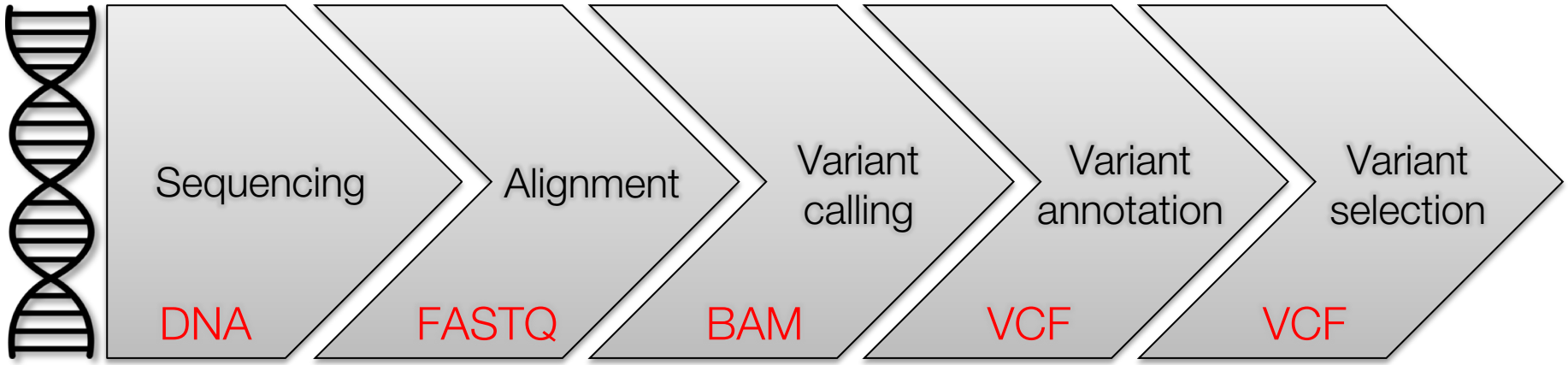
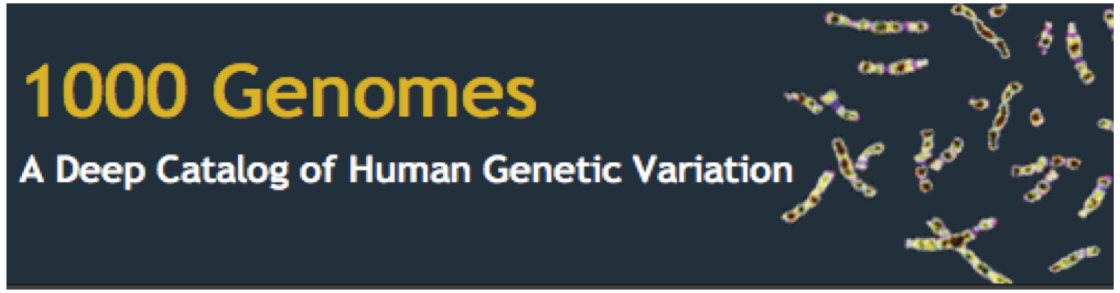
Sequencing workflow



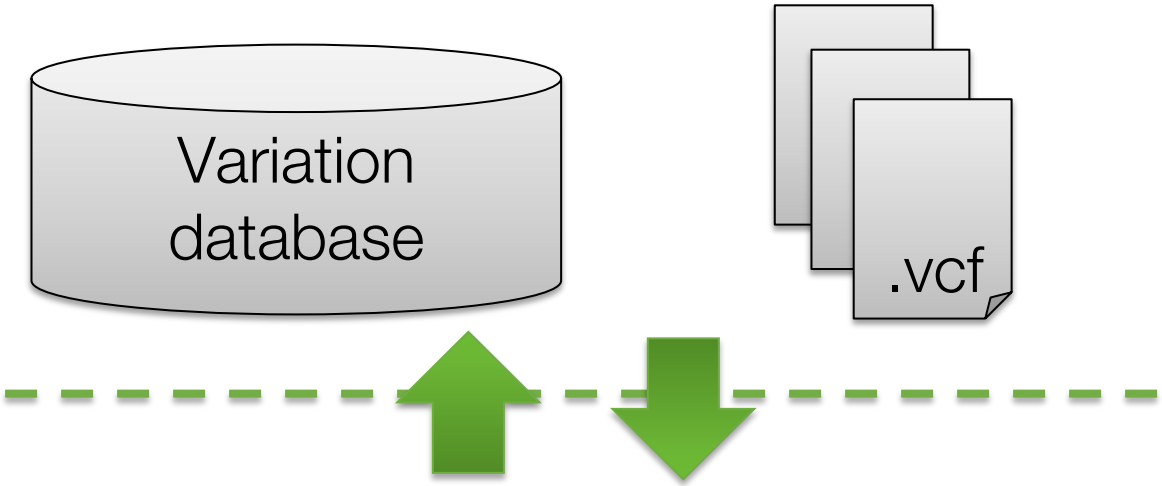


VCF format

1. CHROM – chromosome name
2. POS – reference position
3. ID – unique identifier(s)
4. REF – reference allele
5. ALT – alternate allele(s)
6. QUAL – quality score
7. FILTER – “PASS” or list of failed filters
8. INFO – additional / miscellaneous information
9. FORMAT – genotype specification

```
#CHROM POS     ID        REF ALT    QUAL FILTER INFO              FORMAT NA00001
20     14370   rs6054257 G   A      29   PASS   AF=0.5           GT     0|0
20     17330   .         T   A      3    q10    AF=0.017         GT     1|1
20     1110696 rs6040355 A   G,T    67   PASS   AF=0.333,0.667 GT     0|2
```

VCF backend



Remote @EBI

- Data is stored in databases and VCF files

Local @home

- Use the Ensembl API to
  - compute allele and genotype counts and frequencies
  - Linkage disequilibrium
- calculated on the fly

We have data from VCF files for:

- Human
- Mouse
- Cow
- Sheep
- Goat

The details are specified in a configuration file:

- ensembl-variation/modules/Bio/EnsEMBL/Variation/DBSQL/vcf_config.json

Tell API to look up data from VCF files

```
# Create any adaptor from the variation API
# For example create a variation adaptor
my $va = $registry->get_adaptor('human', 'variation', 'variation');

# Look up data from VCF files and database
$va->db->use_vcf(1)

# Look up data ONLY from VCF files
$va->db->use_vcf(2)
```

Variation

get_all_SampleGenotypes

get_all_PopulationGenotypes

get_all_Alleles

SampleGenotype

- variation
- sample
- genotype_string

PopulationGenotype

- variation
- population
- genotype_string
- frequency

Allele

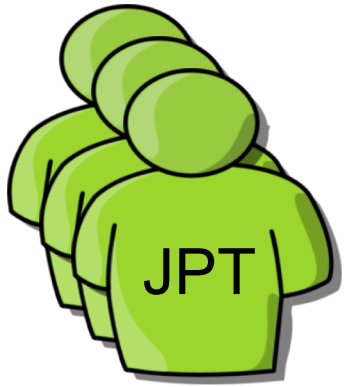
- variation
- population
- allele
- frequency

rs4988235

A|G

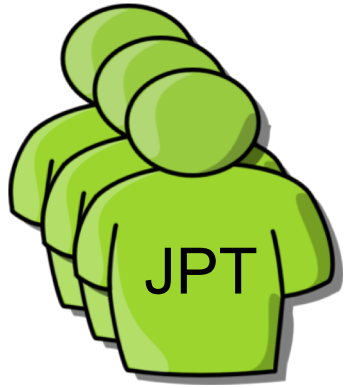
rs4988235

A|A 0.3



rs4988235

A 0.3



Allele

Method	Return type	Example value
`$a->allele()`	String	G
`$a->count()`	Int	34, undef if not defined
`$a->frequency()`	Float	0.15, undef if not defined
`$a->population()`	Population object	Bio::EnsEMBL::Variation::Population, undef if not defined
`$a->variation()`	Variation object	Bio::EnsEMBL::Variation::Variation

