On Modern Statistical Methods for Genetic Association Study: Structured Genome-Transcriptome-Phenome Association Analysis

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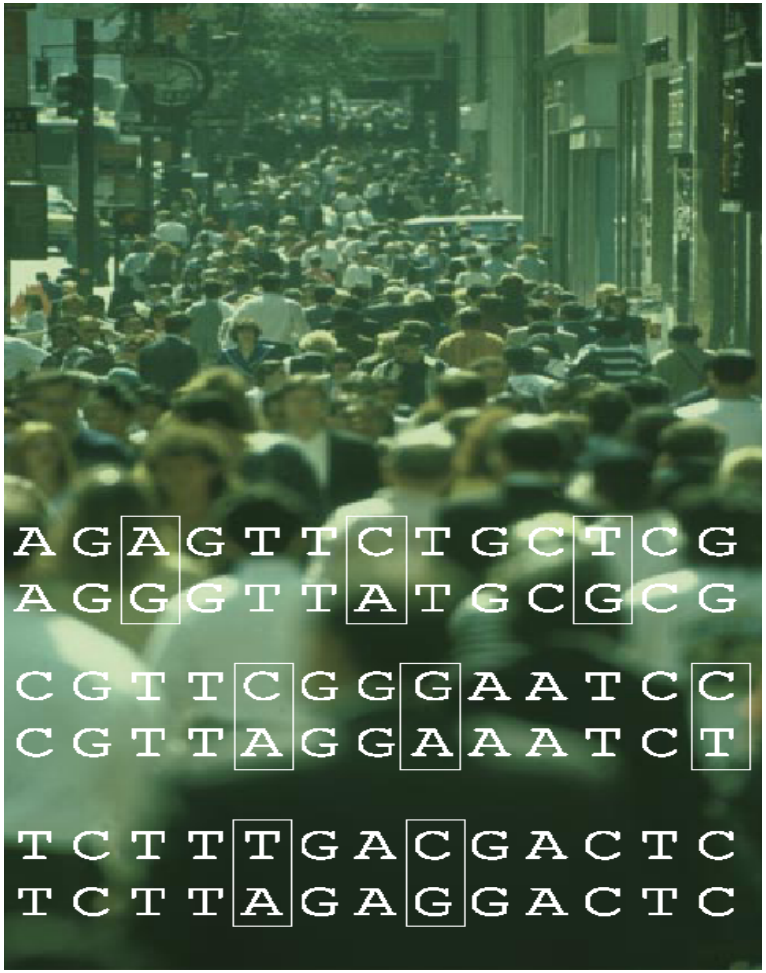
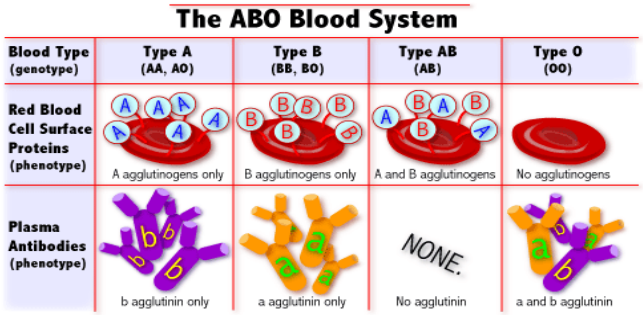
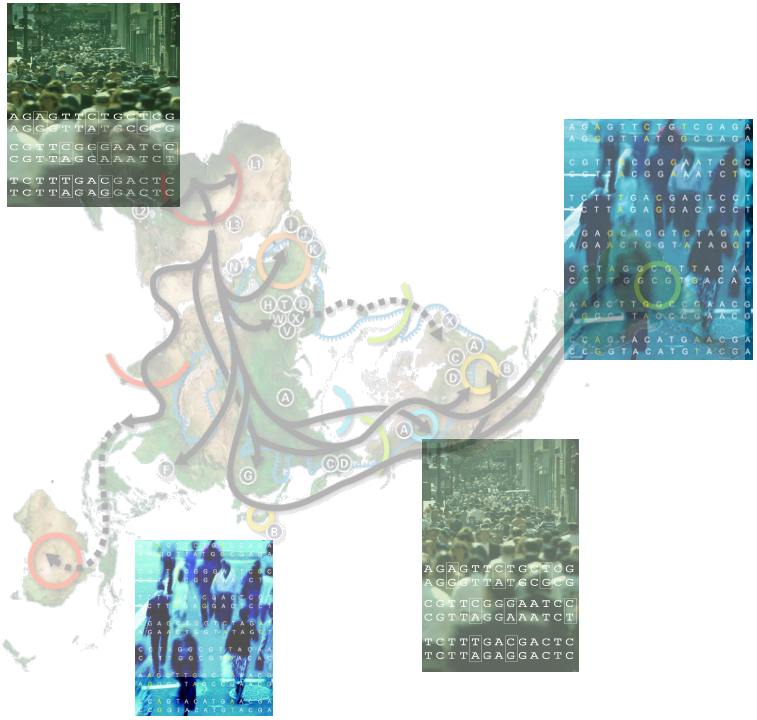
Genome Polymorphisms





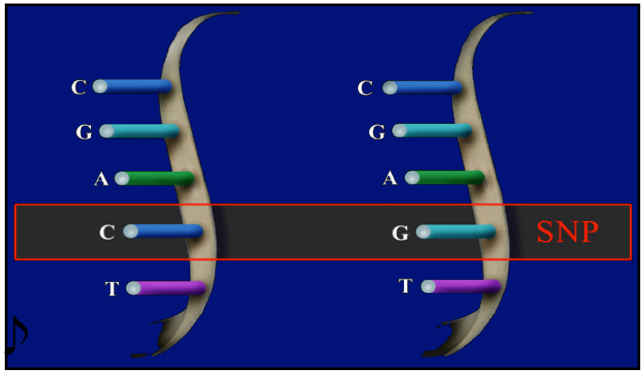


Type of Polymorphisms

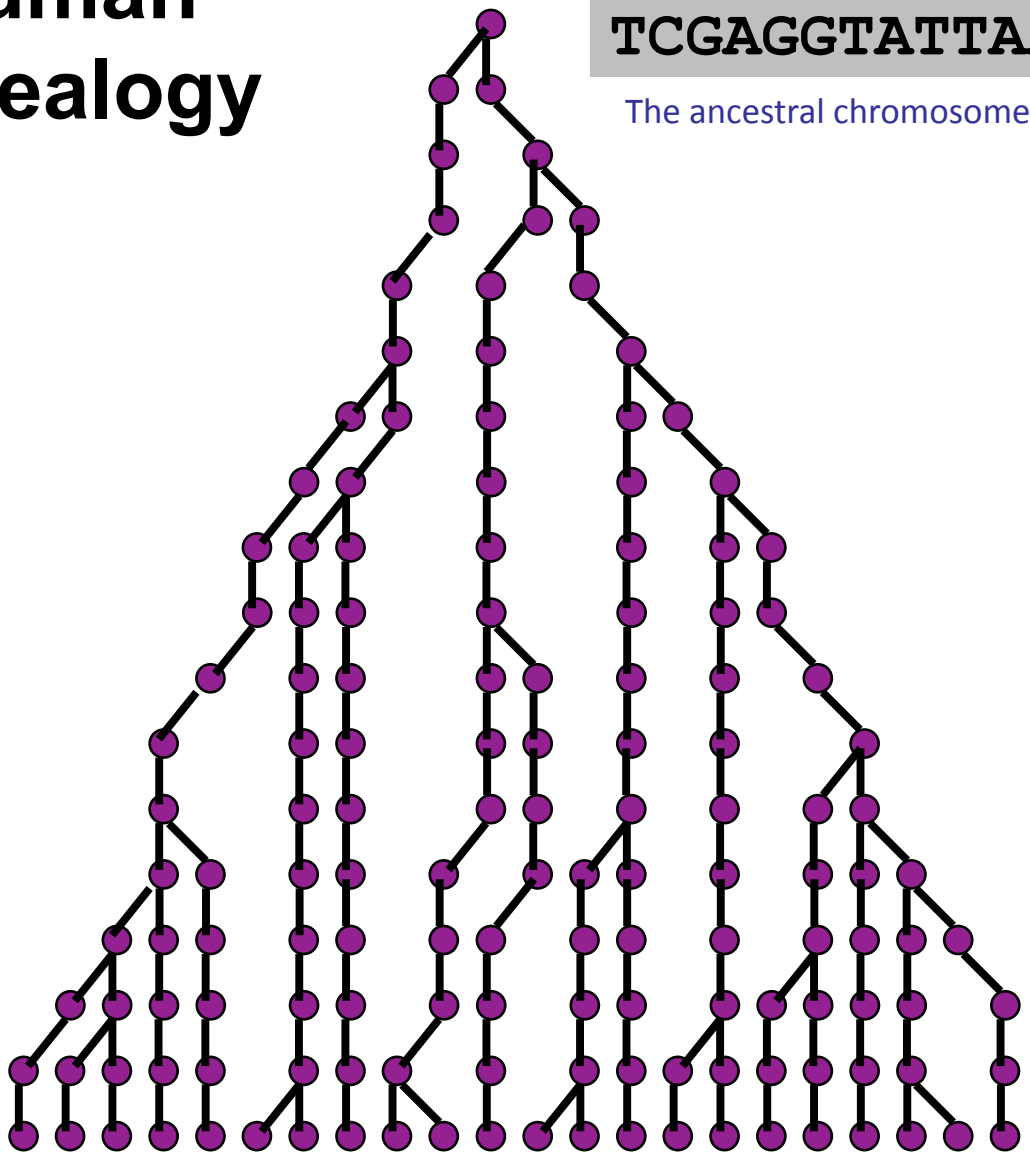
- Insertion/deletion of a section of DNA
  - Minisatellites: repeated base patterns (several hundred base pairs)
  - Microsatellites: 2-4 nucleotides repeated
  - Presence or absence of Alu segments

- **Single Nucleotide Polymorphism (SNP):**
  - DNA sequence variation occurring when a single nucleotide - A, T, C, or G - differs between members of the species
  - Frequency of SNPs greater than that of any other type of polymorphism

  - Each variant is called an "allele"
  - Almost always bi-allelic
  - Account for most of the genetic diversity among different (normal) individual, e.g. drug response, disease susceptibility



