

                print "\n";
        }
}
```

McLaren W, Pritchard B, Rios D, Chen Y, Flicek P, Cunningham F. *Deriving the consequences of genomic variants with the Ensembl API and SNP Effect Predictor.* **BMC Bioinformatics** 26(16):2069-70(2010) Pubmed PMID: 20562413

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HPG VARIANT (aka VARIANT)

HPG-VARIANT web site: http://www.opencb.org/projects/hpg/doku.php?id=variant:overview

- Free and open source. Part of the OpenCB Project
- **3 ways of functionality**: C CLI program, Web application and Java RESTful WS API
- **Cloud** variant annotator. Requires **no installation or updates**
- **Regulatory information**: Conserved genomic regions, TFBSs and miRNA targets. ENCODE DNAse I hypersensitive sites and Histone methylations
- dbSNP and 1000genomes information
- **Phenotypic information**: HGMD, COSMIC and OMIM
- **Cross-link** with many other DDBB (Ensembl, UniProt, PDB, etc)
- **Input**: VCF, GFF and BED. Accepts compressed files in ***tar.gz***
- **11 species** (human, mouse, rat, zebra fish, worm, fly, yeast, dog, pig, mosquito and plasmodium)
- HPG-VARIANT-GWAS to test for **association**

- **Young** program, many **new features coming** in version 2.0 in March 2013
  - PolyPhen and SIFT
  - PhastCons, GERP
  - Many more species (~25 new species)
  - Large structural variants annotation

Medina I, De Maria A, Bleda M, Salavert F, Alonso R, Gonzalez CY, Dopazo J. *VARIANT: Command Line, Web service and Web interface for fast and accurate functional characterization of variants found by Next-Generation Sequencing.* **Nucleic Acids Research**. 2012 Jul;40(Web Server issue):W54-8 Pubmed PMID: 22693211

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HPG VARIANT

3 ways of functionality:

- **Command Line Interface (CLI)**

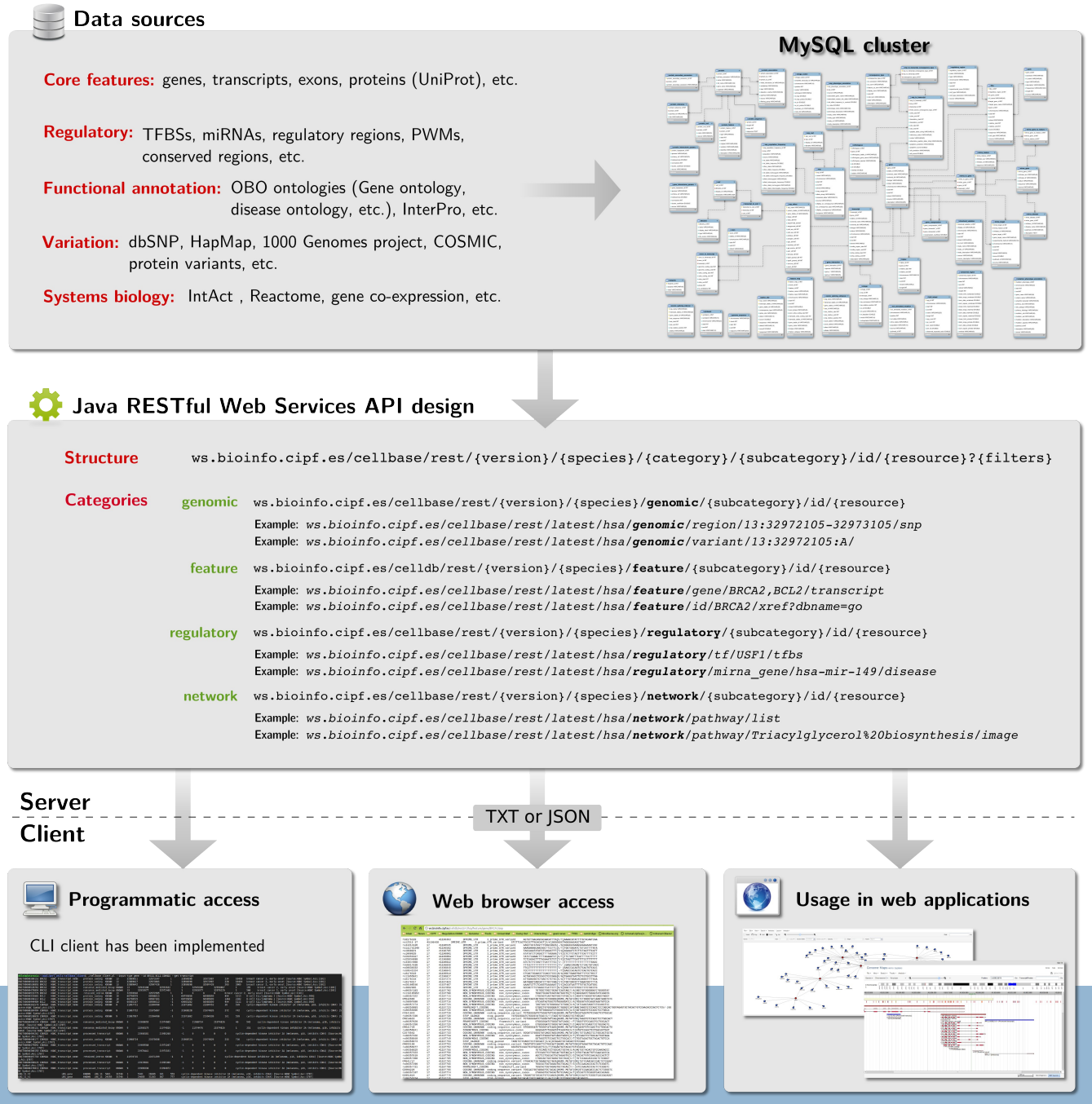
  CLI Tutorial

- **RESTful Web Service**

  WS Tutorial

- **Web Interface**

  Web Tutorial



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HPG VARIANT - RESTful WS API

Java RESTful Web Services API

General Structure:

ws.bioinfo.cipf.es/cellbase/rest/{version}/{species}/{category}/{subcategory}/id/{resource}

ws.bioinfo.cipf.es/cellbase/rest/{version}/{species}/**genomic**/{subcategory}/id/{resource}

ws.bioinfo.cipf.es/cellbase/rest/{version}/{species}/**genomic**/**variant**/id/{resource}

ws.bioinfo.cipf.es/cellbase/rest/{version}/{species}/**genomic**/**variant**/id/**consequence_type**

ID: **Chr:position:reference:variant (i.e.: 1:150044250:T:G)**

http://ws.bioinfo.cipf.es/cellbase/rest/latest/hsa/genomic/variant/1:150044250:T:G/consequence_type