SampleGenotype

Method	Return type	Example value
`$sg->genotype()` `@alleles = @{$sg->genotype}`	Genotype List reference	[A, C]
`$sg->genotype_string()`	Genotype String	A|C
`$sg->variation()`	Variation Object	Bio::EnsEMBL::Variation::**Variation**
`$sg->sample()`	Sample Object	Bio::EnsEMBL::Variation::**Sample**
`$sg->sample->individual()`	Individual	Bio::EnsEMBL::Variation::**Individual**

PopulationGenotype

Method	Return type	Example value
`$pg->genotype()` `@alleles = @{$pg->genotype}`	Genotype List reference	[A, C]
`$pg->genotype_string()`	Genotype String	A|C
`$pg->frequency()`		0.5
`$pg->variation()`	Variation Object	Bio::EnsEMBL::Variation::**Variation**
`$pg->population()`	Population Object	Bio::EnsEMBL::Variation::**Population**

Projects	Population names	Allele Frequency	SampleGenotype PopulationGenotype
gnomAD	gnomAD	✓	✗
1000 Genomes Project	1000GENOMES:phase_3	✓	✓
TOPMed	TOPMed	✓	✗
UK10K	TWINSUK ALSPAC	✓	✗

1000 Genomes Project Allele and Genotype Frequencies

rs4988235

EAS	**G: 1.000 (1008)**		**GIG: 1.000 (504)**			
CDX	G: 1.000 (186)		GIG: 1.000 (93)			
CHB	G: 1.000 (206)		GIG: 1.000 (103)			
CHS	G: 1.000 (210)		GIG: 1.000 (105)			
JPT	G: 1.000 (208)		GIG: 1.000 (104)			
KHV	G: 1.000 (198)		GIG: 1.000 (99)			
EUR	**G: 0.492 (495)**	**A: 0.508 (511)**	**GIG: 0.306 (154)**	**AIA: 0.322 (162)**	**AIG: 0.372 (187)**
CEU	G: 0.263 (52)	A: 0.737 (146)	GIG: 0.071 (7)	AIA: 0.545 (54)	AIG: 0.384 (38)
FIN	G: 0.409 (81)	A: 0.591 (117)	GIG: 0.141 (14)	AIA: 0.323 (32)	AIG: 0.535 (53)
GBR	G: 0.280 (51)	A: 0.720 (131)	GIG: 0.099 (9)	AIA: 0.538 (49)	AIG: 0.363 (33)
IBS	G: 0.542 (116)	A: 0.458 (98)	GIG: 0.318 (34)	AIA: 0.234 (25)	AIG: 0.449 (48)
TSI	G: 0.911 (195)	A: 0.089 (19)	GIG: 0.841 (90)	AIA: 0.019 (2)	AIG: 0.140 (15)

Allele

PopulationGenotype

gnomAD Allele Frequencies

rs4988235

Population	Allele: frequency (count)	
gnomADg:**ALL**	G: 0.589 (18204)	A: 0.411 (12712)
gnomADg:**AFR**	G: 0.875 (7620)	A: 0.125 (1092)
gnomADg:**AMR**	G: 0.797 (668)	A: 0.203 (170)
gnomADg:**ASJ**	G: 0.897 (271)	A: 0.103 (31)
gnomADg:**EAS**	G: 0.999 (1621)	A: 0.001 (1)
gnomADg:**FIN**	G: 0.429 (1496)	A: 0.571 (1994)
gnomADg:**NFE**	G: 0.402 (6013)	A: 0.598 (8959)
gnomADg:**OTH**	G: 0.526 (515)	A: 0.474 (465)

gnomAD VCF file does not contain genotypes. Allele frequencies and counts are taken from the INFO field.

Exercise

- Print allele frequencies and allele counts for variant rs4988235
  - Print only results from the following projects: gnomAD, UK10K and TOPMed
    - $population_name =~ /gnomad|topmed|twinsuk|alspac/i
    - Which population reports frequencies for the C allele?
  - Print only results for the following 1000 Genomes populations: 1000GENOMES:phase_3:**FIN**, 1000GENOMES:phase_3:**CHB**, 1000GENOMES:phase_3:**ASW**
    - $population_name eq '1000GENOMES:phase_3:**FIN**'
    - Which population has the highest allele frequency for allele A?

Exercise

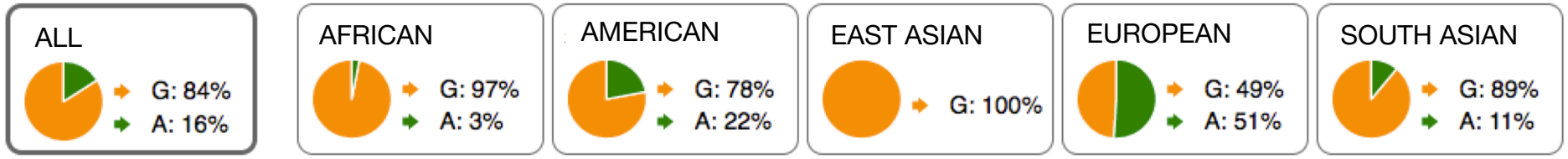
- Find all samples from population 1000GENOMES:phase_3:**ACB** with genotype A|G or G|A for variant rs4988235. Print the sample name and the genotype.
  - `$variation->get_all_SampleGenotypes($population);`

- Print population genotype frequencies and counts observed in 1000GENOMES:phase_3:**ACB** for variant rs4988235.
  - `$variation->get_all_PopulationGenotypes($population)`

Lactose intolerance

- rs4988235: a SNP near the LCT gene controls whether lactase enzyme is turned on or off as a person grows older
- Alleles: G/A

1000 Genomes Project Phase 3 allele frequencies

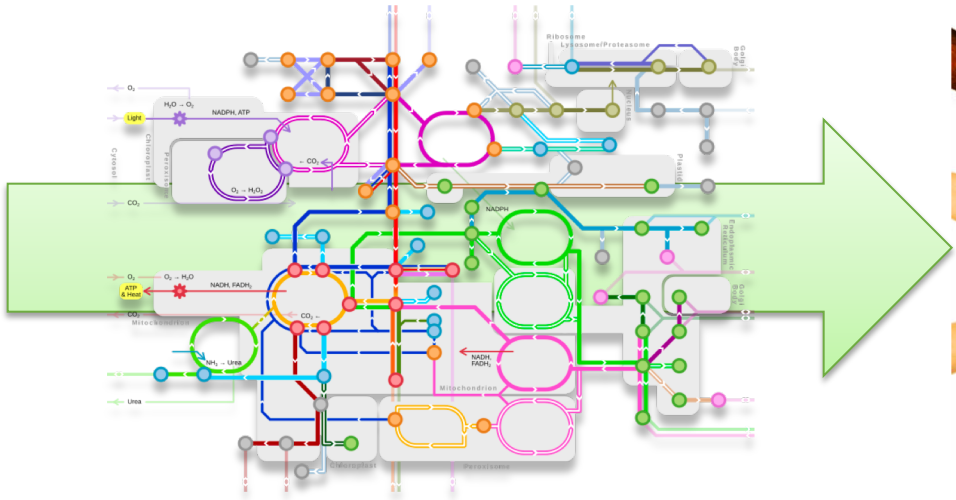


Genotype	What does it mean
G/G	Likely to be lactose intolerant.
G/A	Likely to be tolerant due to lactase persistence.
A/A	Lactose tolerant