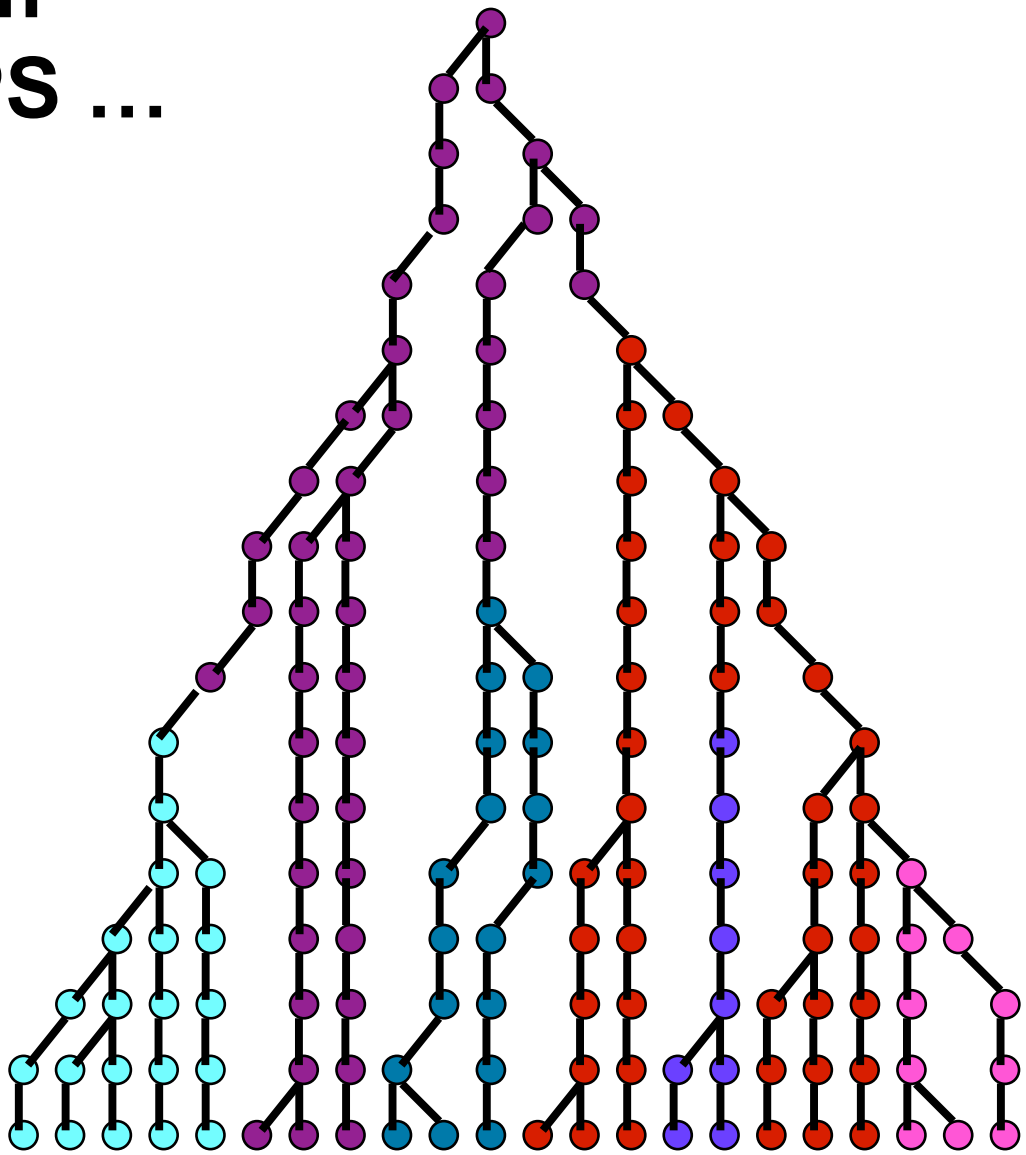
A Human Genealogy



TCGAGGTATTAAC

The ancestral chromosome

From SNPS …

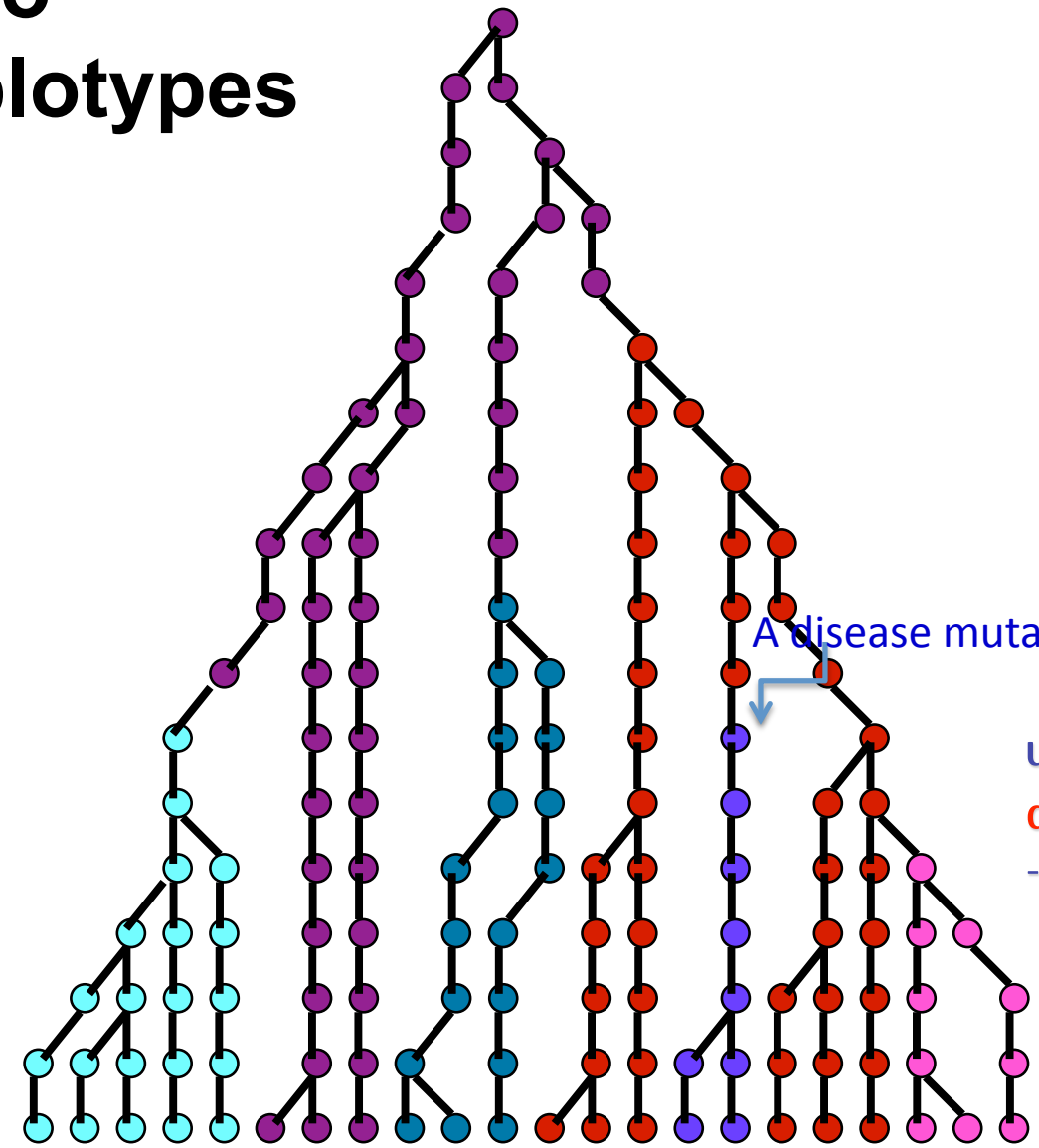


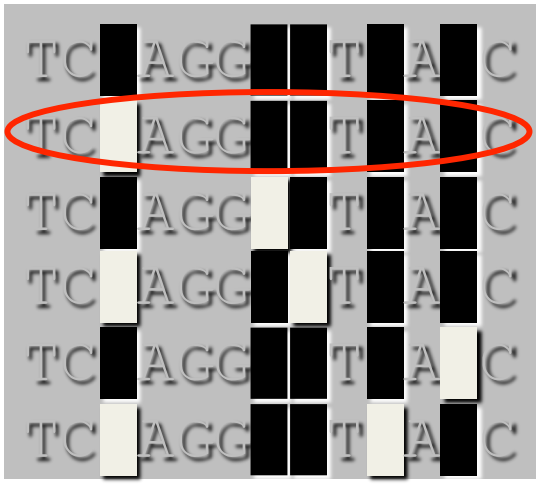
```
TCGAGGTATTAAC
TCTAGGTATTAAC
TCGAGGCATTAAC
TCTAGGTGTTAAC
TCGAGGTATTAGC
TCTAGGTATCAAC

*     **  *  *
```

The SNPs

… To Haplotypes





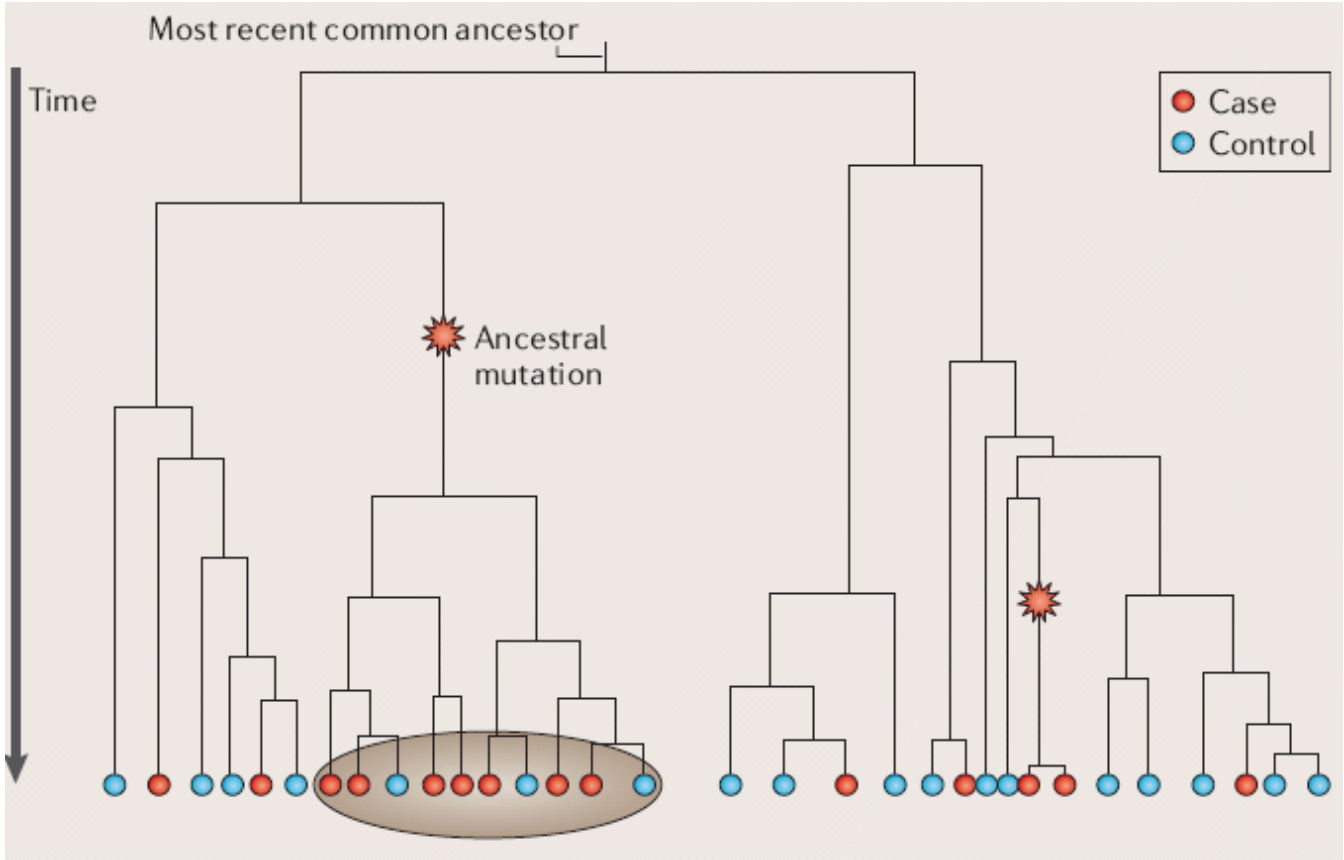
The haplotypes

useful markers for studying disease association

-- landmarks, indicators, co-variates, causes …

Population-Based Association Study

- Case/control data are collected from unrelated individuals
  - All individuals are related if we go back far enough in the ancestry

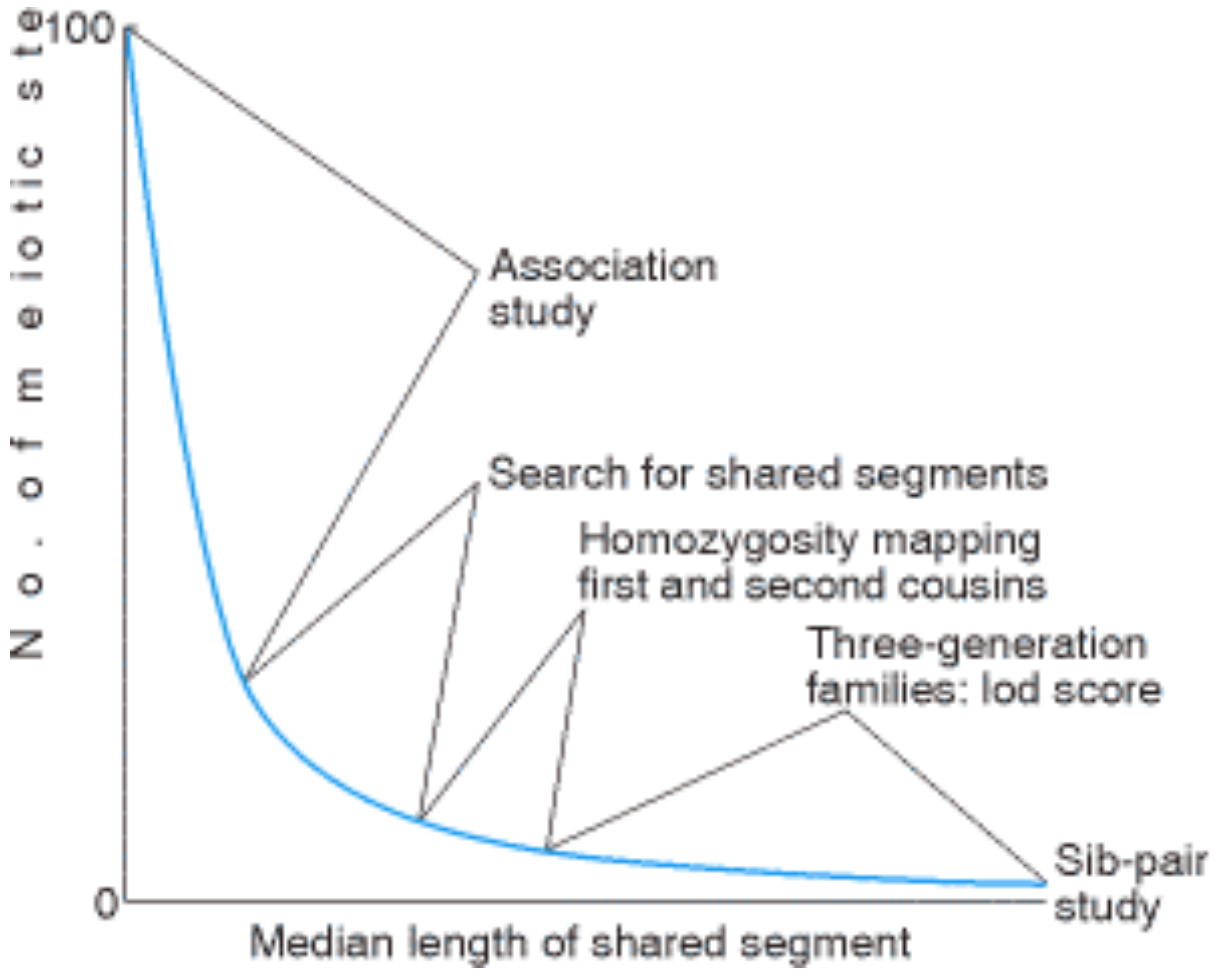


Balding, Nature Reviews Genetics, 2006

Advantages of SNPs in Genetic Analysis of Complex Traits

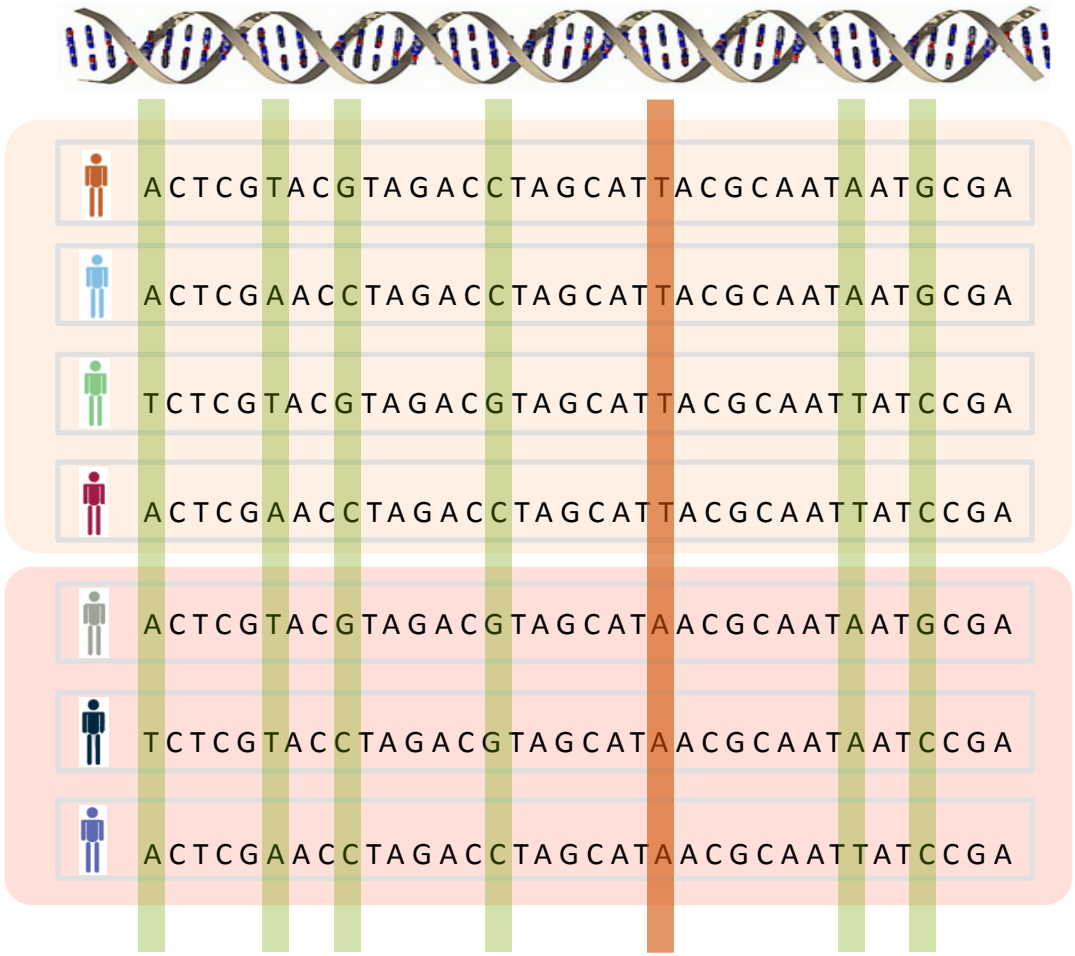
- Abundance: high frequency on the genome
- Position: throughout the genome
  - coding region, intron region, promoter site
- Ease of genotyping
- Less mutable than other forms of polymorphisms
- SNPs account for around 90% of human genomic variation
- About 10 million SNPs exist in human populations
- Most SNPs are outside of the protein coding regions
- 1 SNP every 600 base pairs
- More than 5 million common SNPs each with frequency 10-50% account for the bulk of human DNA sequence difference
- It is estimated that ~60,000 SNPs occur within exons; 85% of exons are within 5 kb of the nearest SNP