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HPG VARIANT - RESTful WS API

Column position	Column header	Description
1	chromosome	Chromosome number
2	position	Position of the variant
3	reference	Reference allele at this position
4	alternative	Non-reference allele called at this position
5	feature ID	Ensembl identifier or name of a genomic feature where the variant has been found. In the case of introns and intergenic regions this field is empty
6	feature name	HGNC symbol of the feature (if exists)
7	consequence type	Consequence type code (see more here)
8	biotype	Biotype of the target transcript
9	feature chromosome	Chromosome number for the feature
10	feature start	Feature start position
11	feature end	Feature end position
12	feature strand	Feature strand
13	snp ID	Single Nucleotide Polymorphism (SNP) rsID. This field is empty unless the position is annotated as a SNP
14	ancestral allele	Ancestral allele
15	alternative allele	Variant allele found
16	gene Ensembl ID	Gene Ensembl ID related with this feature
17	Ensembl transcript ID	Transcript Ensembl ID related with this feature
18	gene name	Gene name related with this feature
19	SO consequence type ID	Sequence Ontology consequence type ID
20	SO consequence type name	Sequence Ontology consequence type name
21	consequence type description	Consequence type description
22	consequence type category	Consequence type category as specified here
23	aminoacid position	If the variant is in a coding region for a transcript it indicates the affected aminoacid position
24	aminoacid change	If the variant is non-synonymous for a transcript it indicates the original and the new aminoacids in 1-letter code
25	codon change	If the variant is non-synonymous for a transcript it indicates the original and the new codons

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HPG VARIANT - CLI program

- Create a folder called `effect` in you mda13 directory:

  mkdir /home/biouser/mda13/effect

- Download the program and save it into your `mda13/effect` folder :

  http://www.opencb.org/projects/hpg/doku.php?id=variant:downloads

	Binaries	Sources
Debian 6	Binary package	
Ubuntu 12.04	Binary package	
Fedora 17	Binary package	Source package
Other	Zipped binaries *	Source tarball

* Only for Debian 6 / Ubuntu 10.04 or greater

- Extract the contents

- Download the example file, save it into the `mda13/effect/hpg-variant-bin-0.4/` folder and extract the content.

  http://bioinfo.cipf.es/courses/mda13genomics/program?&#variant_annotation

- Open a Terminal  and move to the folder where files have been extracted:

  cd /home/biouser/mda13/effect/hpg-variant-bin-0.4/

- Execute it!