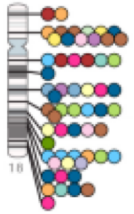
Phenotype data

- Trait
  - Can be described or measured
  - Final product of many molecular and biochemical processes
- Phenotype: Observed state of the trait
- Understand genotype to phenotype link

GIG: 0.318 (34)
AIG: 0.449 (48)
AIA: 0.234 (25)



NHGRI-EBI GWAS Catalog



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IMPC
INTERNATIONAL MOUSE PHENOTYPING CONSORTIUM

RGD

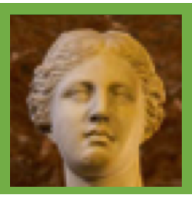
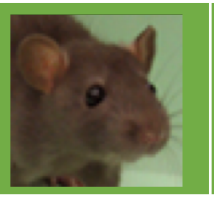
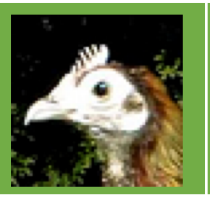
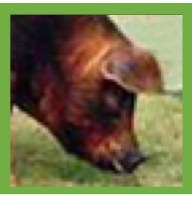
ZFIN

Feature + **Phenotype, Trait, Disease** + **Attributes**

- Genomic Location
  - Gene
  - Variant
  - QTL
  - Structural variant
- Description: as provided by the source
- Clinical significance
- Reported genes
- Most associated risk allele
- P-value
- Inheritance type
- Beta coefficient

PhenotypeFeature

Data available by species

Feature type								
Gene	47736	154,588	64,619	41	132	26	41	50,788
Variant	4,978,589	0	0	0	0	0	0	0
Structural Variant	116,854	0	0	0	0	0	0	0
QTL	0	0	2,266	4,723	100,171	17,588	1,072	0
Sources	17	2	1	3	3	3	3	1

Phenotypes linked to rs2470893

Show All entries | Show/hide columns | Filter

Phenotype, disease and trait	Source(s)	Mapped Terms	Ontology Accessions	Study	Reported gene(s)	Associated allele	Statistics
Caffeine consumption	NHGRI-EBI GWAS catalog	coffee consumption	EFO:0004330	PMID:21490707	EDC3, CYP1A1, CYP1A2, LMAN1L, CSK	T	p-value: $5.00e^{-14}$ beta coefficient: 0.12 mg/day increase
Caffeine metabolism (plasma 1,3,7-trimethylxanthine (caffeine) level)	NHGRI-EBI GWAS catalog	caffeine metabolite measurement	EFO:0007872	PMID:27702941	ARID3B, CLK3, EDC3, CYP1A1	T	p-value: $5.00e^{-18}$ odds ratio: 8.65
Caffeine metabolism (plasma 1,3-dimethylxanthine (theophylline) level)	NHGRI-EBI GWAS catalog	caffeine metabolite measurement	EFO:0007872	PMID:27702941	ARID3B, CLK3, EDC3, CYP1A1	T	p-value: $1.00e^{-7}$ odds ratio: 5.3
Caffeine metabolism (plasma 1,7-dimethylxanthine (paraxanthine) to 1,3,7-trimethylxanthine (caffeine) ratio)	NHGRI-EBI GWAS catalog	caffeine metabolite measurement	EFO:0007872	PMID:27702941	ARID3B, CLK3, EDC3, CYP1A1	T	p-value: $4.00e^{-15}$ odds ratio: 7.85
Coffee consumption	NHGRI-EBI GWAS catalog	coffee consumption, cups of coffee per day measurement	EFO:0004330, EFO:0006782	PMID:21876539	CYP1A1, CYP1A2	T	p-value: $2.00e^{-11}$ beta coefficient: 0.0675 unit increase
Coffee consumption	NHGRI-EBI GWAS catalog	coffee consumption, cups of coffee per day measurement	EFO:0004330, EFO:0006782	PMID:25288136	CYP1A1, CYP1A2	T	p-value: $5.00e^{-19}$ beta coefficient: 0.2 unit increase
Platelet distribution width	NHGRI-EBI GWAS catalog	platelet distribution width	EFO:0007984	PMID:27863252	CYP1A1	T	p-value: $4.00e^{-10}$ beta coefficient: 0.02388056 unit decrease

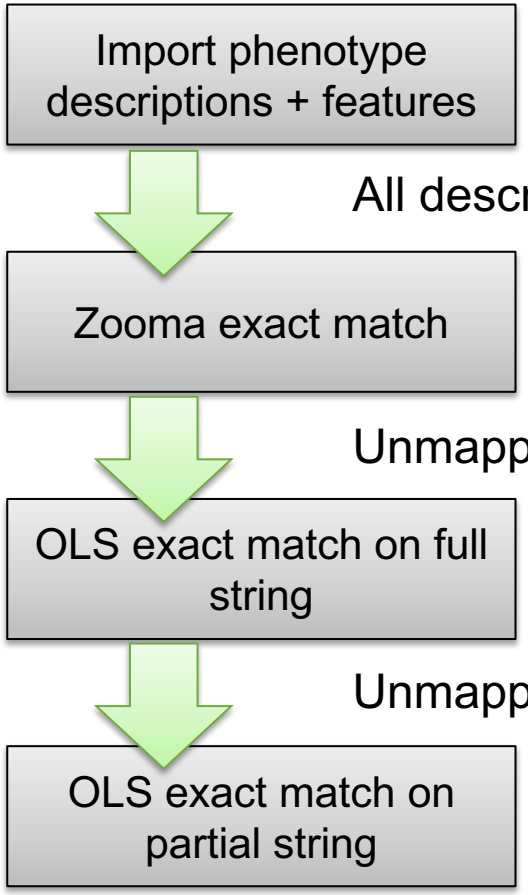
The naming problem

- Different sources describe the phenotypes/ diseases in different ways
  - We need to normalise the descriptions for easy querying
  - Also need to respect the original data
  - Features are often reported as associated with a disease sub type making it complex to extract all loci of interest

The solution

- Use phenotype and disease ontologies to organise descriptions and allow query and display by synonym and child/parent term.