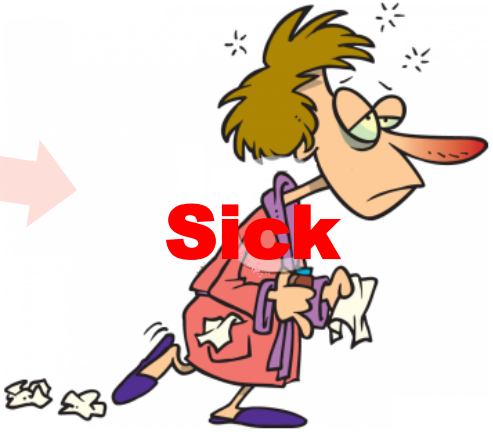
Linkage Analysis vs. Association Analysis



Strachan & Read, Human Molecular Genetics, 2001

Genetic Basis of Diseases



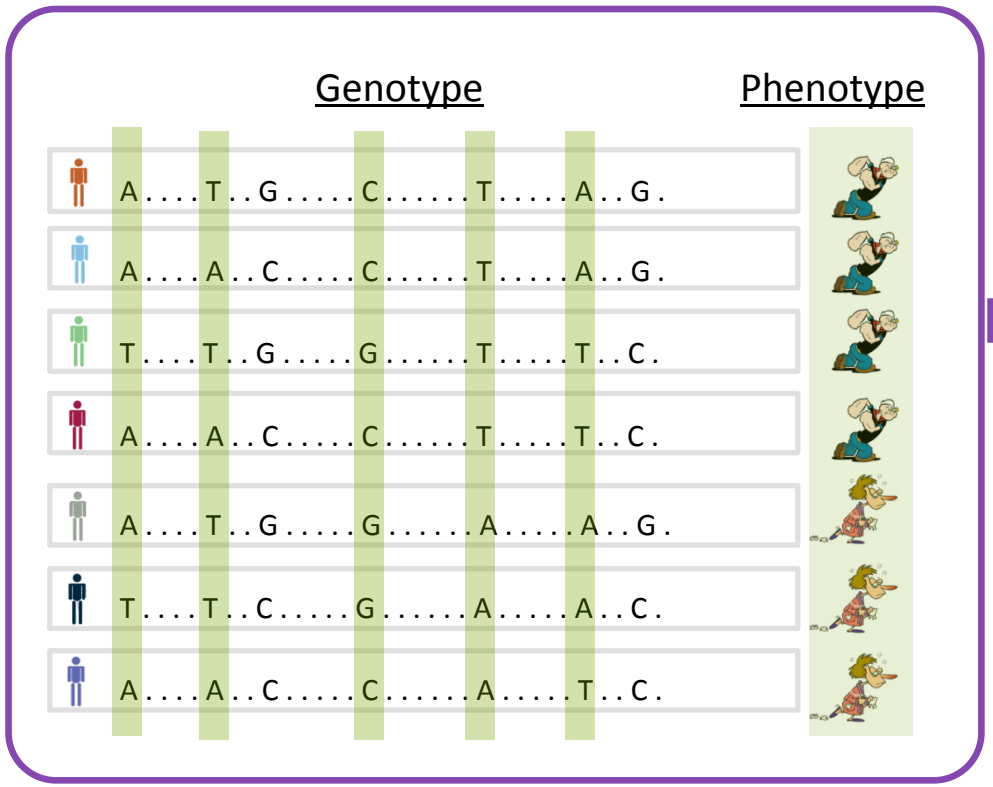


Single nucleotide polymorphism (SNP)

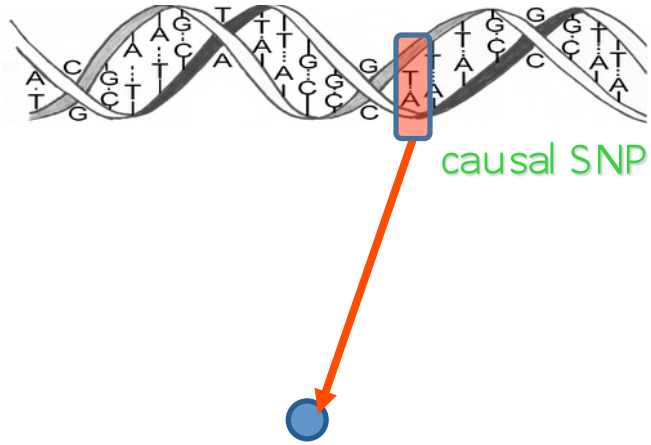
Association SNP

Genetic Association Mapping

Data



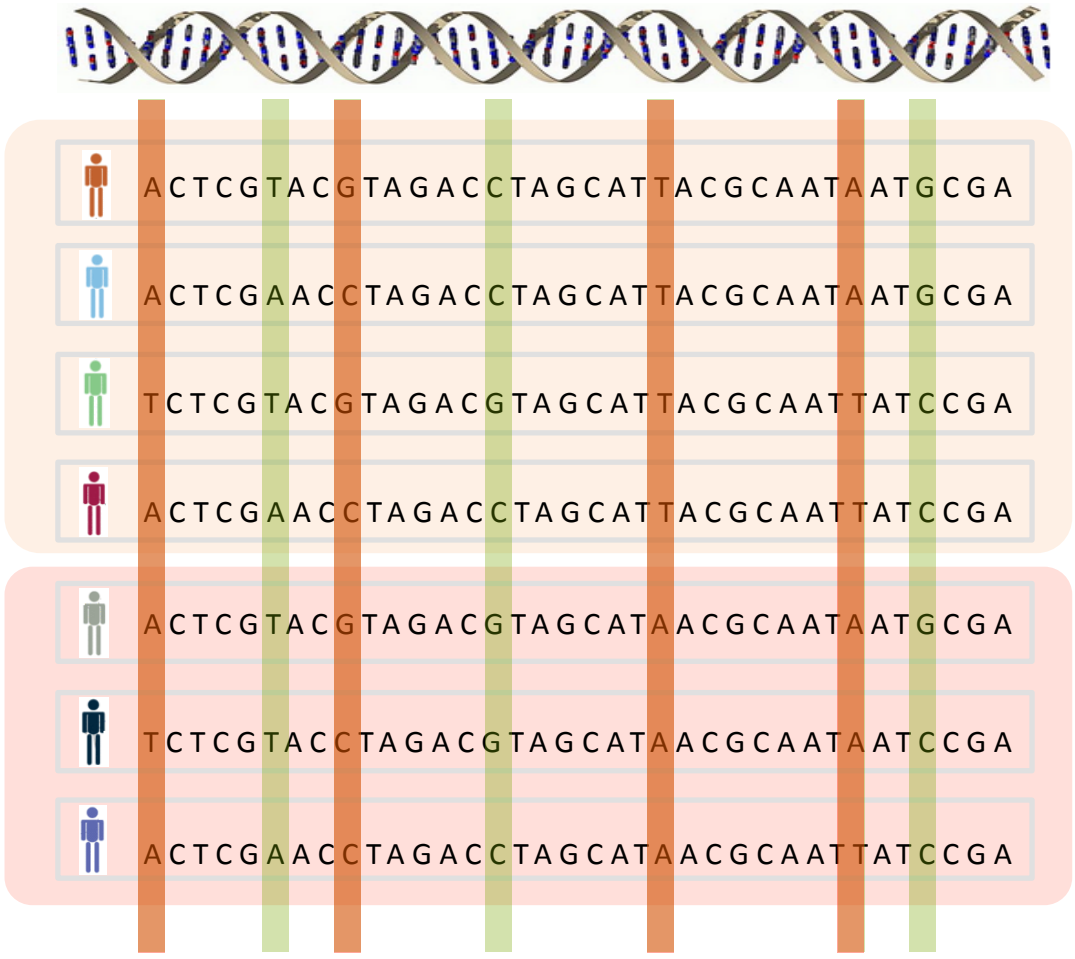
Standard Approach

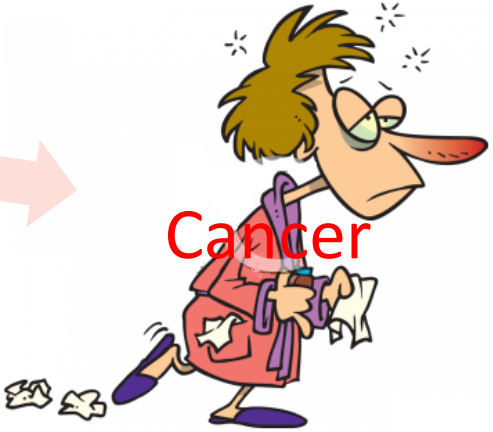


a univariate phenotype:
e.g., disease/control

- Cancer: Dunning et al. 2009.
- Diabetes: Dupuis et al. 2010.
- Atopic dermatitis: Esparza-Gordillo et al. 2009.
- Arthritis: Suzuki et al. 2008

