Variant prioritization

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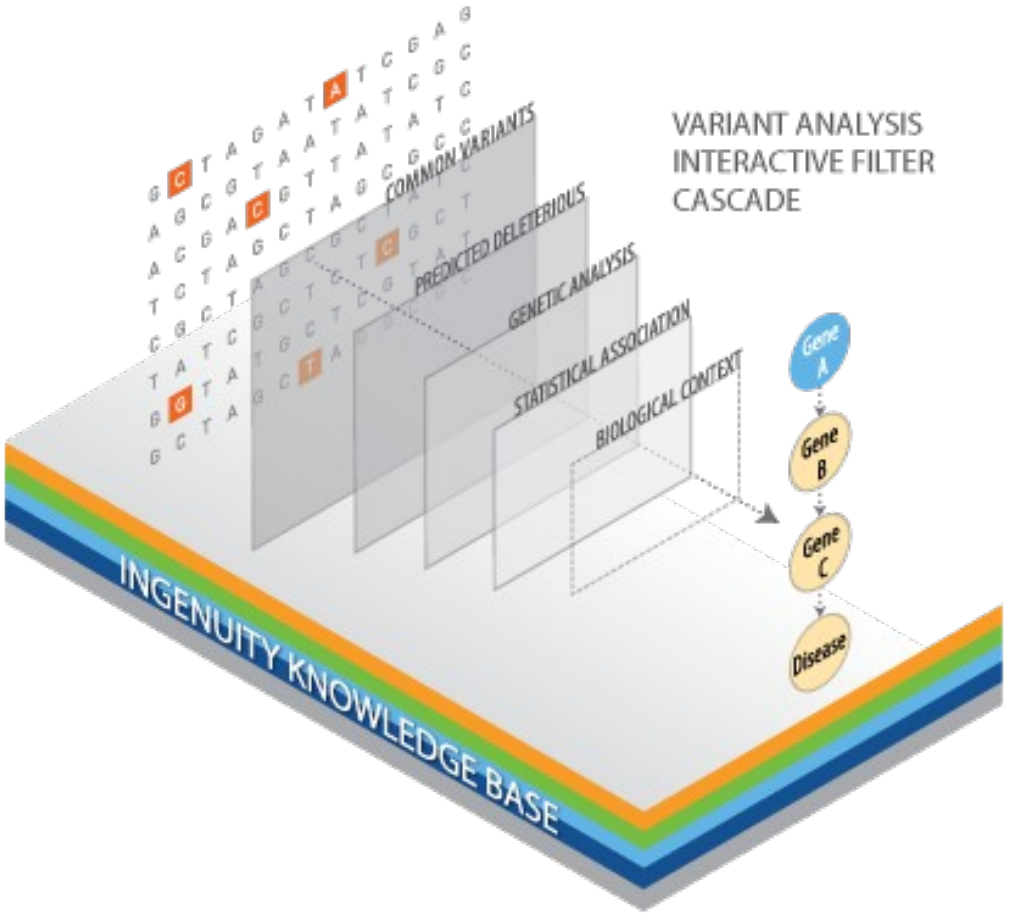
PRINCIPE FELIPE
CENTRO DE INVESTIGACION

UNIVERSITY OF CAMBRIDGE

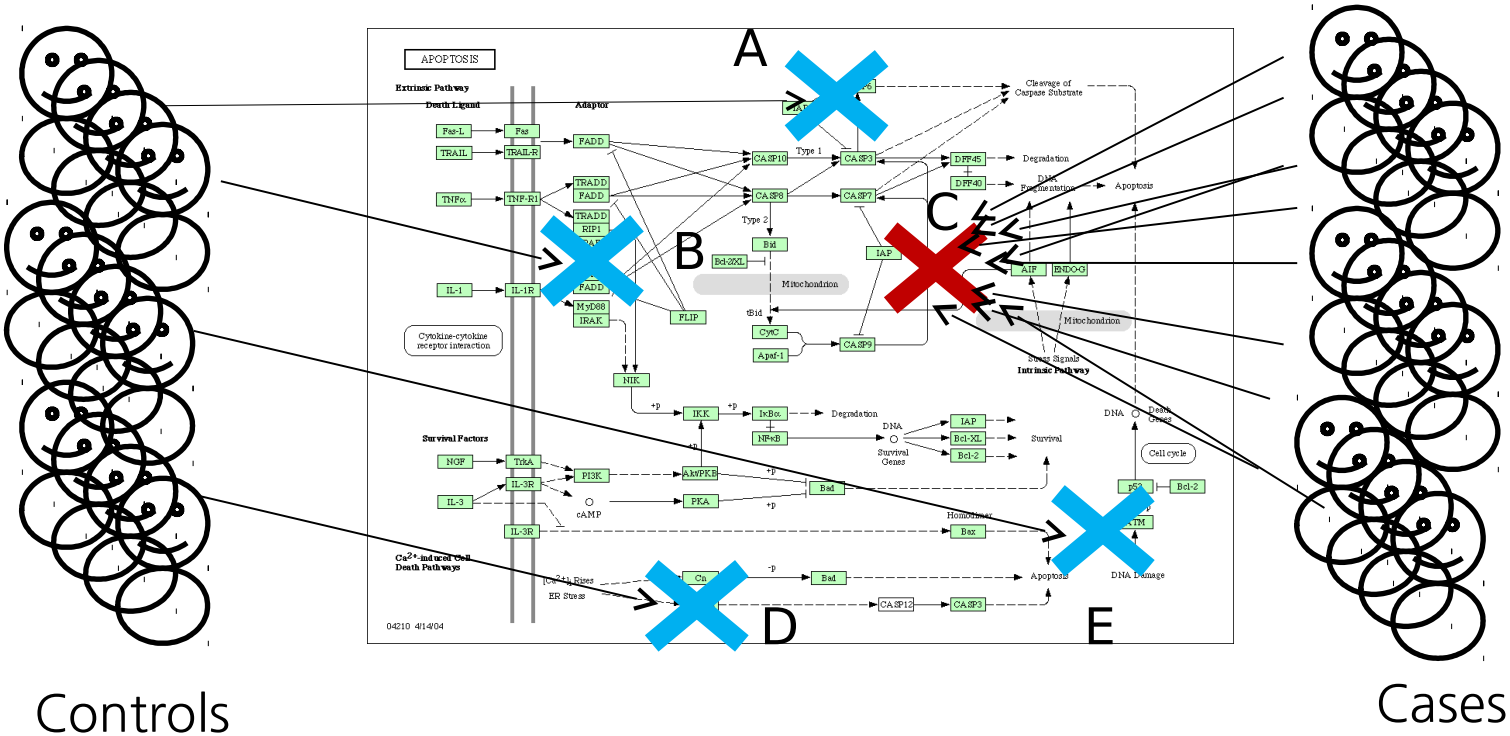
The objective



And now what?