Import and mapping process



https://www.ebi.ac.uk/spot/ontology/

Ontology mappings

rs2470893

Show All entries | Show/hide columns | Filter

Phenotype, disease and trait	Source(s)	Mapped Terms	Ontology Accessions	Study	Reported gene(s)	Associated allele	Statistics
Caffeine consumption	NHGRI-EBI GWAS catalog	coffee consumption	EFO:0004330	PMID:21490707	EDC3, CYP1A1, CYP1A2, LMAN1L, CSK	T	p-value: $5.00e^{-14}$ beta coefficient: 0.12 mg/day increase
Caffeine metabolism (plasma 1,3,7-trimethylxanthine (caffeine) level)	NHGRI-EBI GWAS catalog	caffeine metabolite measurement	EFO:0007872	PMID:27702941	ARID3B, CLK3, EDC3, CYP1A1	T	p-value: $5.00e^{-18}$ odds ratio: 8.65
Caffeine metabolism (plasma 1,3-dimethylxanthine (theophylline) level)	NHGRI-EBI GWAS catalog	caffeine metabolite measurement	EFO:0007872	PMID:27702941	ARID3B, CLK3, EDC3, CYP1A1	T	p-value: $1.00e^{-7}$ odds ratio: 5.3
Caffeine metabolism (plasma 1,7-dimethylxanthine (paraxanthine) to 1,3,7-trimethylxanthine (caffeine) ratio)	NHGRI-EBI GWAS catalog	caffeine metabolite measurement	EFO:0007872	PMID:27702941	ARID3B, CLK3, EDC3, CYP1A1	T	p-value: $4.00e^{-15}$ odds ratio: 7.85
Coffee consumption	NHGRI-EBI GWAS catalog	coffee consumption, cups of coffee per day measurement	EFO:0004330, EFO:0006782	PMID:21876539	CYP1A1, CYP1A2	T	p-value: $2.00e^{-11}$ beta coefficient: 0.0675 unit increase
Coffee consumption	NHGRI-EBI GWAS catalog	coffee consumption, cups of coffee per day measurement	EFO:0004330, EFO:0006782	PMID:25288136	CYP1A1, CYP1A2	T	p-value: $5.00e^{-19}$ beta coefficient: 0.2 unit increase
Platelet distribution width	NHGRI-EBI GWAS catalog	platelet distribution width	EFO:0007984	PMID:27863252	CYP1A1	T	p-value: $4.00e^{-10}$ beta coefficient: 0.02388056 unit decrease

http://www.ensembl.org/Homo_sapiens/Variation/Phenotype?r=15:74726608-74727608;v=rs2470893;vdb=variation;vf=1851694

PhenotypeFeature

Method	Return type	Example value
`$pf->type()`	String	Gene, Variation, StructuralVariation, QTL
`$pf->object_id()`	String	Feature name e.g. rs2470893
`$pf->phenotype()`	Phenotype Object	Bio::EnsEMBL::Variation::Phenotype
`$pf->phenotype->description`	String	Caffeine consumption
`$pf->source()`	Source Object	Bio::EnsEMBL::Variation::Source
`$pf->source->name`	String	NHGRI-EBI GWAS catalog
`$pf->associated_gene()`	String	CDKN2BAS,NOTCH2
`$pf->risk_allele()`	String	C
`$pf->p_value()`	Float	6e-07
`$pf->get_all_ontology_accessions`	Arrayref of String	[EFO:0004330, EFO:0006782]
`$pf->seq_region_name()`	String	15, X
`$pf->seq_region_start()` `$pf->seq_region_end()`	Int	74727108 74727108

Add ontologies

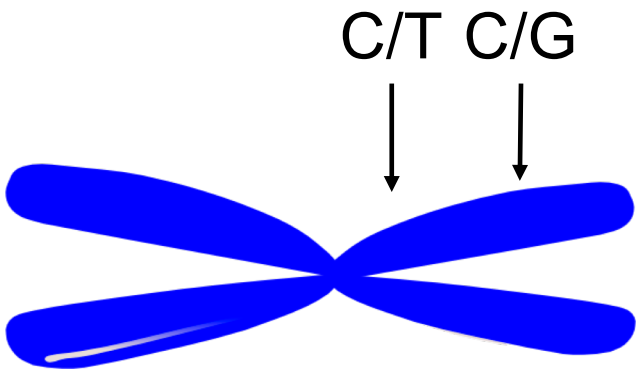
```
# Create a PhenotypeFeature adaptor
# For example create a variation adaptor
my $pfa = $registry->get_adaptor('human', 'variation', 'PhenotypeFeature');

# Add ontology mappings to the output
$pfa->_include_ontology(1);
```

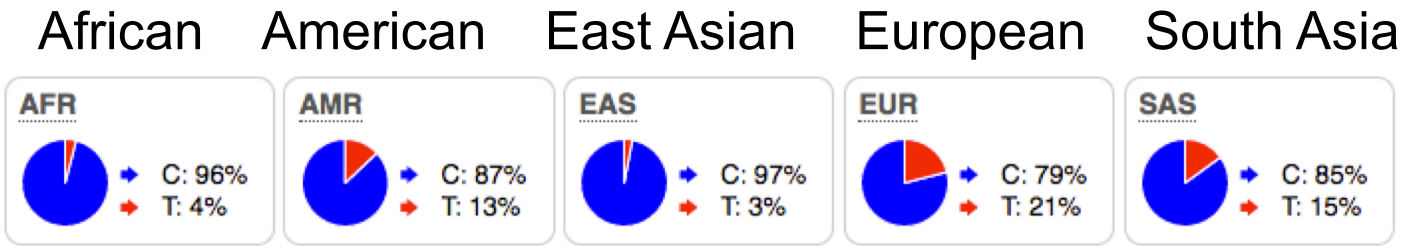
Exercise

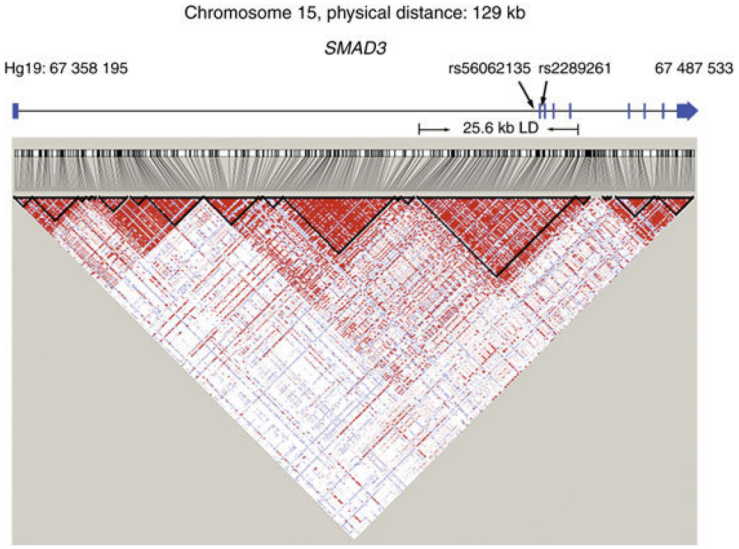
- After reading a publication about the first genome-wide association study of habitual caffeine intake you want to collect all phenotype data that has been linked to rs2470893.
  - Fetch all PhenotypeFeatures for variation rs2470893
  - For each PhenotypeFeature print phenotype description, source name, risk allele, p-value and ontology accessions
- You want to study all features that have been linked to coffee consumption (phenotype accession = EFO:0007872)
  - Fetch all PhenotypeFeatures for phenotype accession EFO:0007872
  - For each PhenotypeFeature print type, object_id, phenotype description and source name. You can use *fetch_all_by_phenotype_accession_source* without providing a source