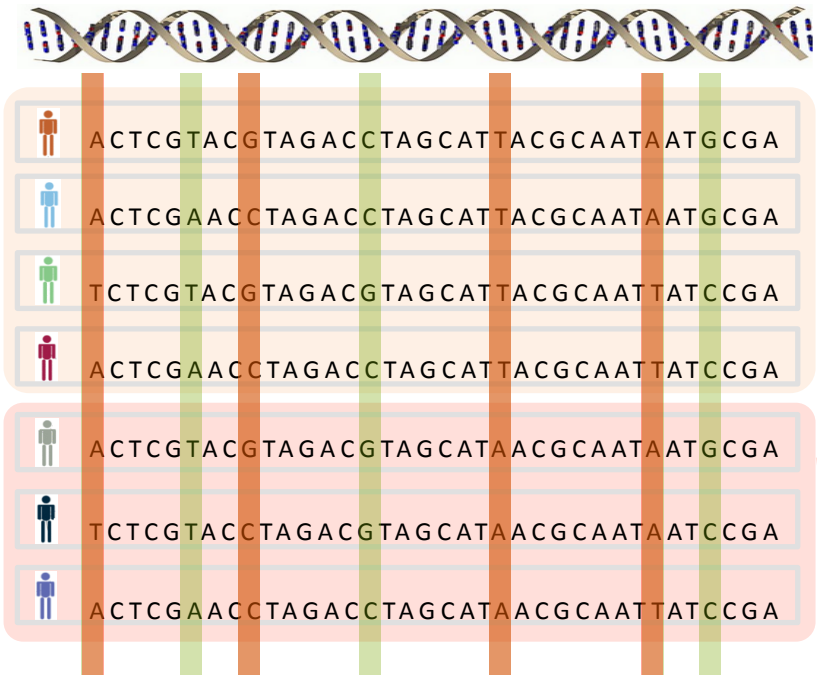
Genetic Basis of Complex Diseases



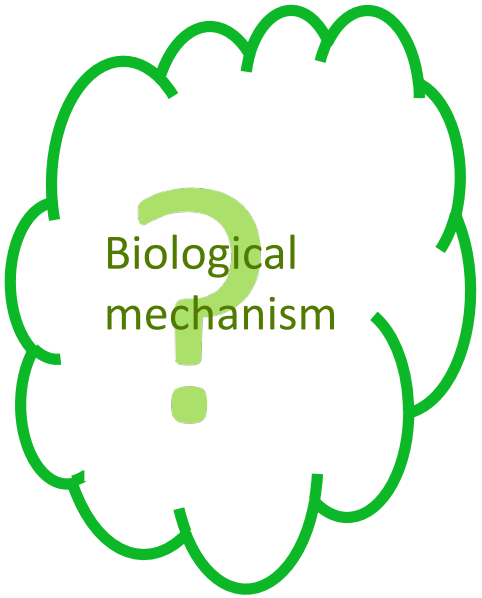


Causal SNPs

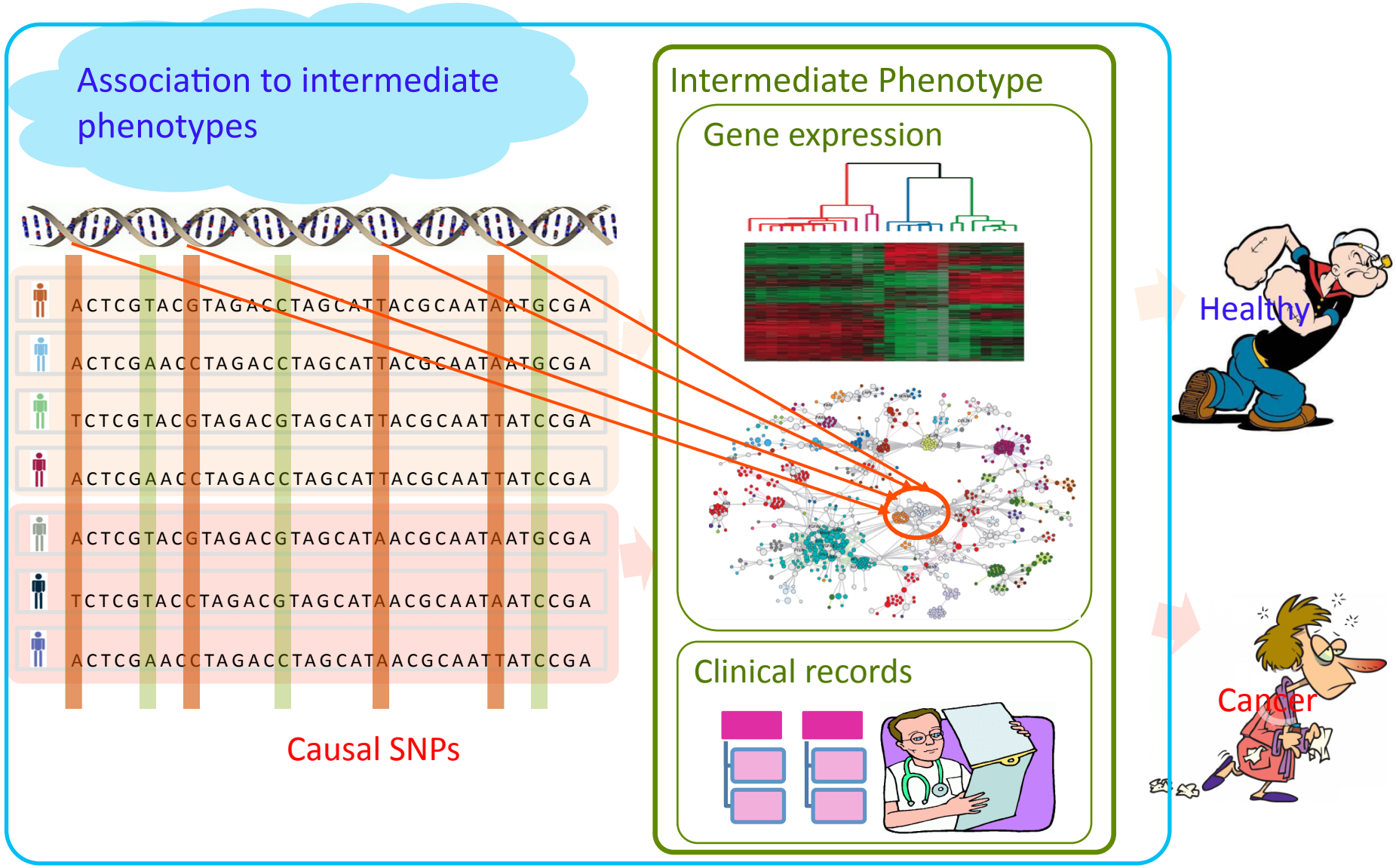
Genetic Basis of Complex Diseases



Causal SNPs



Genetic Basis of Complex Diseases



Population association analysis

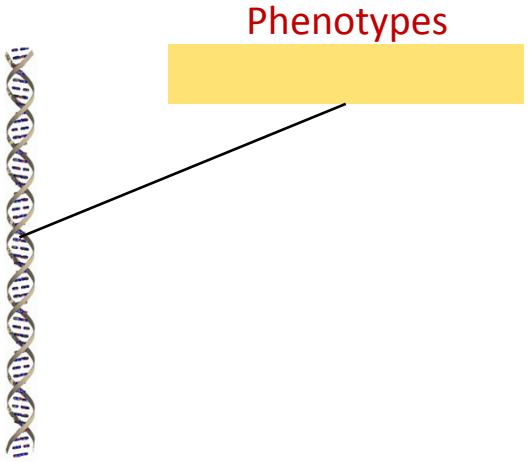
Standard Approach

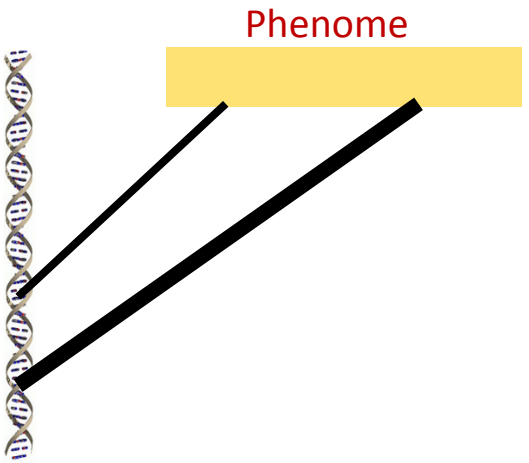
Consider **one phenotype** at a time

vs.

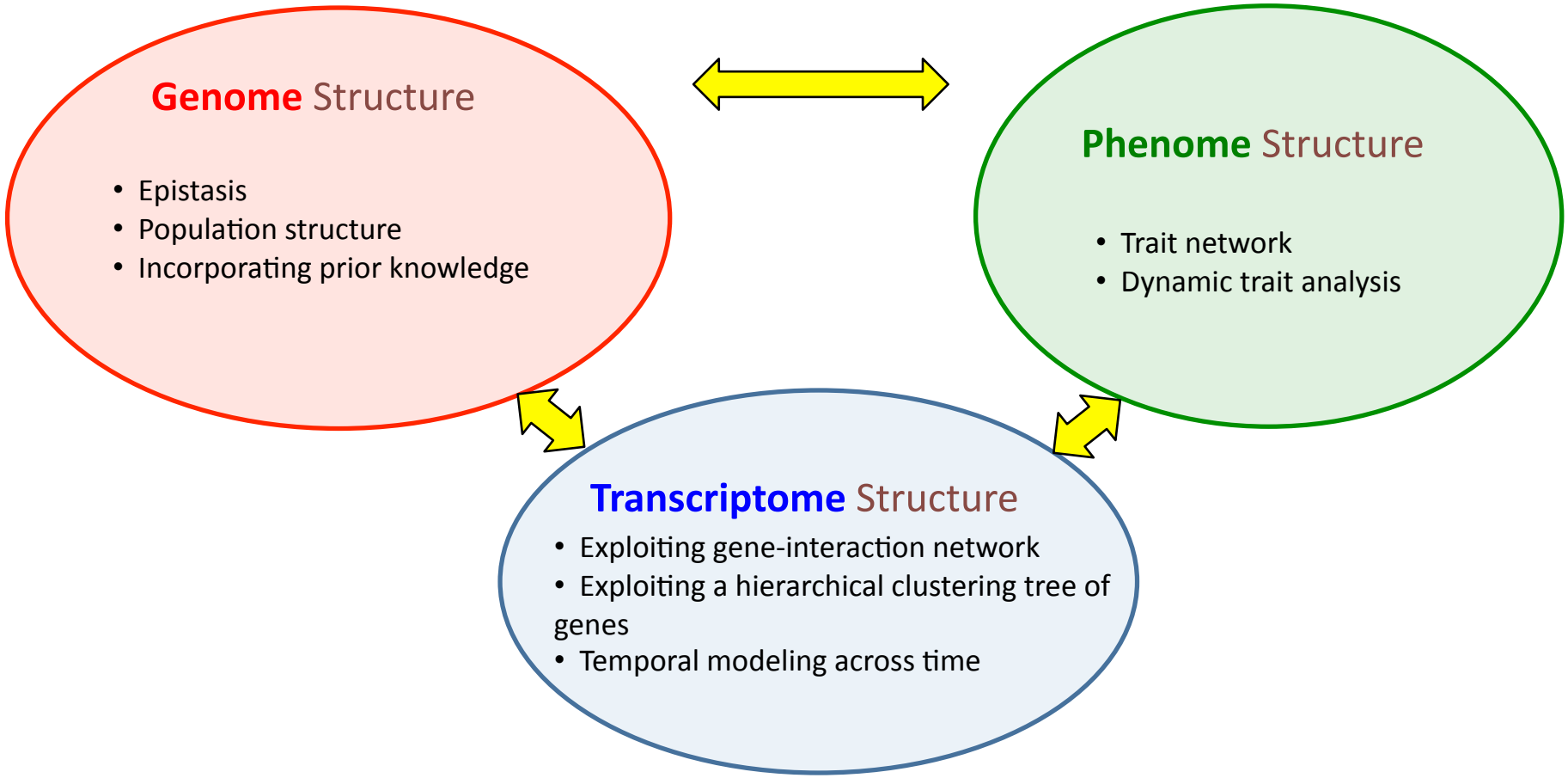
New Approach

Consider **multiple correlated phenotypes (phenome) and genotypes (genome) jointly**



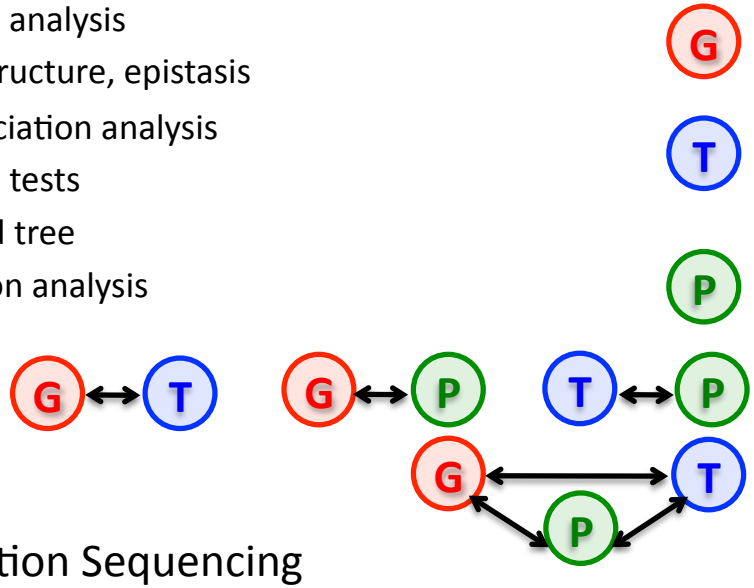


Summary: Structured Genome-Transcriptome-Phenome Association Analysis



Outline

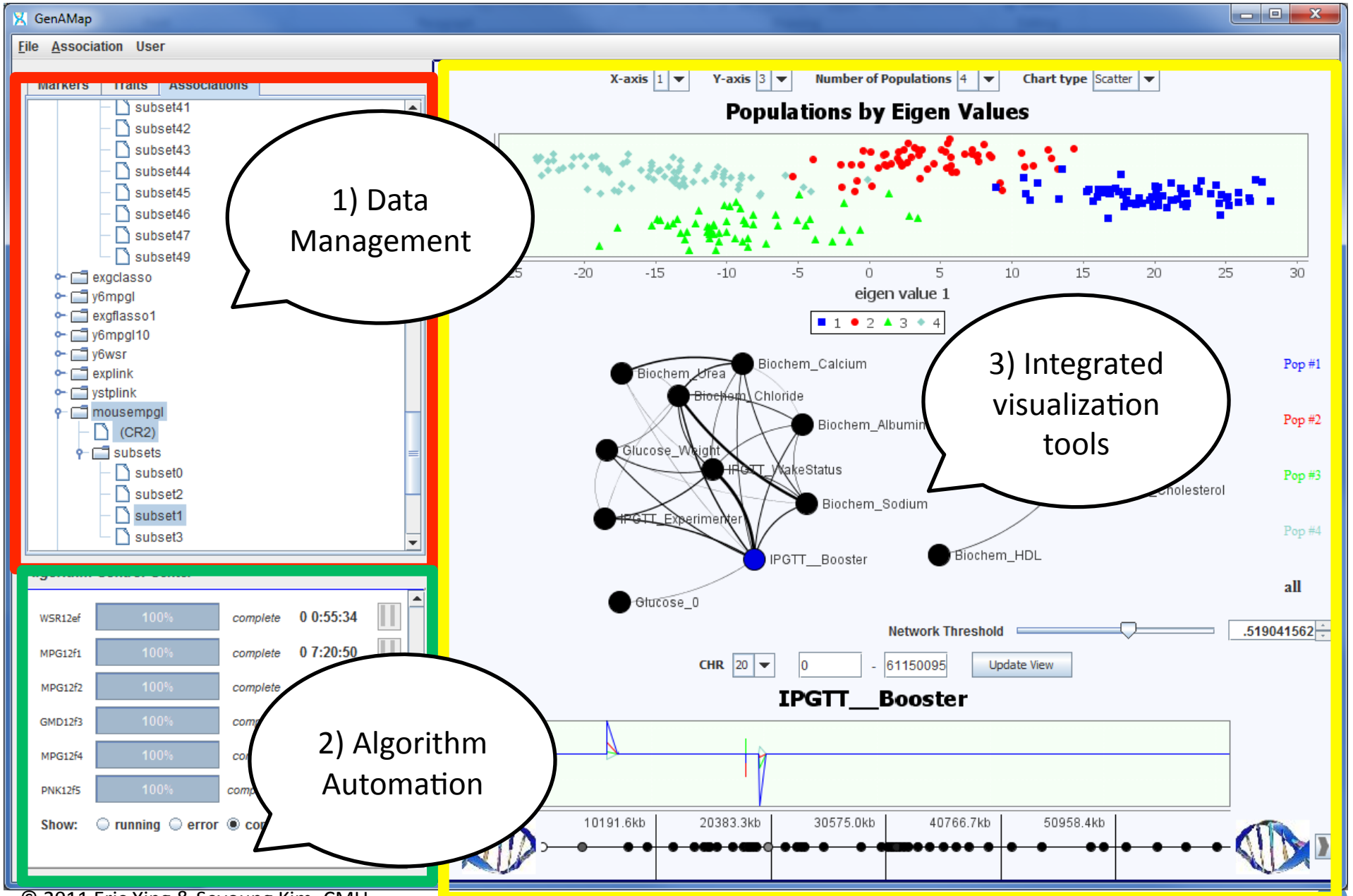
- Preparing Data for Association Analysis
  - Missing genotypes/phenotypes, tag SNP selection, haplotype inference, population structure
- Background on Association Analysis: Single Phenotype Methods
  - Single SNP approach : case/control study, quantitative trait as phenotype
  - Simultaneous analysis of all SNPs: Sparse regression method
- Structured Geome-Phenome-Transcriptome Analysis
  - Exploiting **genome structure** in association analysis
    - Linkage disequilibrium, population structure, epistasis
  - Exploiting **transcriptome structure** in association analysis
    - Pleiotropy : Pathway-based statistical tests
    - Leveraging trait structures: graph and tree
  - Exploiting **phenome structure** in association analysis
    - Pleiotropy, dynamic-trait association
  - **Two-way** structured association
  - **Three-way** structured association