Finding the mutations causative of diseases

The **simplest case**: monogenic disease due to a single gene

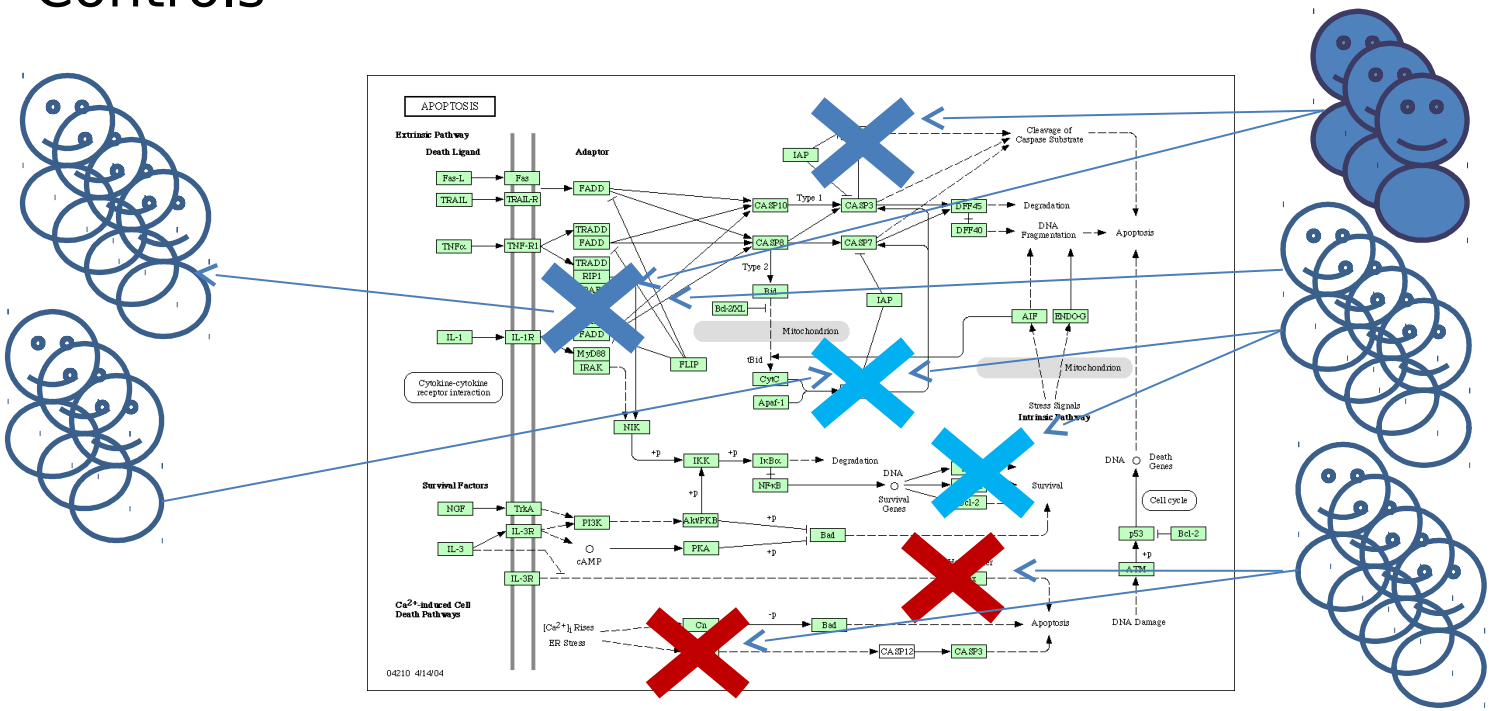


And now what?

Finding the mutations causative of diseases

Controls

Cases



Clear individual **gene associations are difficult to find** in some diseases

Same phenotype can be due to **different mutations and different genes** (or combinations)

Many cases have to be used to obtain significant associations to many markers

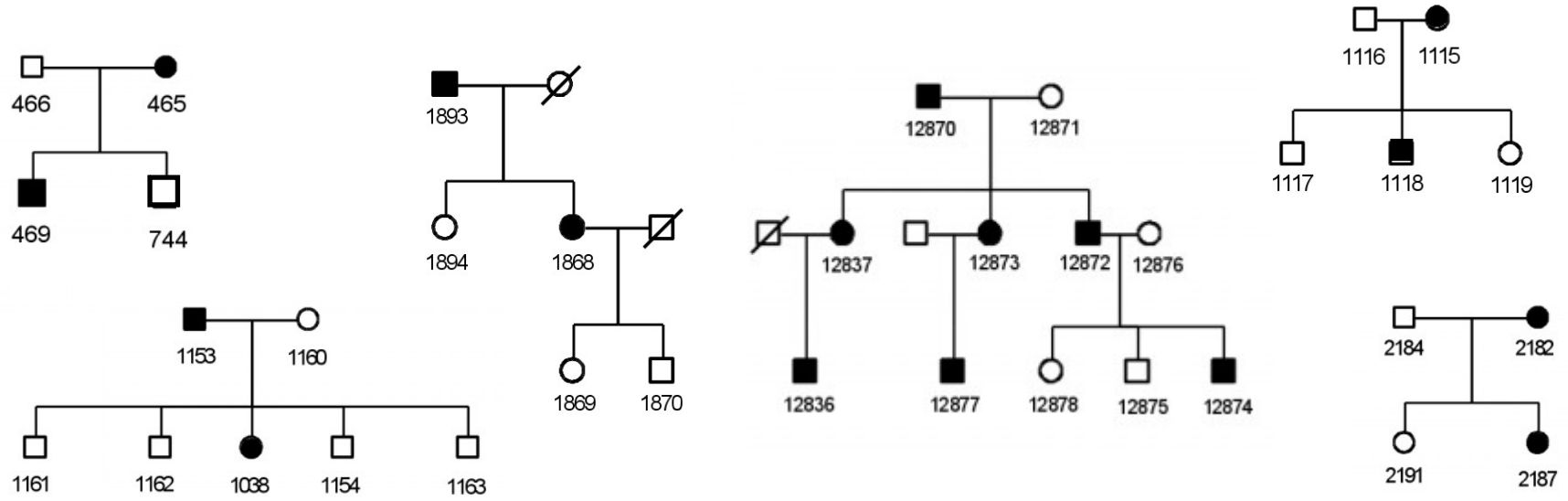
The only common element is the **pathway** (yet unknown) affected

Strategies

- Filtering using **family information**
- **Network** (Systems biology) approaches
  - PPIs
  - Gene regulatory elements (miRNAs, Tfs)
  - GO terms
- GWAS
- Burden tests for rare variants….