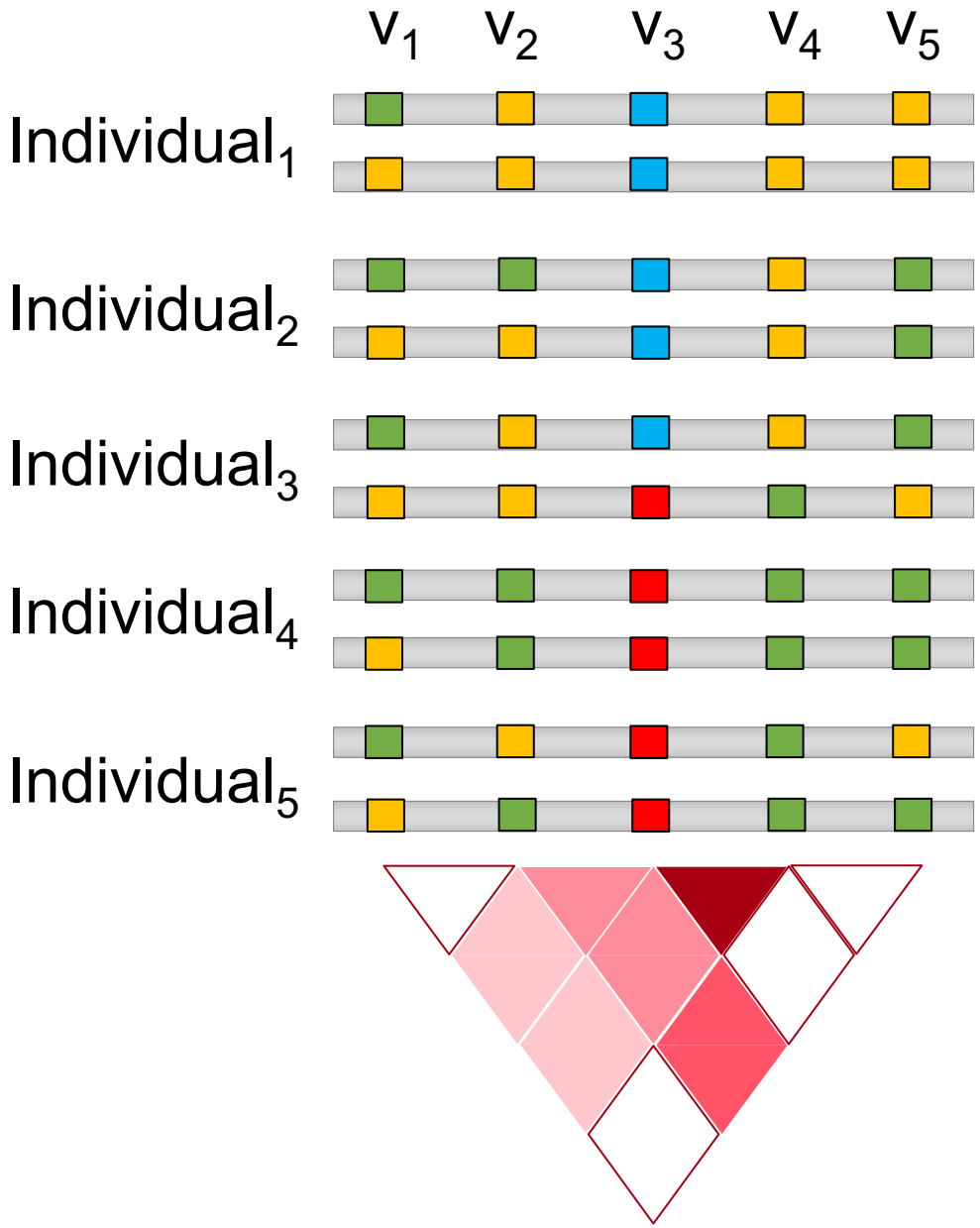
Linkage Disequilibrium

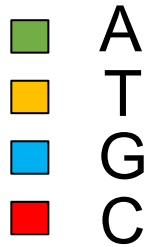


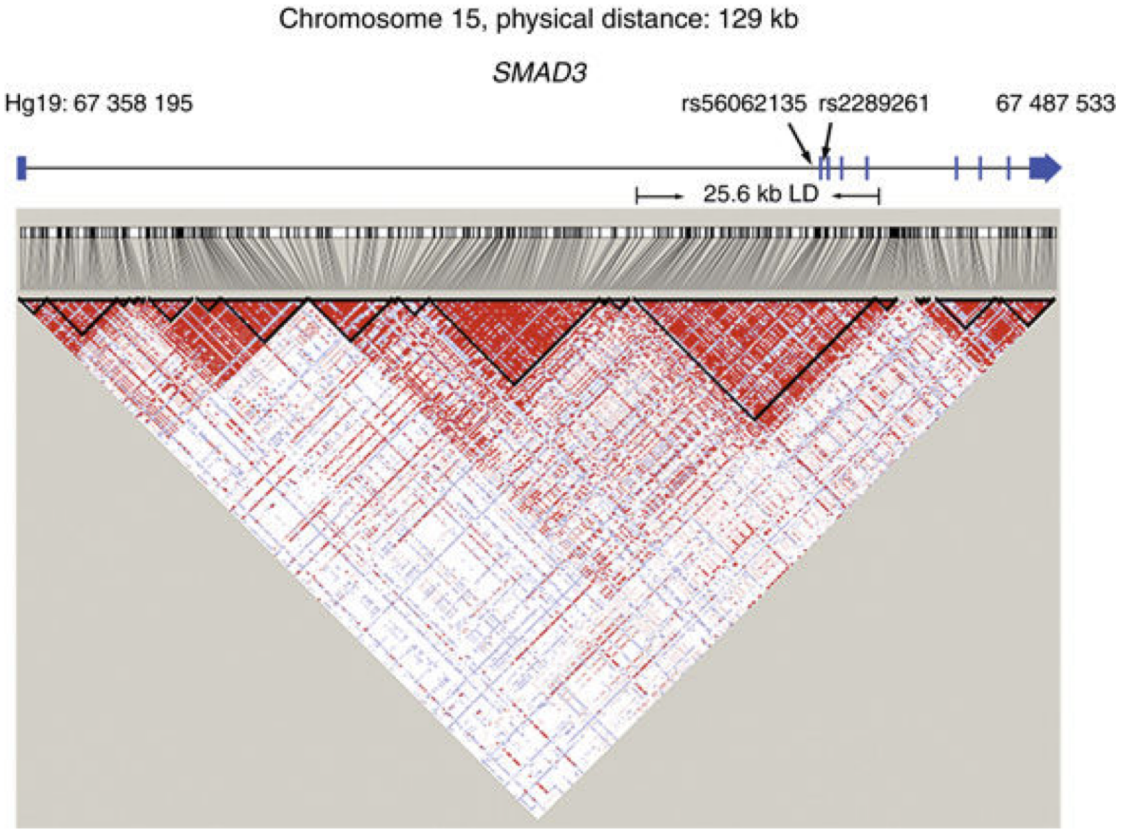
- Nonrandom association of alleles at different loci
- LD is a population-specific measurement