- Association Analysis and Next-generation Sequencing
  - Going beyond SNPs: Structural variants
  - From common variants to rare variants

GenAMap: Visual analytics software for structured association mapping

Curtis and Xing, Carnegie Mellon University



Part I

Preparing Data for Association Analysis

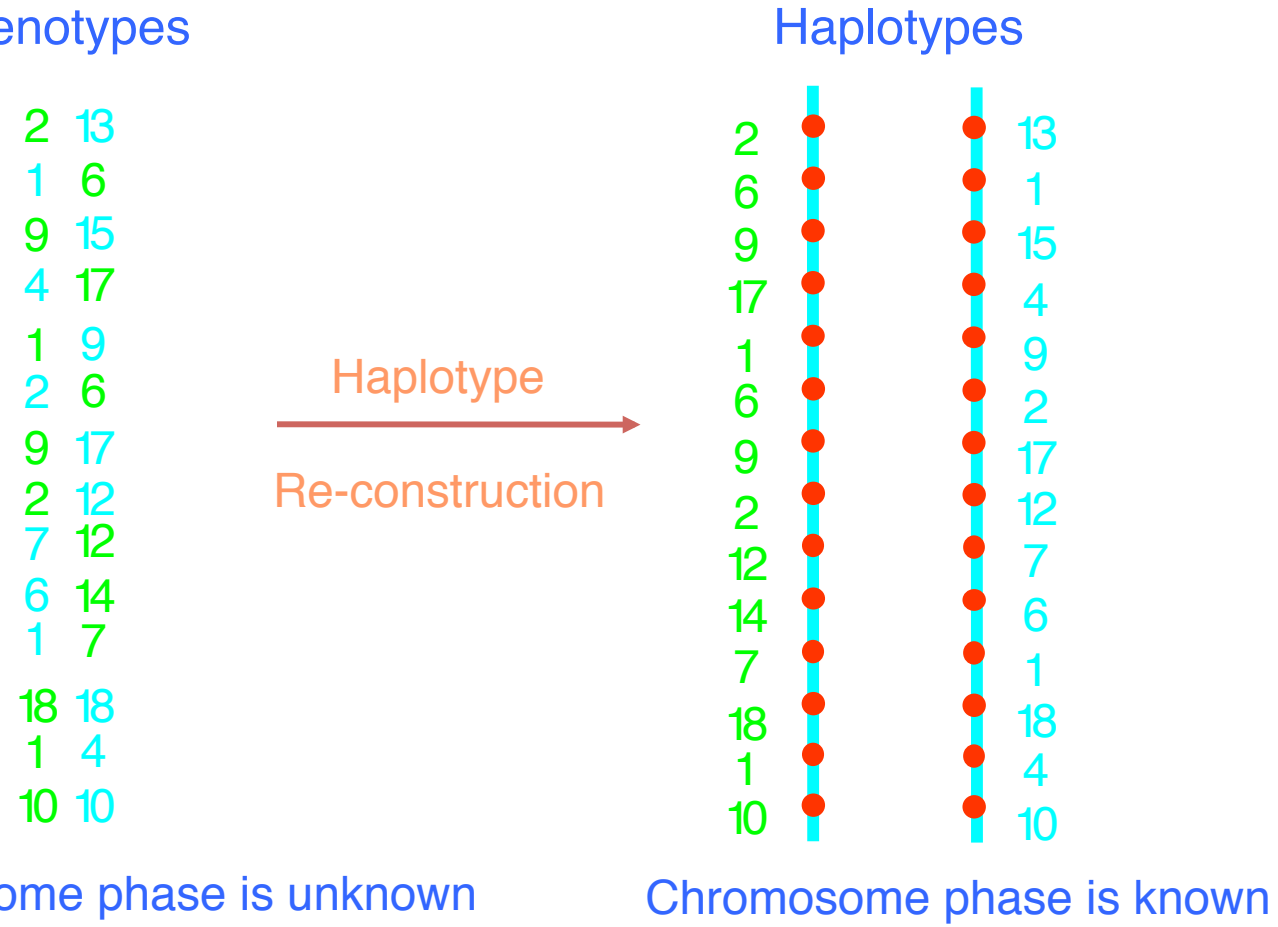
Overview

- Preparing genotype data
  - Haplotype inference
  - Tag SNP selection
  - How to handle missing genotype values
  - Population structure

- Preparing phenotype data
  - How to handle missing phenotype values
  - Data normalization
  - What structure?

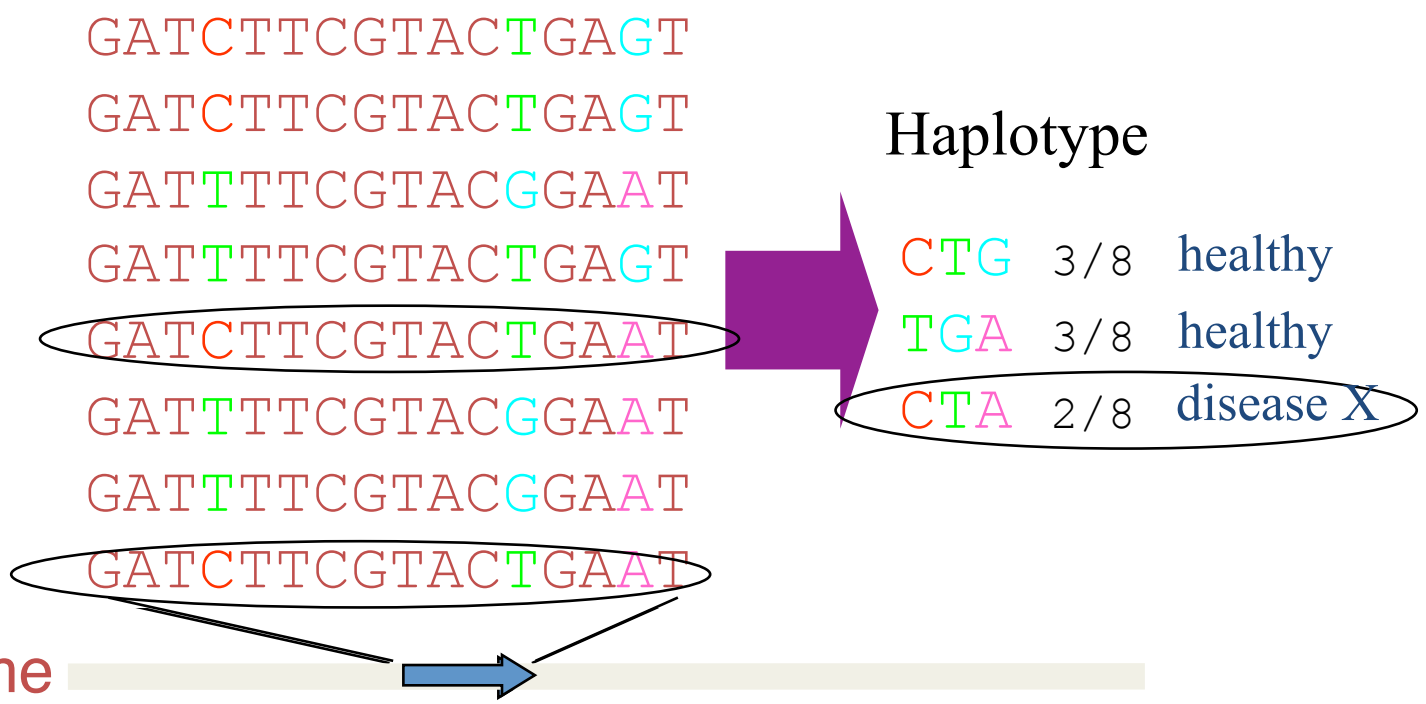
Haplotype and Genotype

- A collection of alleles derived from the same chromosome



Why Haplotype in Association Mapping?

-- a more discriminative state of a chromosomal region



- Consider J binary markers in a genomic region
- There are 2^J possible haplotypes
  - but in fact, far fewer are seen in human population
- Good genetic marker for population, evolution and hereditary diseases …

Haplotype Analyses

- Haplotype analyses
  - Linkage disequilibrium assessment
  - Disease-gene discovery
  - Genetic demography
  - Chromosomal evolution studies

- Why Haplotypes
  - Haplotypes are more powerful discriminators between cases and controls in disease association studies
  - Use of haplotypes in disease association studies reduces the number of tests to be carried out.

Linkage Disequilibrium

- LD reflects the relationship between alleles at different loci.
  - Alleles at locus A: frequencies $\mathbf{p}_1,\ldots, \mathbf{p}_m$
  - Alleles at locus B: frequencies $\mathbf{q}_1,\ldots,\mathbf{q}_n$
  - Haplotype frequency for A_iB_j:
    - equilibrium value: $\mathbf{p}_i\ \mathbf{q}_j$
    - Observed value: $\mathbf{h}_{ij}$
    - Linkage disequilibrium: $\mathbf{h}_{ij}\ -\mathbf{p}_i\ \mathbf{q}_j$
  - Linkage disequilibrium is an allelic association measure (difference between the actual haplotype frequency and the equilibrium value)
  - More precisely: **gametic association**
- Association studies.
  - If inheriting a certain allele at the disease locus increases the chance of getting the disease, and the disease and marker loci are *in LD*, then the frequencies of the marker alleles will **differ** between diseased and non-diseased individuals.

Haplotype Inference

- Given a random sample of multilocus genotypes at a set of SNPs
  - Frequency estimation of all possible haplotypes
  - Haplotype reconstruction for individuals
  - How many out of all possible haplotypes are plausible in a population

- Haplotype reconstruction algorithm
  - Clark's parsimony algorithm (Clark, Mol. Biol. Evol. 1990)
  - Haplotyper (Niu et al., AJHG 2002)
  - PHASE (Stephens et al., AJHG 2001)

PHASE

(Stephens et al., AJHG 2001)

- Treat unknown haplotypes as unobserved random quantities and estimate the conditional probability of haplotypes given observed genotypes

- Gibbs sampling approach
  - Start with initial guesses on haplotypes
  - Iteratively reconstruct the haplotype of each individual assuming the haplotypes of other individuals have been correctly reconstructed.

PHASE

(Stephens et al., AJHG 2001)

- Given the genotype data G, start with some initial haplotype reconstruction $H^{(0)}$. For $t = 0, 1, 2, \ldots,$ obtain $H^{(t+1)}$ from $H^{(t)}$ using the following three steps:

  1. Choose an individual, i, uniformly and at random from all ambiguous individuals (i.e., individuals with more than one possible haplotype reconstruction).

  2. Sample $H_i^{(t+1)}$ from $P(H_i | G, H_{-i}^{(t)})$, where H_{-i} is the set of haplotypes excluding individual i.

  3. Set $H_j^{(t+1)} = H_j^{(t)}$ for $j=1,\ldots,n$, $j \neq i$

Reducing Genotyping Costs with Tag SNPs

- Nearby SNPs in the genome are in linkage disequilibrium (LD), and thus contain redundant information.

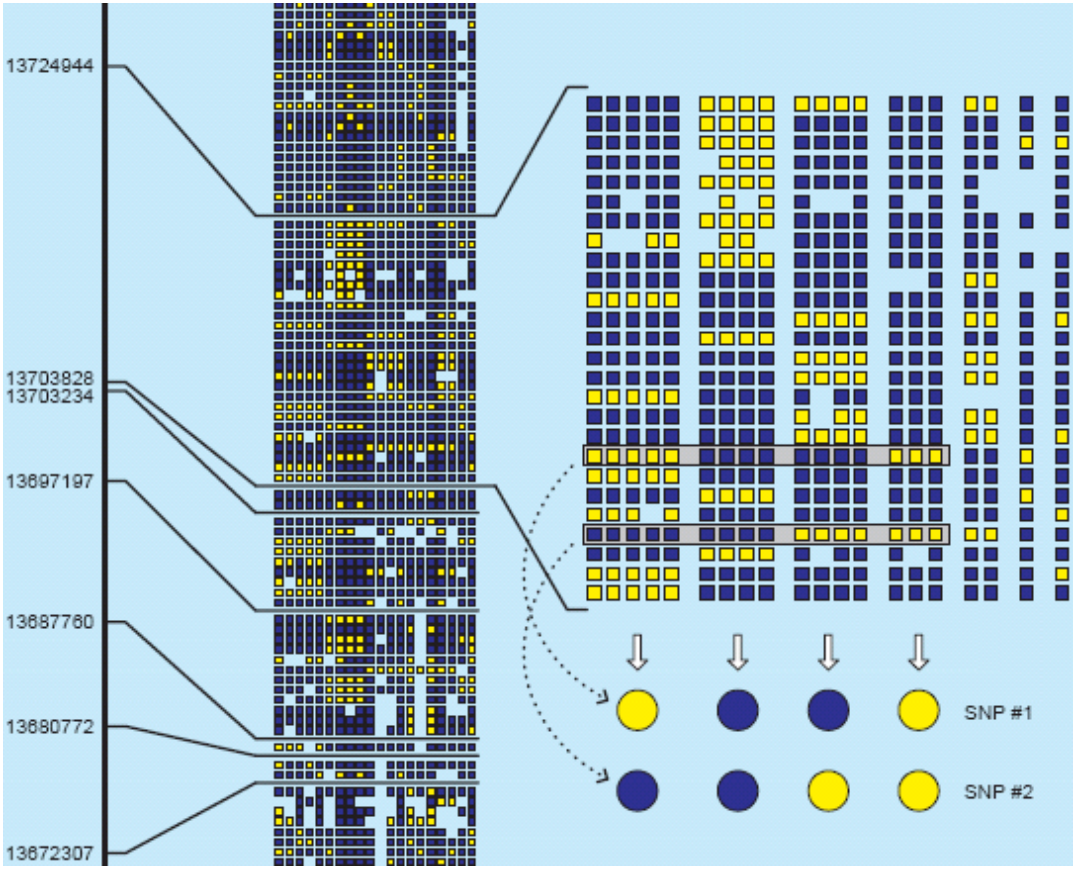
- If we knew which SNPs are in LD, we can pre-select the representative SNPs for each LD block of chromosome, and genotype only for those SNPs.