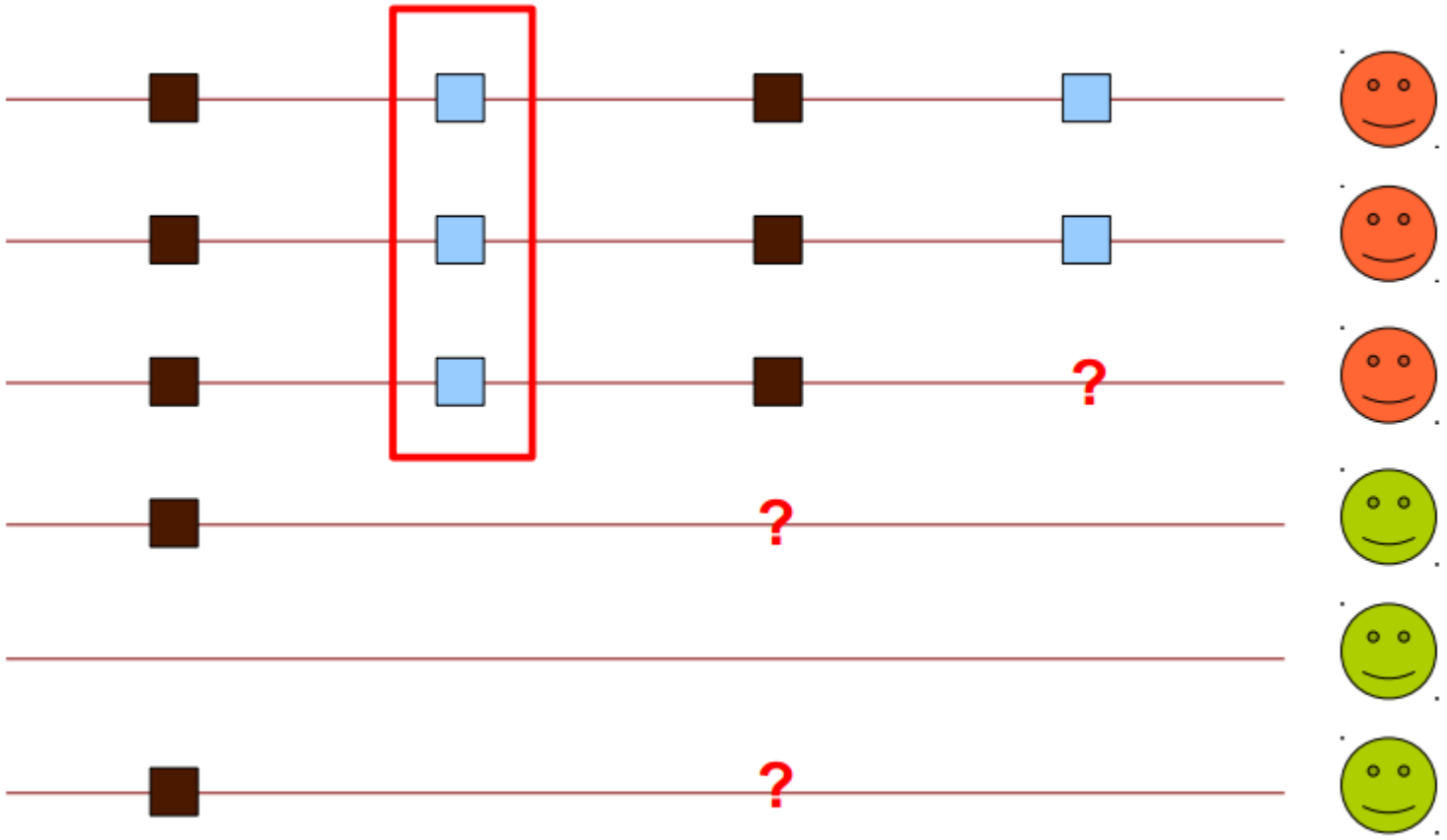
Using family information

- Families containing **control and disease** individuals can help us to **reduce** the number of variants obtained
- Individuals from the same family → **less variability**
- **Filter** variants present in healthy people