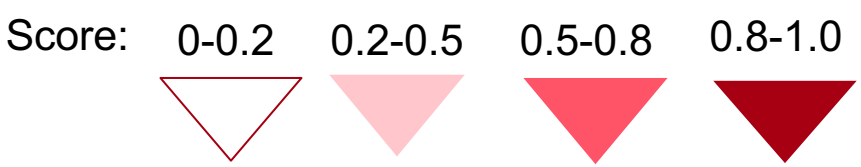




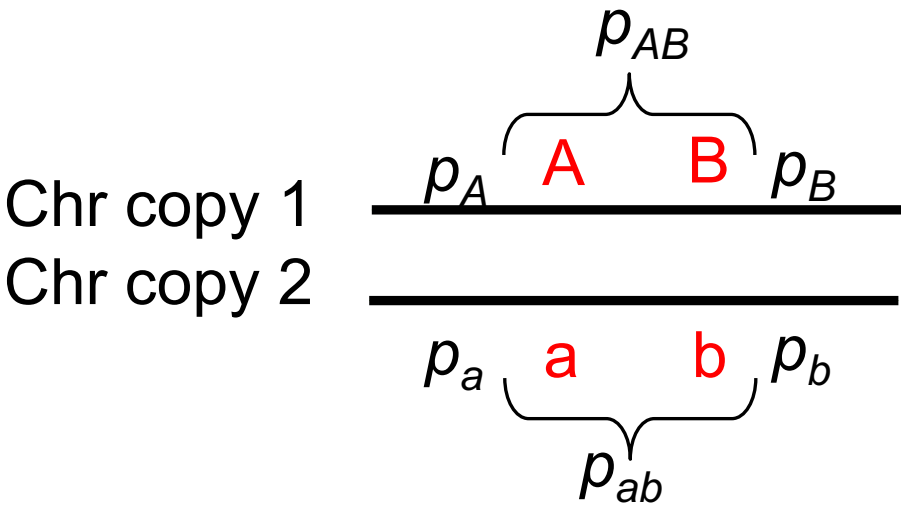

V1
V2
V3
V4
V5
Individual1
Individual2
Individual3
Individual4
Individual5


A
T
G
C


Chromosome 15, physical distance: 129 kb
SMAD3
Hg19: 67 358 195
rs56062135
rs2289261
67 487 533
25.6 kb LD


Score:
0-0.2
0.2-0.5
0.5-0.8
0.8-1.0

LD calculation



Allele	A	a	probability
B	p_{AB}	p_{aB}	p_B
b	p_{Ab}	p_{ab}	p_b
probability	p_A	p_a	1.0

Haplotype frequencies: p_{AB}, p_{ab}, p_{Ab}, p_{aB}
Allele frequencies: p_A, p_B, p_a, p_b
LD = observed - expected

$$D = p_{AB} - p_A p_B$$
$$|D'| = D/D_{max}$$
$$r^2 = D^2/p_A p_a p_B p_b$$

Interpreting LD values *D'* and r^2

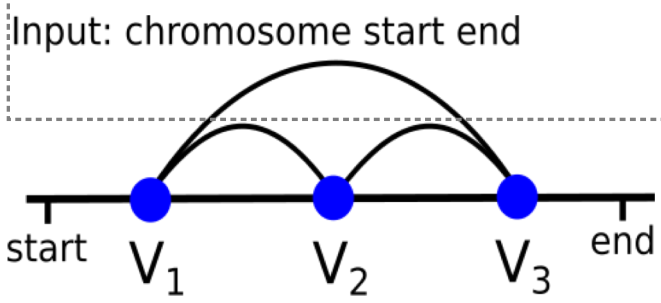
- High *D'* and high r^2
  - Tendency to the presence of only 2 haplotypes, small difference in allele frequency of coupled alleles
- High *D'* and low r^2
  - Tendency to the presence of only 3 haplotypes, different allele frequencies of the coupled alleles
- Low *D'* and low r^2
  - Tendency toward random coupling of alleles and presence of all 4 haplotypes

LDFeatureContainerAdaptor

```
# Create LDFeatureContainerAdaptor
my $ldfca = $registry->get_adaptor('human', 'variation', 'LDFeatureContainer');

# TODO fetch population object

# Compute LD in a region
# TODO fetch slice object for your region
my $ld_feature_container = $ldfca->fetch_by_Slice($slice, $population);
```



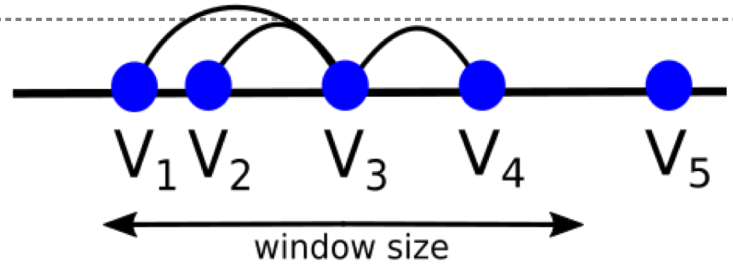
LDFeatureContainerAdaptor

```
# Create LDFeatureContainerAdaptor
my $ldfca = $registry->get_adaptor('human', 'variation', 'LDFeatureContainer');

# TODO fetch Population object

# Compute LD for a VariationFeature and all surrounding
# VariationFeatures that lie within a given window size
# max window size is XXX, default window size is XXX
# TODO fetch VariationFeature object
my $ld_feature_container = $ldfca->fetch_by_VariationFeature($vf, $population);
```

Input: Variant V_3, window size



LDFeatureContainer

- Container of pairwise LD values
- Calculated on the fly (using a script written in C)
- Use `$ldfc->get_all_ld_values` to get all computed LD values that are stored in the container $ldfc
- get_all_ld_values returns an array reference of hash references

Key	Value
variation1	VariationFeature object of one of the two variations used for the calculation
variation_name1	String value
variation2	VariationFeature object of the second variation used for the calculation
variation_name2	String value
r2	0 to 1
d_prime	0 to 1

```
foreach my $ld_result (@{$ldfc->get_all_ld_values}) {
  print $ld_result->{r2}, "\n";
…
}
```

LD populations

```
# Create Population adaptor
my $pa = $registry->get_adaptor('human', 'variation', 'Population');

my $ld_populations = $pa->fetch_all_LD_Populations();

foreach my $ld_population (@$ld_populations) {
    my $name = $ld_population->name;
    my $description = $ld_population->description;
    print "$name $description\n";
}
```

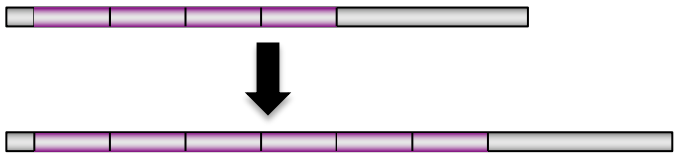
Exercise

- LD in a region `fetch_by_Slice($slice, $population)`
  - Compute all LD values for the region chromosome 12 between 11053716-11073715 and population 1000GENOMES:phase_3:CEU
  - Only print results where D' = 1 and r^2 = 1. Print D' (d_prime), r^2 (r2), variation_name1 and variation_name2
- LD for a variation feature `fetch_by_VariationFeature($vf, $population)`
  - Compute all LD values for rs7304579 and population 1000GENOMES:phase_3:YRI
  - Get the VariationFeature for rs7304579
  - Print all results. Print D' (d_prime), r^2 (r2), variation_name1 and variation_name2