Two-phase Genotyping Using Tag SNPs

- A two-phase approach
  - Phase 1: Collect a set of SNPs densely distributed across genome for a small number of individuals. Select tag SNPs based on this dataset.
  - Phase 2: Genotype only for tag SNPs for a large number of individuals

Tag SNP Selection

- Tag SNPs summarize information across multiple SNPs in linkage disequilibrium



Patil et al., Science 2001

Algorithm for Finding Tag SNP

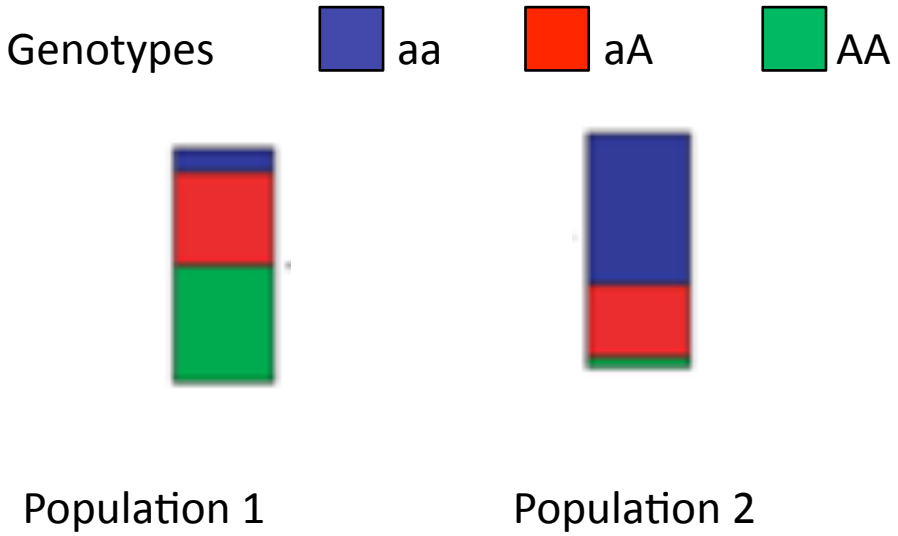
- Problem: Find a set of tag SNPs that cover all of the non-tag SNPs in LD (r^2>α) with the tag SNPs
  - α : parameter that needs to be specified by the user (e.g., 0.8)

- Greedy search (Carlson et al., AJHG 2004)
  - Repeatedly select the SNP that cover the largest number of non-tag SNPs given α

- Dynamic programming approach (Zhang et al., PNAS 2002)

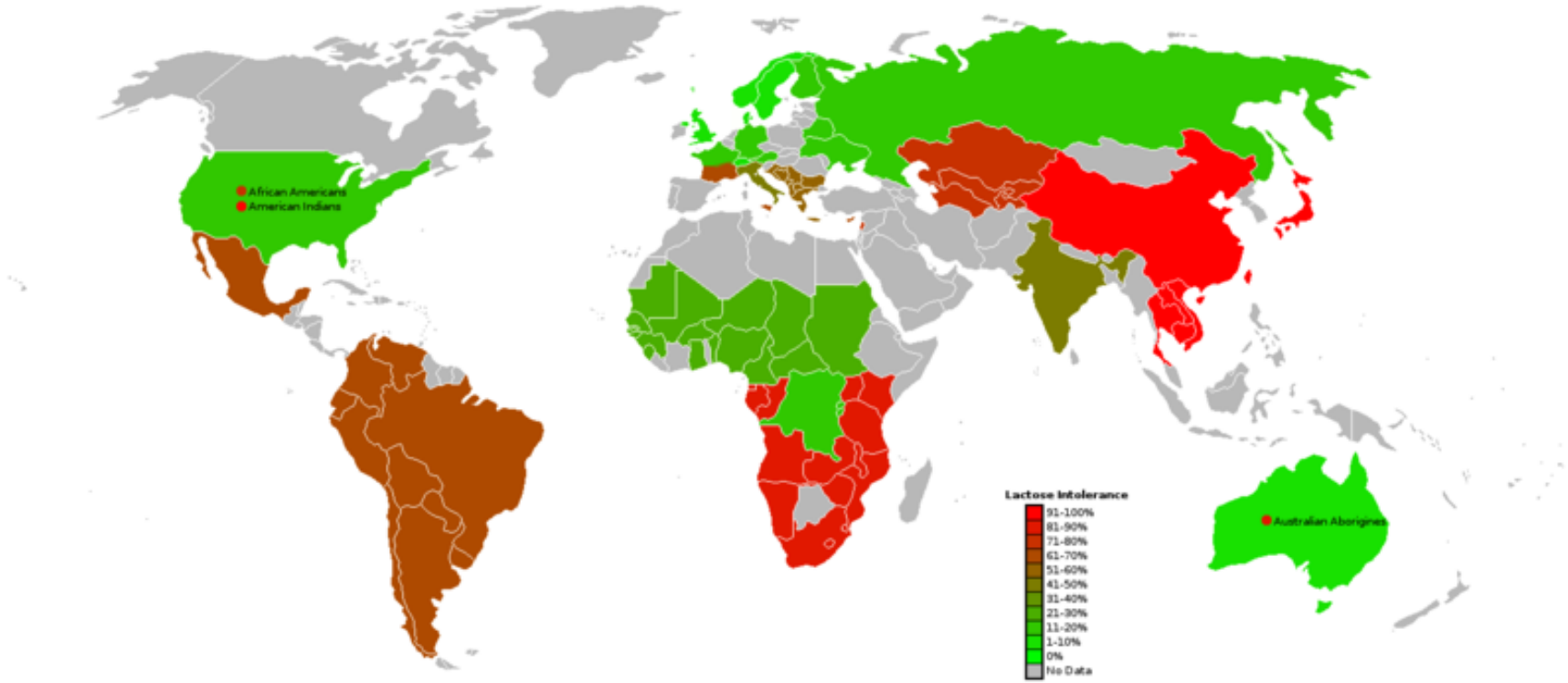
What is population structure?

- Population Structure
  - A set of individuals characterized by some measure of genetic distinction
  - A "population" is usually characterized by a distinct distribution over genotypes
  - Example



Motivation

- **Reconstructing individual ancestry:** The Genographic Project
  - https://genographic.nationalgeographic.com/genographic/index.html
- **Studying human migration**



Methods for Learning Population Structure from Genetic Markers

- Low-dimensional projection
  - PCA-based methods (Patterson et al., PLoS Genetics 2006)
- Clustering
  - Distance-based (Bowcock et al., Nature 1994)
  - Model-based
    - STRUCTURE (Pritchard et al., Genetics 2000)
    - mStruct (Shringarpure & Xing, Genetics 2008)

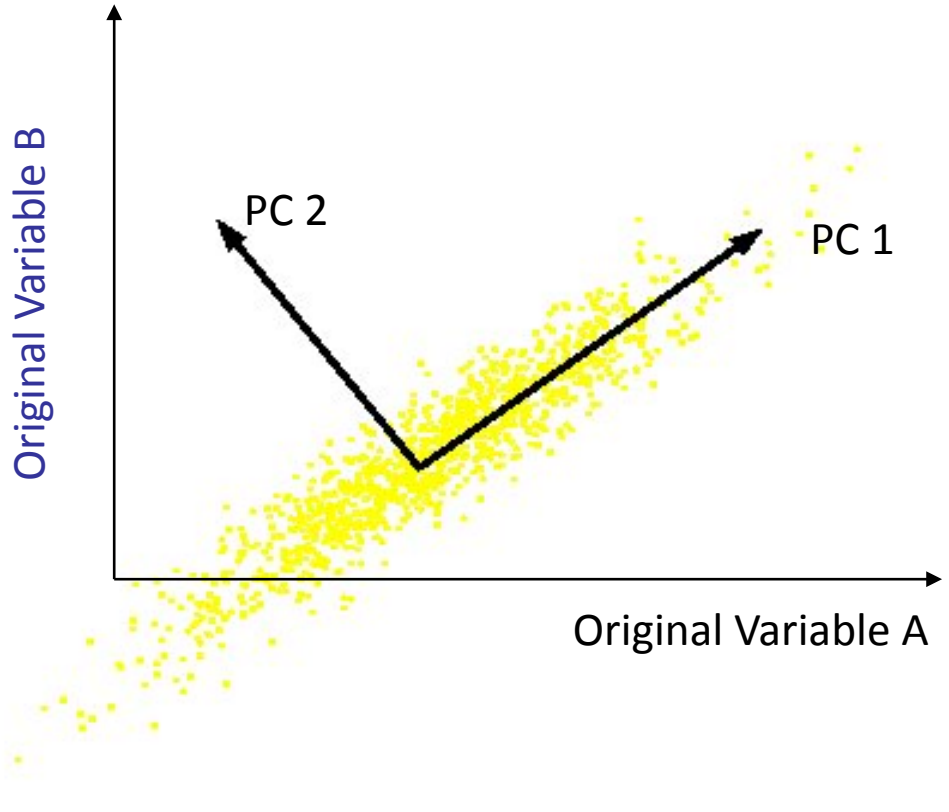
Low-dimensional Projections

- Genetic data is very large
  - Number of markers may range from a few hundreds to hundreds of thousands
  - Thus each individual is described by a high-dimensional vector of marker configurations
  - A low-dimensional projection allows easy visualization
- Technique used
  - Factor analysis
  - Many statistical methods exist – ICA, PCA, NMF etc.
  - Principal Components Analysis (next slide)
- Allows projection of individuals into a low dimensional space
- Usually projected to 2 dimensions to allow visualization

Principal Component Analysis

- Most common form of factor analysis
- The new variables/dimensions ...
  - Are linear combinations of the original ones
  - Are uncorrelated with one another
    - Orthogonal in original dimension space
  - Capture as much of the original variance in the data as possible
  - Are called Principal Components
- Demo at http://www.cs.mcgill.ca/~sqrt/dimr/dimreduction.html

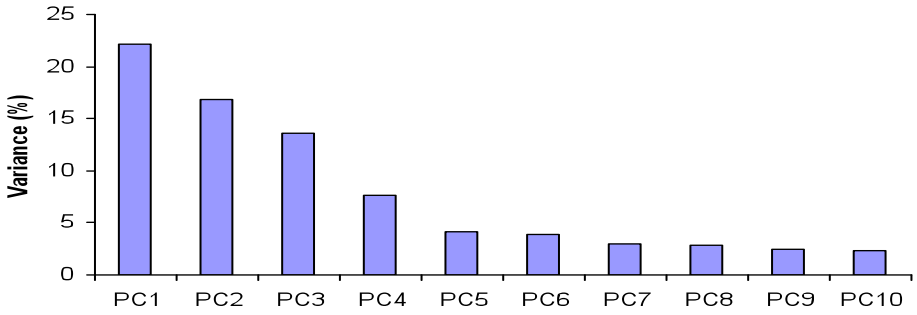
What are the new axes?



- Orthogonal directions of greatest variance in data
- Projections along PC1 discriminate the data most along any one axis

Dimensionality Reduction

Can *ignore* the components of lesser significance.



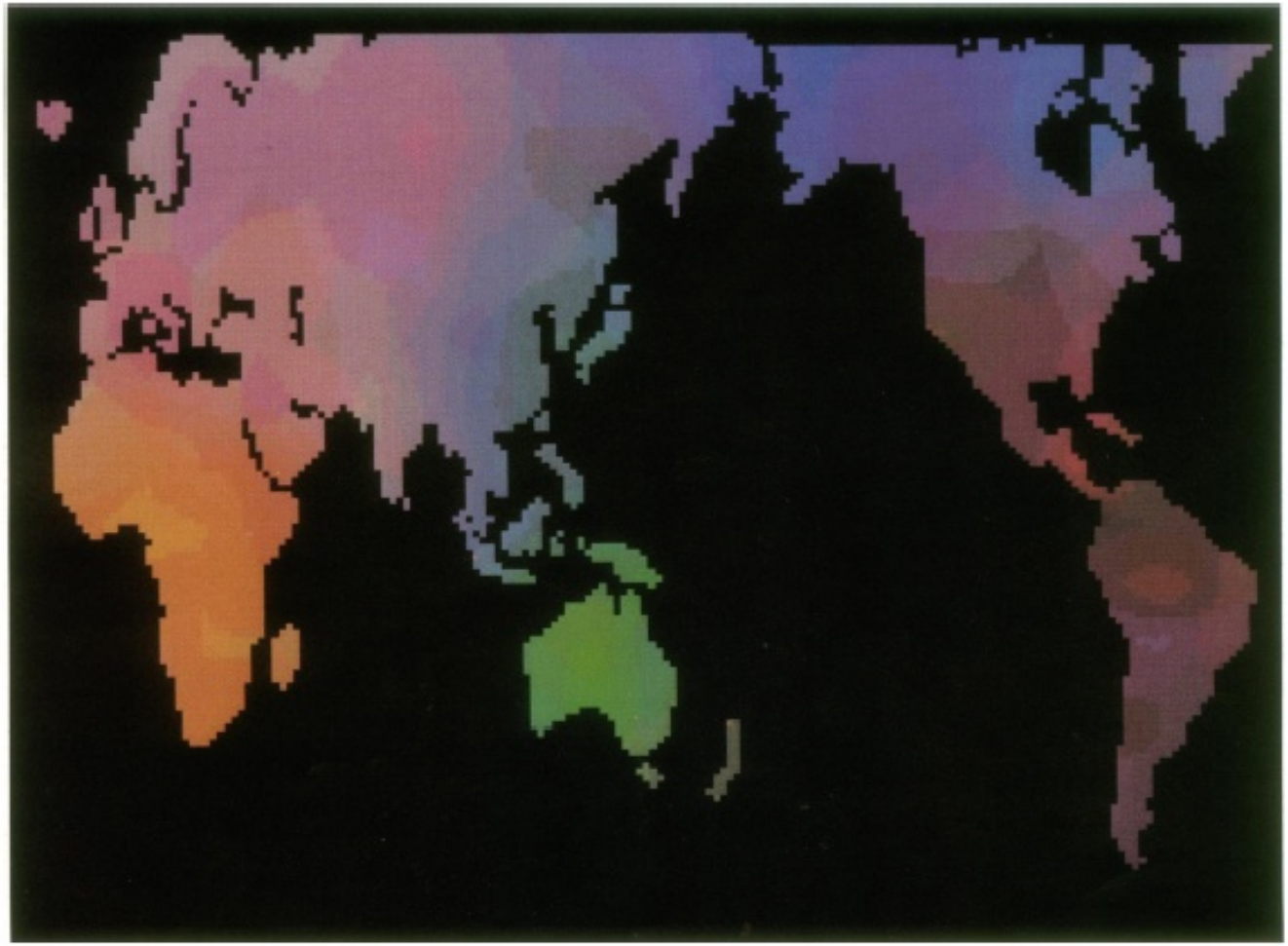
You do lose some information, but if the eigenvalues are small, you don't lose much