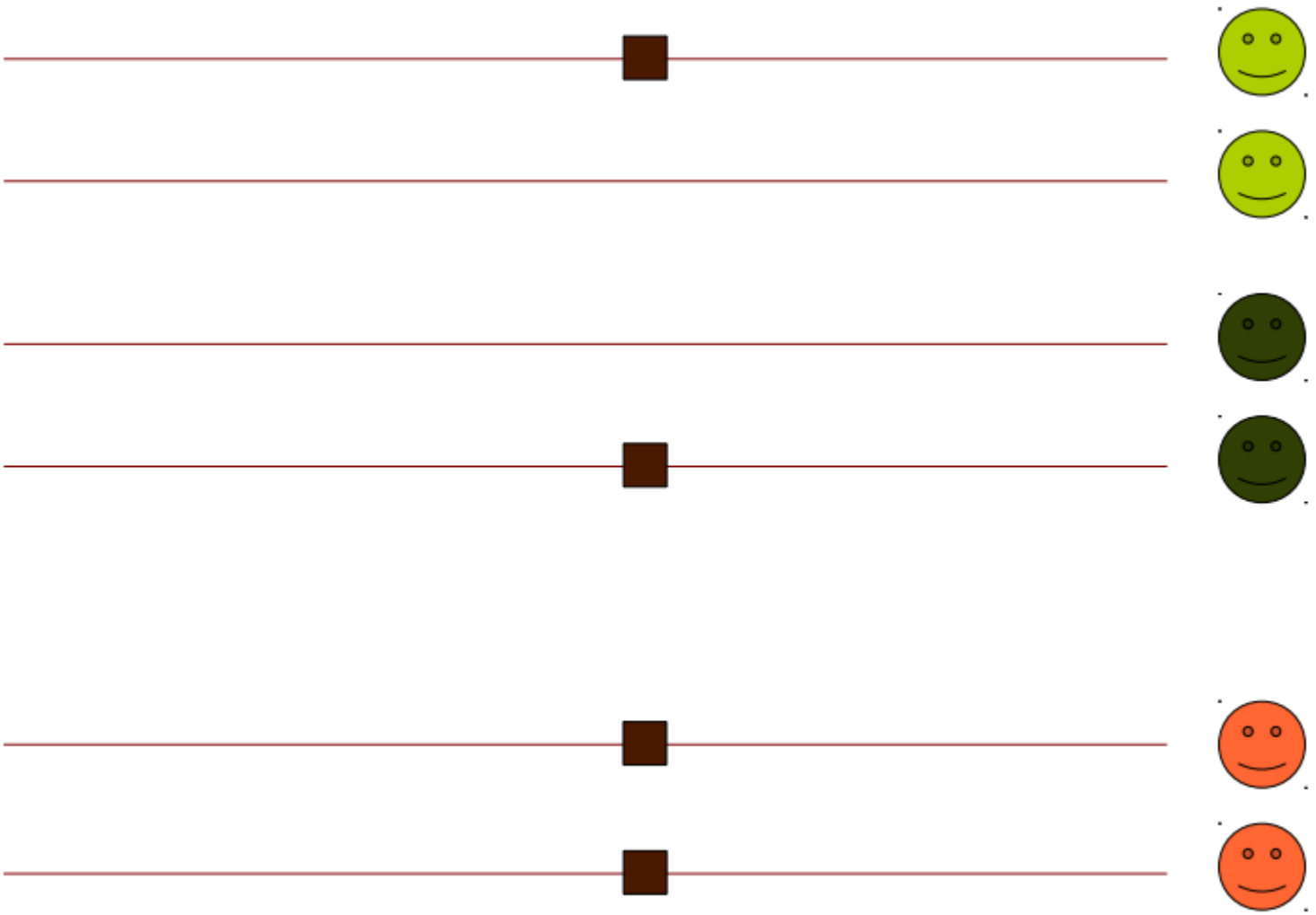
Using family information

Dominant inheritance



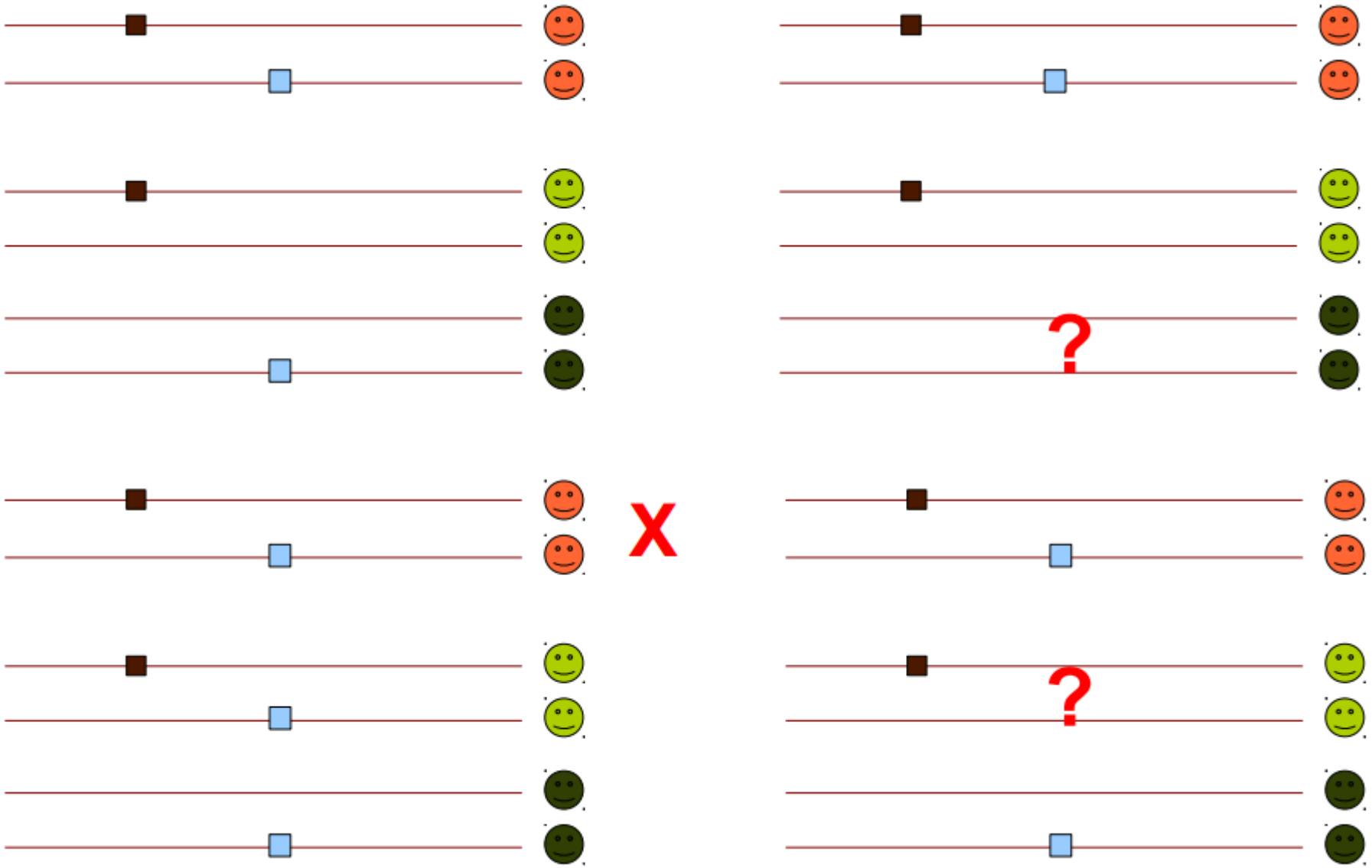
Using family information

Recessive homozygous



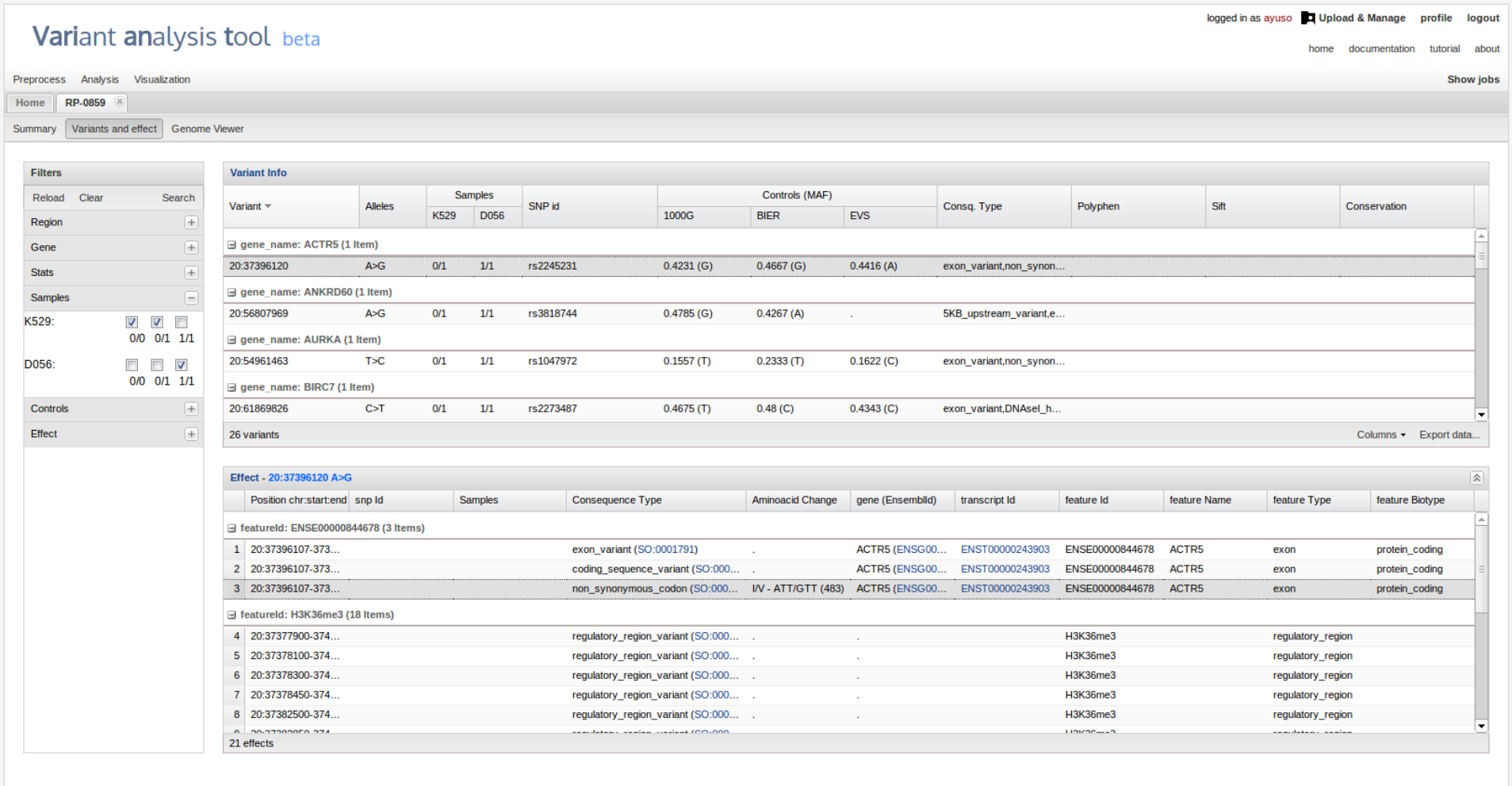
Using family information