Structural Variation

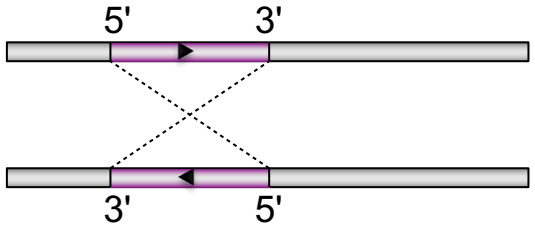
- Usually represents a large segment of variable DNA sequence (> 1kb)
- Different processes give rise to different types of structural variations:

Copy number variation (CNV)

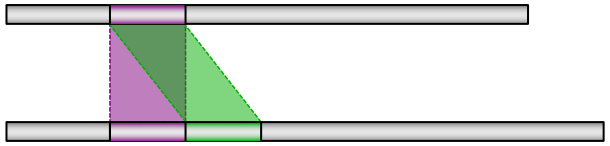


→ Allele type “Gain”

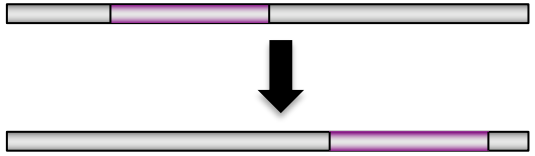
Inversion



Duplication



Translocation



Example of a Structural Variant

Structural variant: nsv917561

Variation class	CNV (SO:0001019)
Source	DGVa – Database of Genomic Variants Archive
Study	nstd75 – "International Standards for Cytogenomic Arrays Consortium (prenatal dataset)." PMID:21844811, PMID:20466091
Location	Chromosome 1:146987841-148359881 (forward strand)

Supporting evidence

Supporting evidence	Chr:bp (strand)	Allele type	Clinical significance	Individual name
nssv1605931	1:146987841-148359881 (+)	Gain	pathogenic	ISCA_ID_pn_1622
nssv1606072	1:146987841-148359881 (+)	Gain	-	ISCA_ID_pn_1746

Structural variant: nsv917561

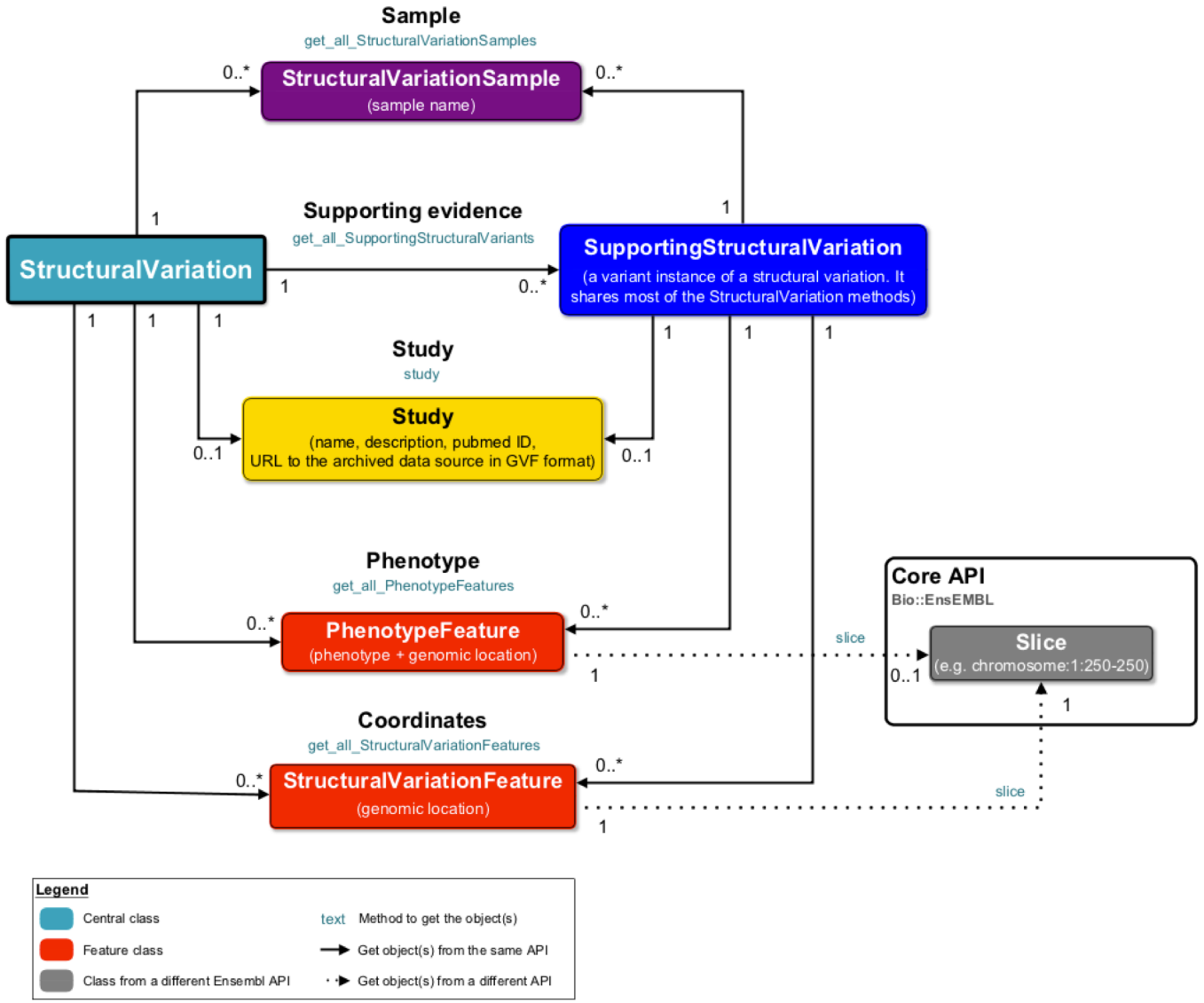
Variation class	CNV (SO:0001019)
Allele type(s)	gain (SO:0001742)
Source	DGVa - Database of Genomic Variants Archive
Study	nstd75 - International Standards for Cytogenomic Arrays Consortium (prenatal dataset) PMID:21844811 PMID:20466091
Alias	ISCA_VAR_pn_694
Clinical significance	
Location	Chromosome **1:146987841-148435812** (forward strand) | View in location tab
Genomic size	1,447,972 bp
About this structural variant	This structural variant overlaps 162 transcripts, is associated with 2 phenotypes and is supported by 2 pieces of evidence.