- n dimensions in original data
- calculate n eigenvectors and eigenvalues
- choose only the first p eigenvectors, based on their eigenvalues
- final data set has only p dimensions

PCA Analysis

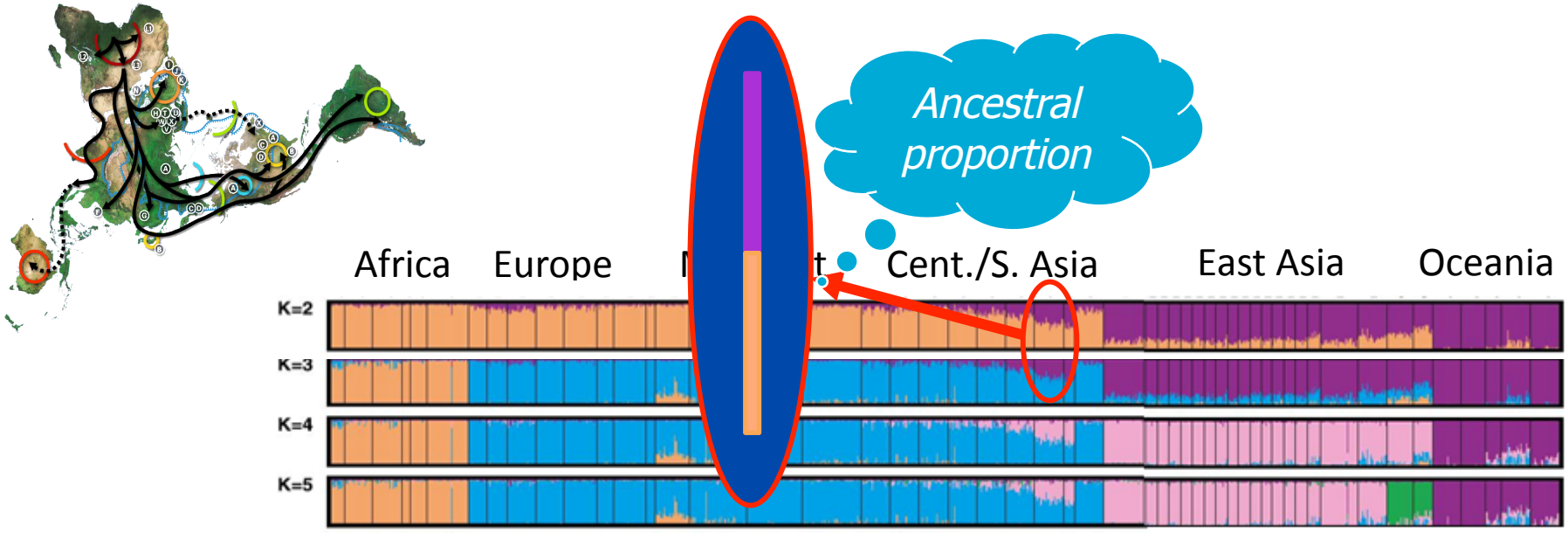
(Cavalli-sforza,1978)

- Plot of geographical distribution of 3 PCs (Intensity proportional to value of each component)
  - First – blue
  - Second - green
  - Third - red



Model-based Clustering for Discovering Population Structure

- How to display population structure?
  - *Structure* (Pritchard et al., Genetics 2000)



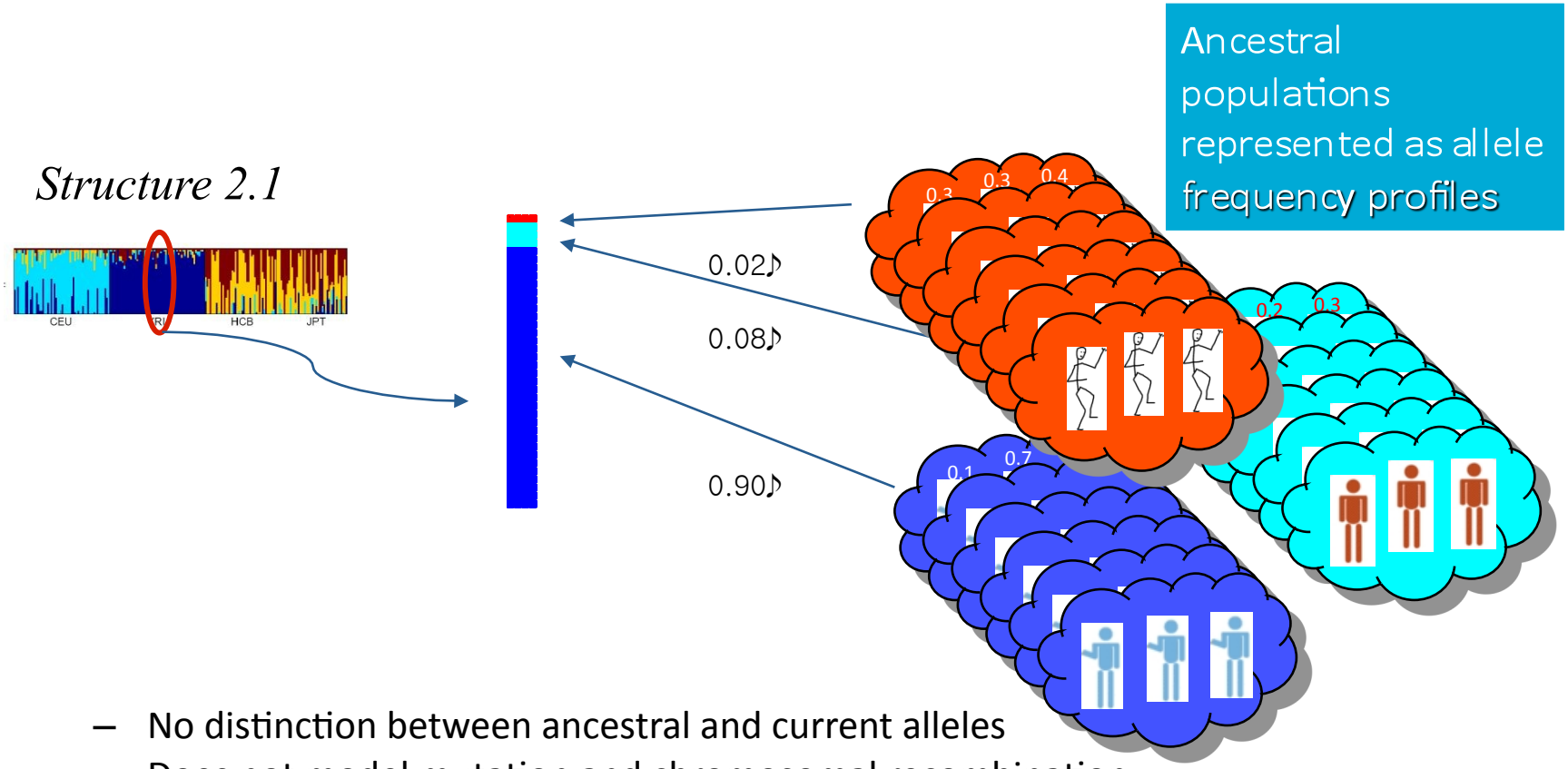
Genetic structure of Human Populations (Rosenberg et al., Science 2002)

Structure Model

- Hypothesis: Modern populations are created by an intermixing of ancestral populations.
- An individual's genome contains contributions from one or more ancestral populations.
- The contributions of populations can be different for different individuals.
- Other assumptions
  - Hardy-weinberg equilbrium
  - No linkage disequilbrium
  - Markers are i.i.d (independent and identically distributed)

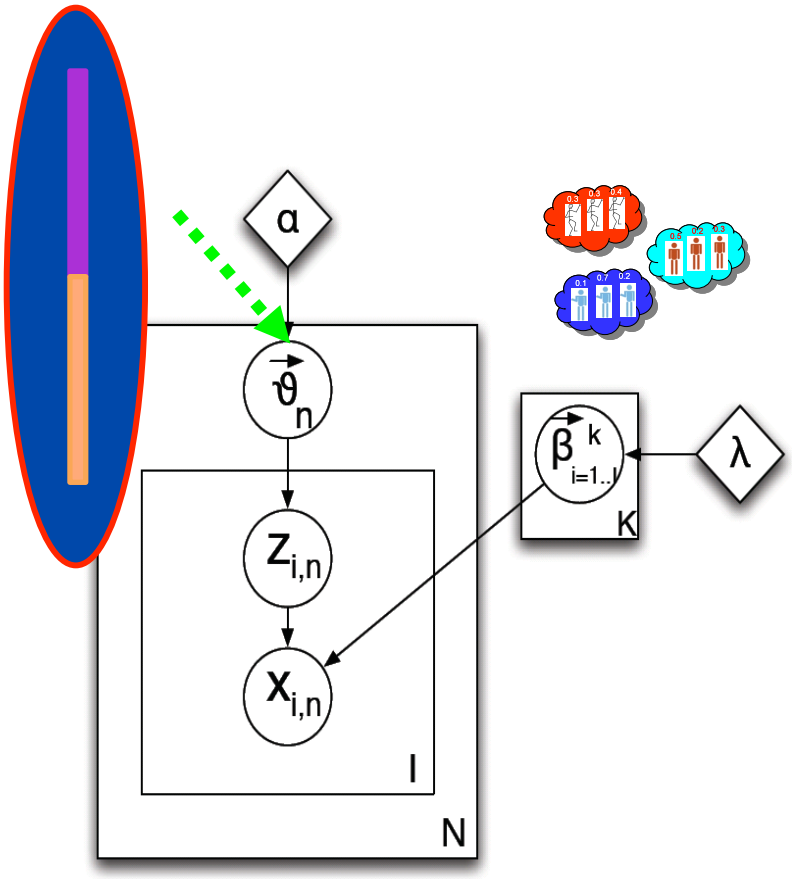
The Admixture Model

- Admixture of "ancestral frequency profiles (AP)"



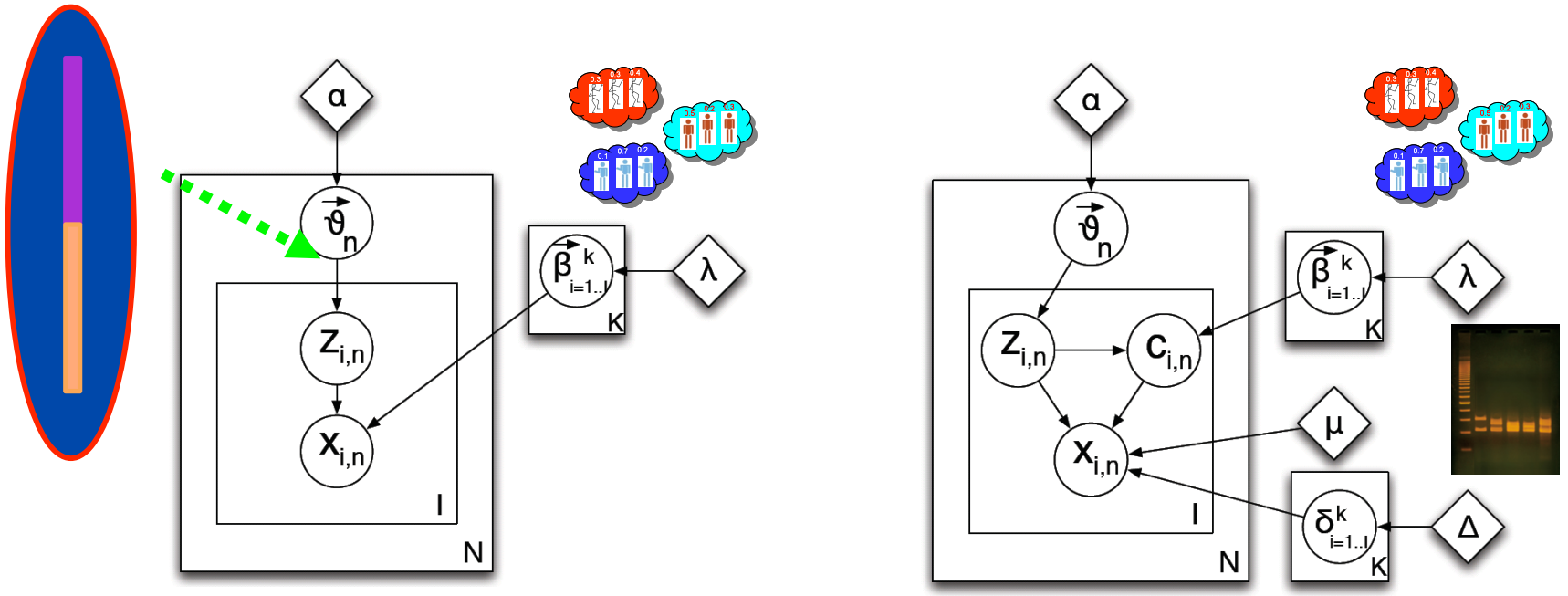
  - No distinction between ancestral and current alleles
  - Does not model mutation and chromosomal recombination