Recessive - Compound heterozygosity

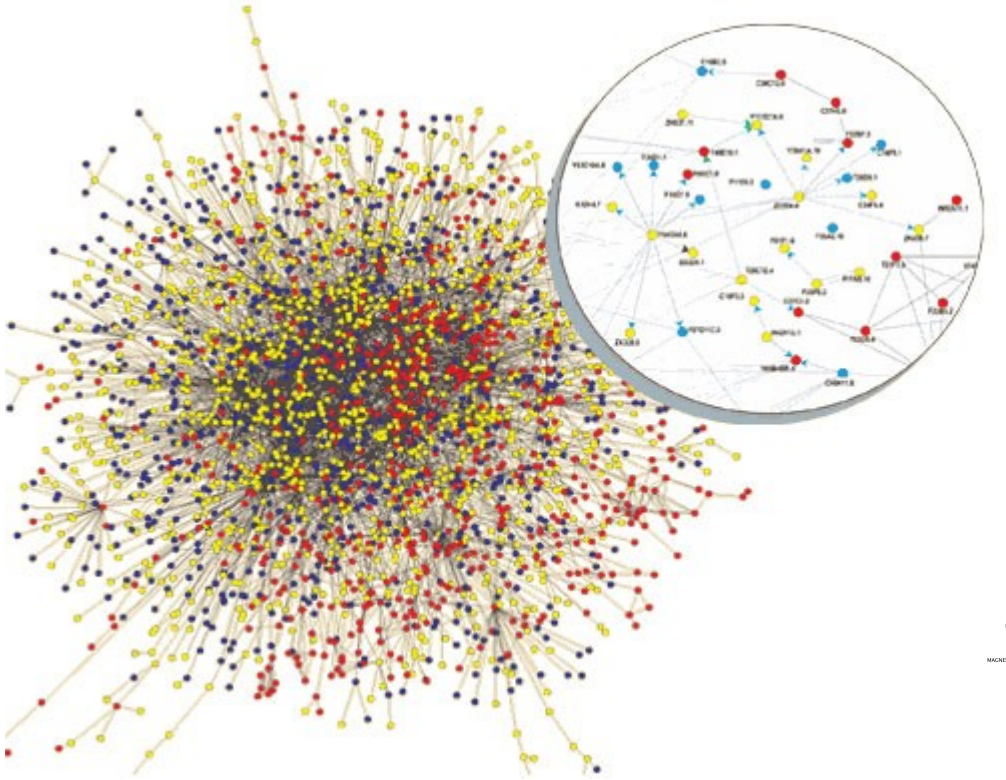


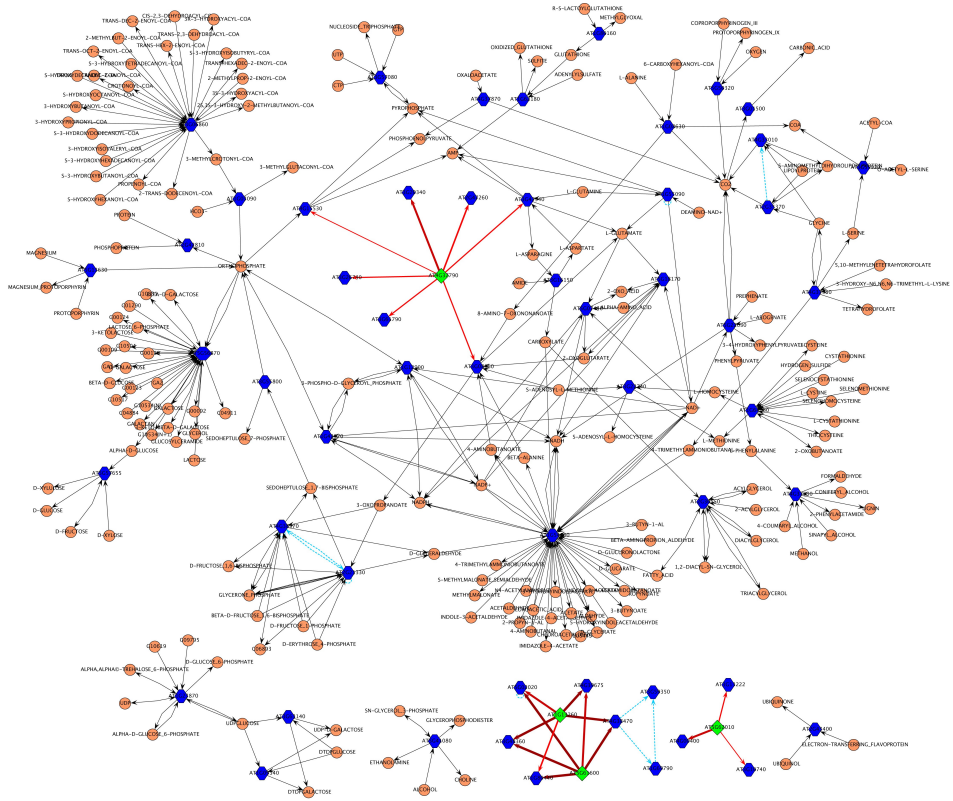
BierApp

Bierapp.babelomics.org



Using network information



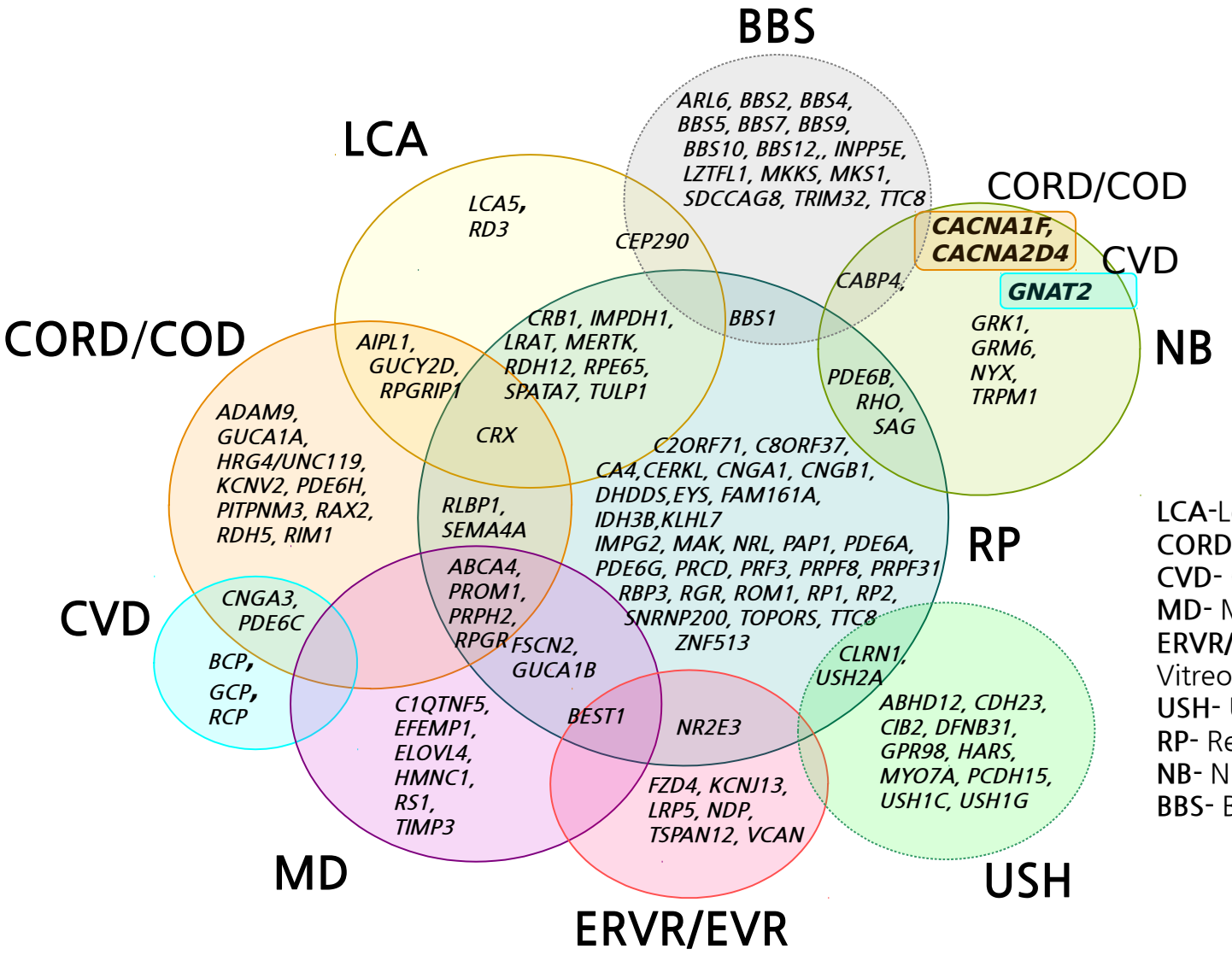


Example with Inherited Retinal Dystrophies (IRD)

- Prevalence 1 in 3000
- Clinically and genetically very **heterogeneous**
- 190 GENES account for aprox. 50% of IRDs.

Is genetic overlapping among IRDs related to protein interaction?