Explore this SV

http://www.ensembl.org/Homo_sapiens/StructuralVariation/Explore?sv=nsv917561

EnsEMBL Variation API Overview - StructuralVariation centered

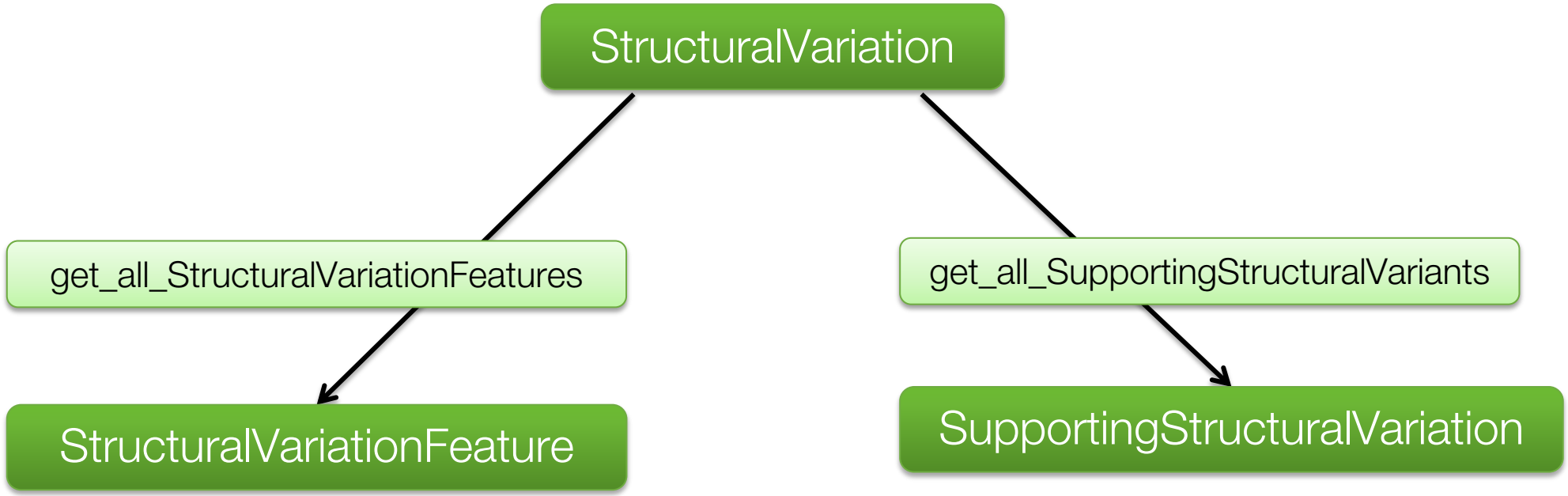
Bio::EnsEMBL::Variation



StructuralVariation

Method	Return type	Example value
`$sv->variation_name()`	String	esv214236
`$sv->var_class()`	String	CNV
`$sv->study()`	Study object	Bio::EnsEMBL::Variation::Study, undef if not defined
`$sv->get_all_SupportingStructuralVariants()`	Listref of objects	[Bio::EnsEMBL::Variation::SupportingStructuralVariation]

Supporting structural variation

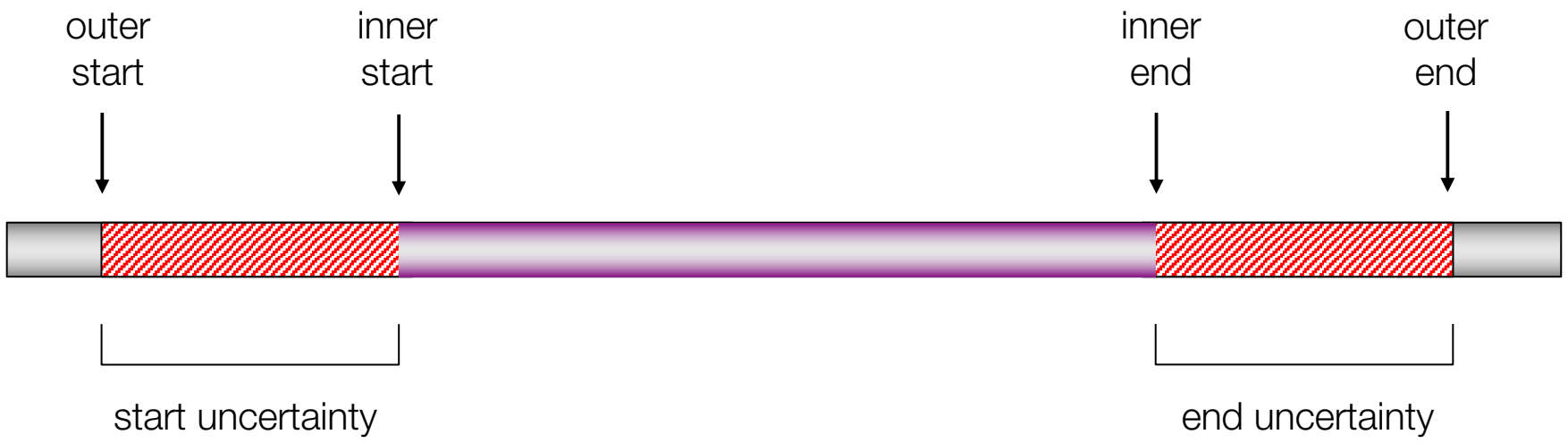


Region of the genome that a submitter has defined as containing structural variations.

Actual variant calls that were made within a study.

Structural variation coordinates

- Usually a structural variation has only a start and an end
- But sometimes, the breakpoint locations cannot be determined precisely



StructuralVariationFeature

- Can be retrieved from the StructuralVariationFeature adaptor and the StructuralVariation object

Attribute	Example value(s)	Method(s)
Structural variation name	esv214236	`$svf->variation_name()`
Chromosome	15, X	`$svf->seq_region_name()`

Coordinates		`$svf->start()`
		`$svf->end()`
		`$svf->seq_region_start()`
		`$svf->seq_region_end()` — "Classic" coordinates
		
		`$svf->outer_start()`
		`$svf->inner_start()`
		`$svf->inner_end()`
		`$svf->outer_end()` — SV specific coordinates

Class	CNV	`$svf->var_class()`

Exercise

- Fetch the following information for the structural variation esv275264 in human :
  - Structural variation class
  - Study name and description
  - Coordinates
- Fetch the names and the classes (sequence ontology term) of its supporting structural variations.

Ensembl Acknowledgements

The Entire Ensembl Team

Daniel R. Zerbino[1], Premanand Achuthan[1], Wasiu Akanni[1], M. Ridwan Amode[1], Daniel Barrell[1,2], Jyothish Bhai[1], Konstantinos Billis[1], Carla Cummins[1], Astrid Gall[1], Carlos García Giroń[1], Laurent Gil[1], Leo Gordon[1], Leanne Haggerty[1], Erin Haskell[1], Thibaut Hourlier[1], Osagie G. Izuogu[1], Sophie H. Janacek[1], Thomas Juettemann[1], Jimmy Kiang To[1], Matthew R. Laird[1], Ilias Lavidas[1], Zhicheng Liu[1], Jane E. Loveland[1], Thomas Maurel[1], William McLaren[1], Benjamin Moore[1], Jonathan Mudge[1], Daniel N. Murphy[1], Victoria Newman[1], Michael Nuhn[1], Denye Ogeh[1], Chuang Kee Ong[1], Anne Parker[1], Mateus Patricio[1], Harpreet Singh Riat[1], Helen Schuilenburg[1], Dan Sheppard[1], Helen Sparrow[1], Kieron Taylor[1], Anja Thormann[1], Alessandro Vullo[1], Brandon Walts[1], Amonida Zadissa[1], Adam Frankish[1], Sarah E. Hunt[1], Myrto Kostadima[1], Nicholas Langridge[1], Fergal J. Martin[1], Matthieu Muffato[1], Emily Perry[1], Magali Ruffier[1], Dan M. Staines[1], Stephen J. Trevanion[1], Bronwen L. Aken[1], Fiona Cunningham[1], Andrew Yates[1] and Paul Flicek[1,3]

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Funding

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SAVE THE TASMANIAN DEVIL PROGRAM APPEAL

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MedBioinformatics

Co-funded by the European Union