  hpg-var-effect -v CHB.exon.2010_03.sites.vcf --outdir effect_output/

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HPG VARIANT - CLI program

- Open the `effect_output` directory and let's see what is in!

- **Is there any variant affecting a splice donor site?**

  Yes! There are 4 variants in a splice donor site affecting 5 genes: CEP104, HSE4, C1orf159, CALML6 and C1ORF222.

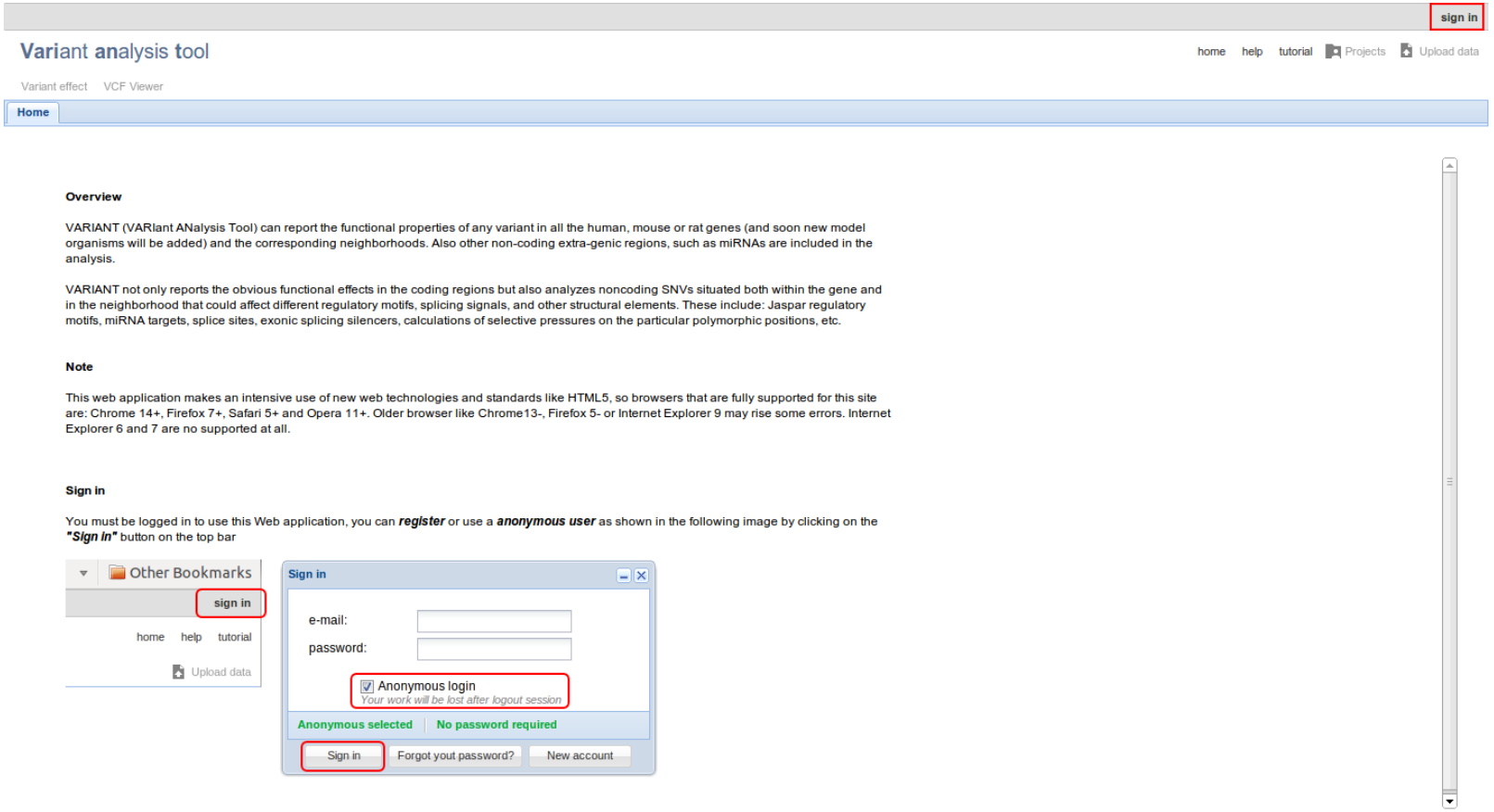
- **Is there any SNP with known phenotype?**

  Yes! There are 39 SNPs with known phenotype. They have been associated with Migraine, Alzheimer's disease, Ulcerative colitis, Rheumatoid arthritis, etc.

HPG VARIANT - Web application

- Web application

  http://variant.bioinfo.cipf.es/



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Thank you!

Questions?

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