Example with Inherited Retinal Dystrophies (IRD)



LCA-Leber Congenital Amaurosis
CORD/COD- Cone and cone-rod dystro.
CVD- Colour Vision Defects
MD- Macular Degeneration
ERVR/EVR- Erosive and Exudative Vitreoretinopathies
USH- Usher Syndrome
RP- Retinitis Pigmentosa
NB- Night Blindness
BBS- Bardet-Biedl Syndrome

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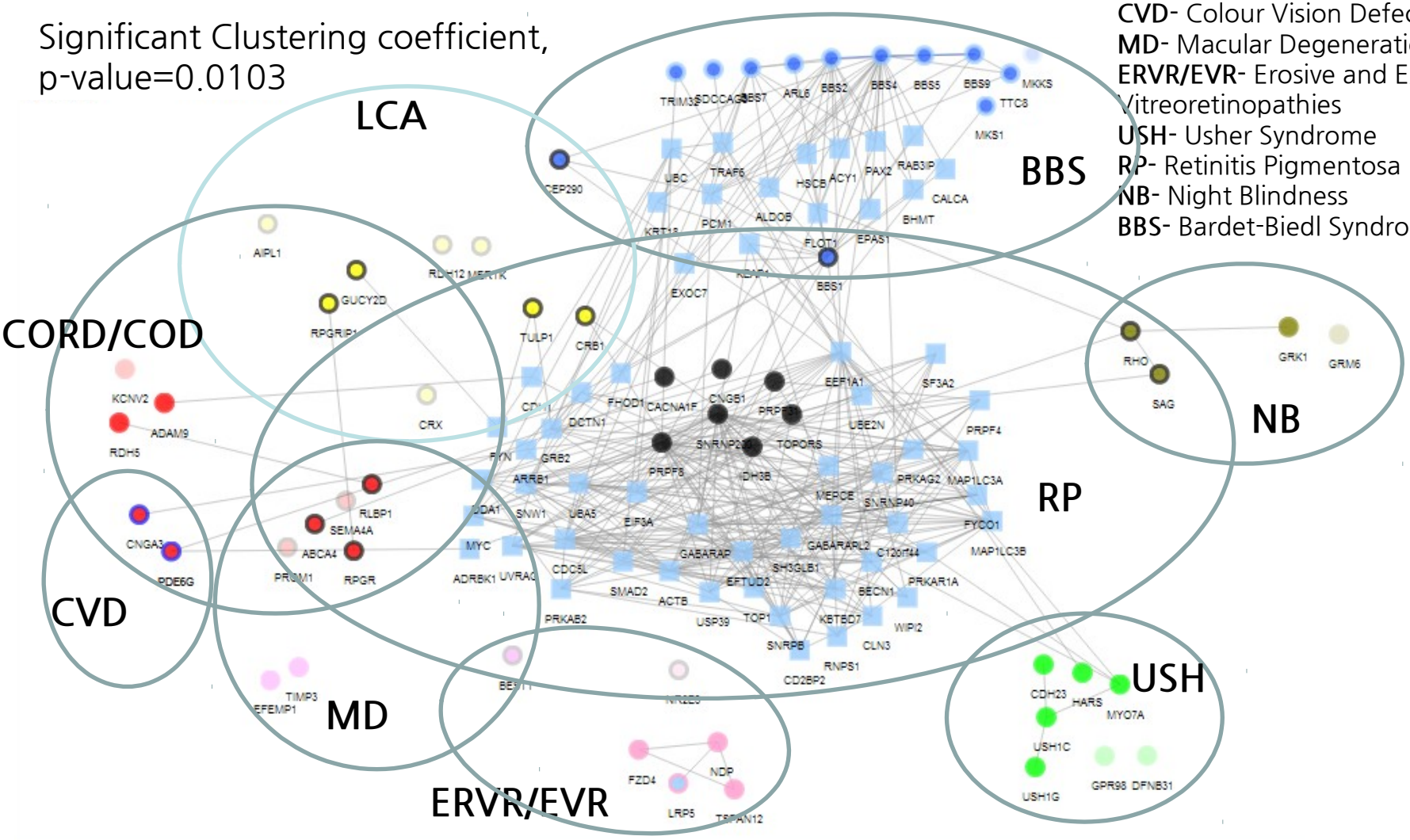
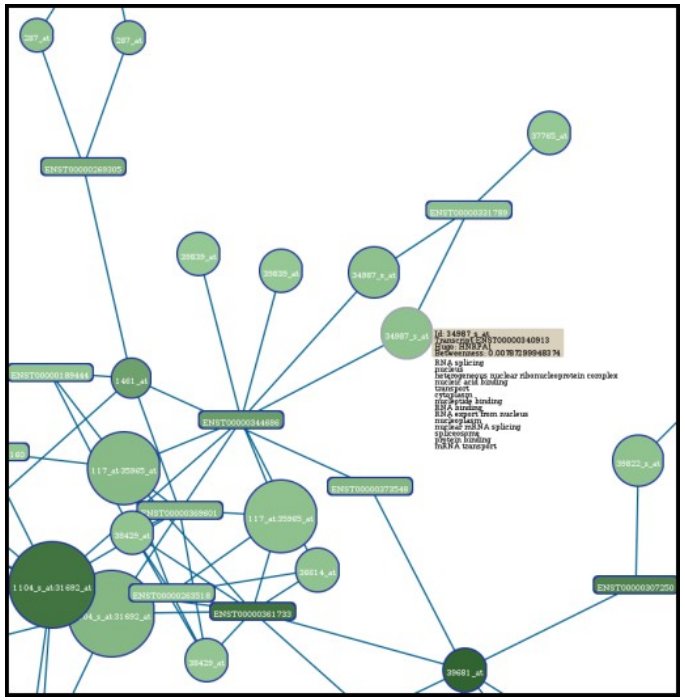
Significant Clustering coefficient, p-value=0.0103



SNOW Tool. *Minguez et al., NAR 2009 Implemented in Babelomics (http://www.babelomics.org)*

SNOW

- The SNOW tool introduces **protein-protein interaction data** into the functional profiling of genomic data
  - Evaluates **role of the list within the interactome**: identifies hubs in the list of proteins/genes (nodes) and evaluates the topological parameters of the within the interactome
  - Evaluates the list's cooperative behavior as a **functional module**



http://babelomics.bioinfo.cipf.es/functional.html

NetworkMiner

Prioritizing disease candidate genes

Scenario

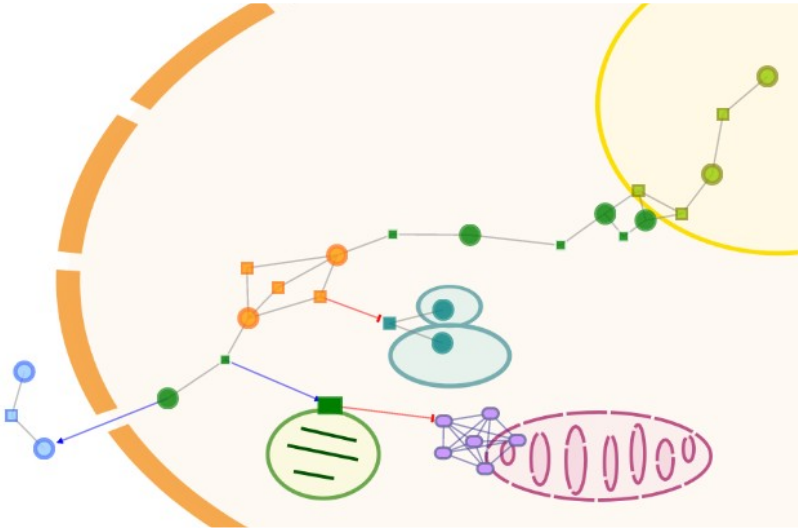
http://babelomics.bioinfo.cipf.es/functional.html

You have:

1. a list of **disease candidates** (ranked by their populational frequency)
2. a list of **genes** that are known to be **associated to the disease**

You want to see:

which of your candidates are functionally related or interacting with the known disease genes



NetworkMiner Study

Tests whether any of the candidates is significantly located in the neighborhood of the known disease genes

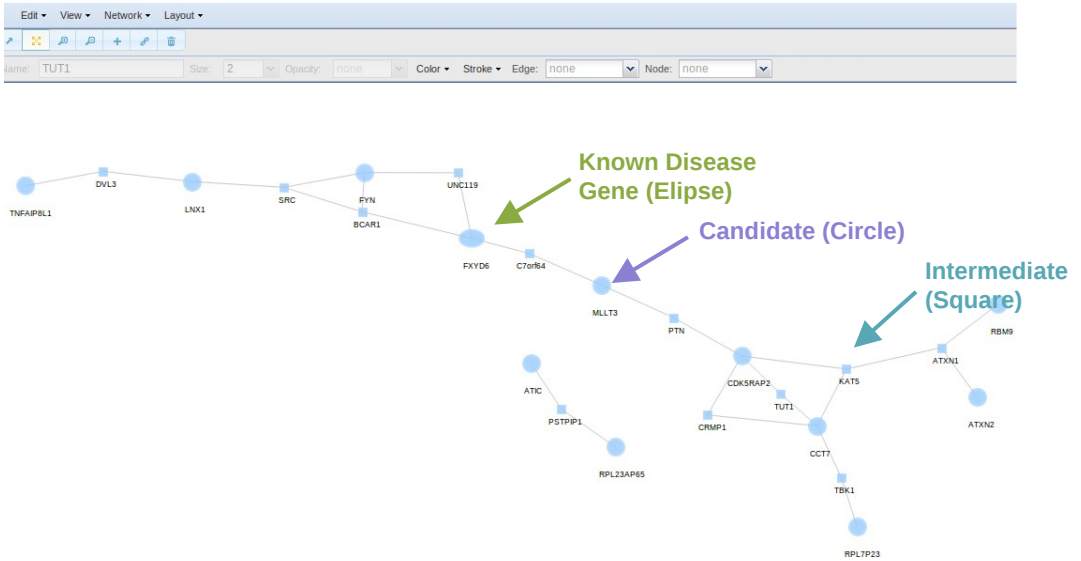
NetworkMiner

Prioritizing disease candidate genes

Example: Genome-Wide Association Study in Bipolar Disorder

Seed list: Genes associated to Bipolar Disorder

Ranked list: Genes ranked according the association degree in a Case-Control Association Study



RENATO (REgulatory Network Analsis TOol)

Identifying common regulatory elements

- Sometimes, the problem is not in the gene but in its regulators
- Tool for the **interpretation and visualization** of transcriptional (TFs) and post-transcriptional (miRNAs) **regulatory information**
- Designed to identify **common regulatory elements** in a list of genes
- RENATO maps these genes to the regulatory network, extracts the corresponding regulatory connections and evaluate each regulator for **significant over-representation** in the list.

http://renato.bioinfo.cipf.es

significant_your_annotation_0.05.txt

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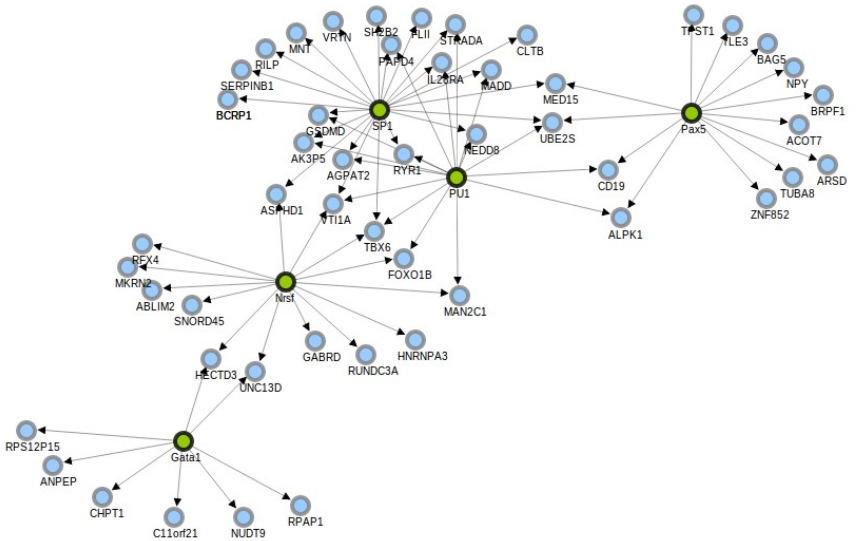
Term	List1 annotateds	List1 unannotateds	List2 annotateds	List2 unannotateds	Odds ratio (log e)	pvalue	Adjusted pvalue
SP1	22	39	1178	17240	2.1108949872	1.19202e-11	3.09925e-10
Pax5	13	48	343	18075	2.6583029464	1.15497e-10	1.50146e-9
Nrsf	14	47	641	17777	2.1115410369	2.07537e-8	1.79865e-7
Gata1	8	53	186	18232	2.6943365253	2.33672e-7	0.00000151887
PU1	16	45	2230	16188	0.94819487401	0.00204712	0.010645



THANK YOU.