The Admixture Model



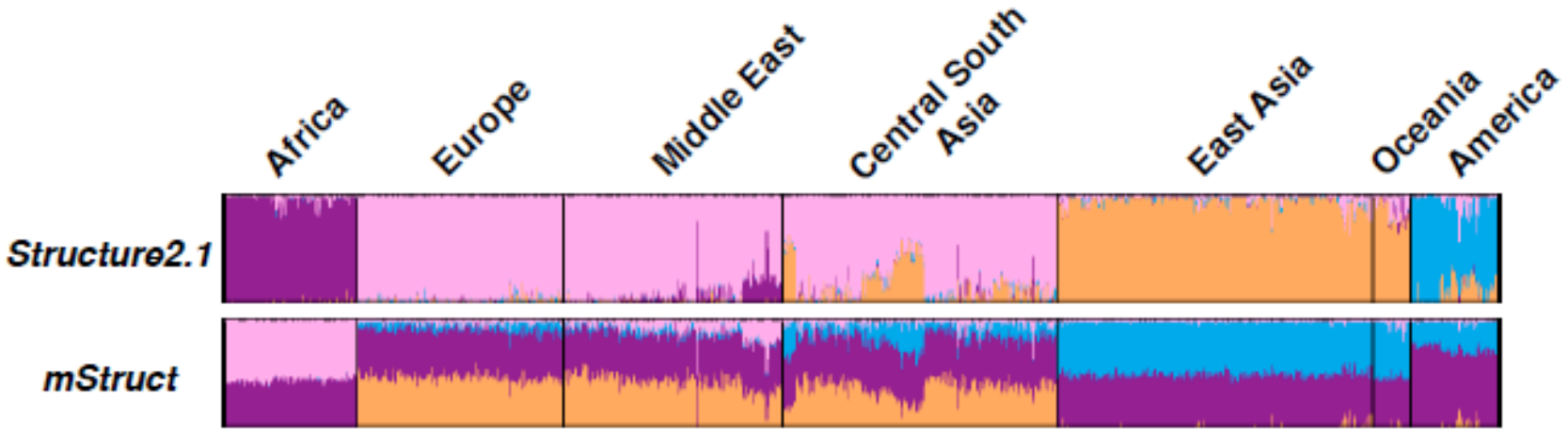
- β = Distribution over alleles
  - One per population –locus pair
- To generate an individual's genome
- Sample θ from Dirichlet(α)
- For each locus
  - Sample z from Multinomial(θ)
  - Sample x from β corresponding to the population chosen by z

From *Structure* to *mStruct* : Modelling Mutations



- From admixture of APs to admixture of MIMs
  - MiM: population-specific Mixture of Inheritance Models
- The inheritance model:
  - Microsatellite: $P(b|a) = \frac{1-\delta}{1-\delta^a+\delta}\delta^{|b-a|}.$
  - SNPs: $P(b|a) = \delta^{\mathcal{I}[b=a]} \times (1-\delta)^{\mathcal{I}[b\neq a]}; \quad a,b \in \{0,1\}.$

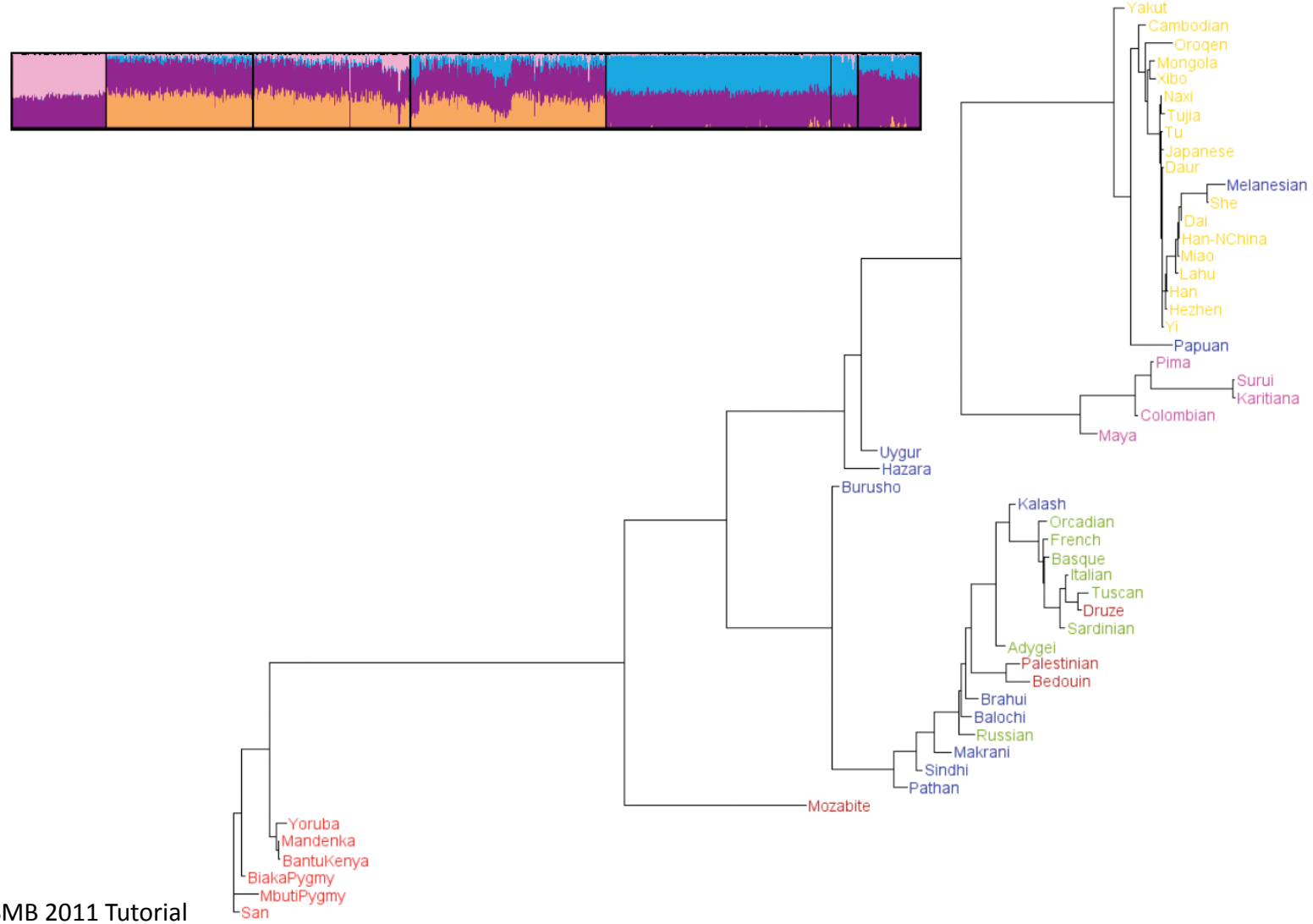
Comparing Population Structure Maps



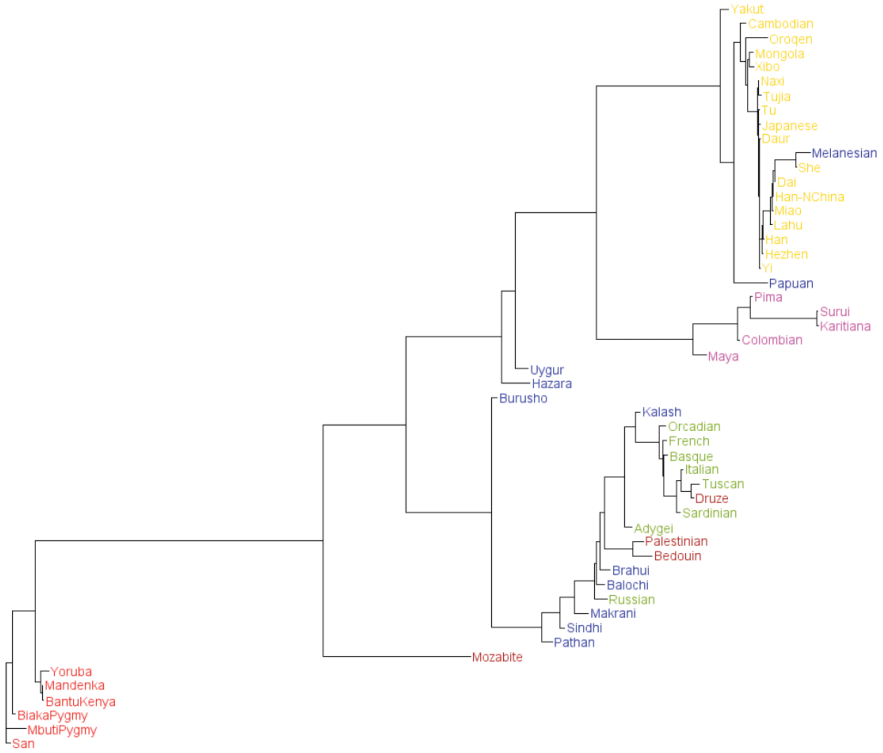
Ancestry structure maps inferred from microsatellite portion of the HGDP dataset, using *mStruct* and *Structure* with 4 ancestral population. The colors represent different ancestral populations.

- A common ancestral population is now seen across all continents!
- Clusters remain unchanged

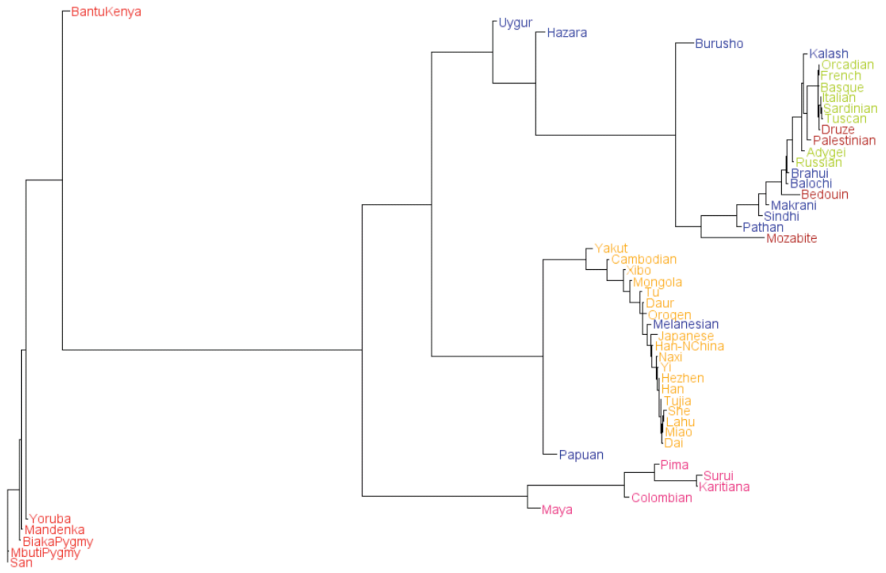
Phylogenetic tree from mStruct Structural map



Neighbour-joining Phylogenetic Trees from the Structural Maps



mStruct



Structure

Comparison of Different Methods

	PCA	Model-based Clustering (Structure, mStruct)
Advantages	• Statistical tests for significance of results (Patterson et al. 2006) • Easy visualization	• Generative process that explicitly models admixture • Clustering is probabilistic: it is possible to assign confidence level of clusters

Disadvantages	• No intuition about underlying processes	• Computational more demanding
		• Based on assumptions of evolutionary models:
		  • Structure: No models of mutation, recombination
		  • Mutation added in mStruct
		  • Recombination added in extension by Falush et al.

Summary: data preparation

- Preparing genotype data
  - Haplotypes inferred
  - Tag SNP selected
  - Missing genotype values imputed
  - Population structures stratified

- Preparing phenotype data
  - Handle missing phenotype values
  - Data normalization
  - Structure discovery: network inference, hierarchical clustering

Part II

Background on Association Analysis: Single Phenotype Method

Overview

- Single SNP association test
  - Discrete-valued phenotype: case/control study
  - Continuous-valued phenotype: quantitative traits
  - Correcting for multiple testing

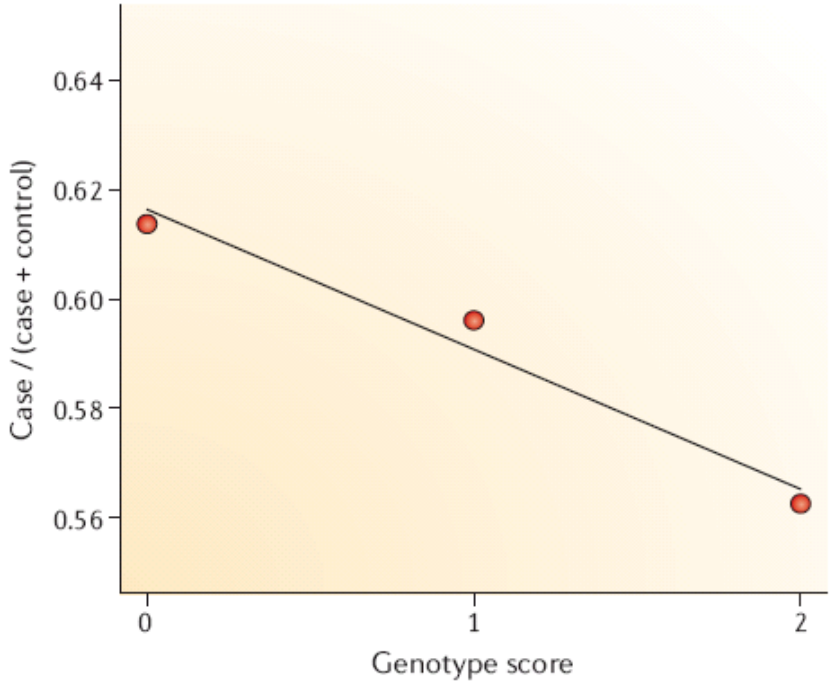
- Simultaneous analysis of all SNPs
  - Sparse regression method and convex optimization

Single SNP Association Analysis: Case/Control Study

- For each marker locus, find the 3x2 contingency table containing the counts of three genotypes

Genotype	Case	Control
AA	$N_{case,AA}$	$N_{control,AA}$
Aa	$N_{case,Aa}$	$N_{control,Aa}$
aa	$N_{case,aa}$	$N_{control,aa}$
Total	N_{case}	$N_{control}$

- χ^2 test with 2 df, or Fisher's exact test under the null hypothesis of no association



Genotype score = the number of minor alleles

Single SNP Association Analysis: Case/Control Study

- Alternatively, assume an additive model, where the heterozygote risk is approximately between the two homozygotes
- Form a 2x2 contingency table. Each individual contributes twice from each of the two chromosomes.

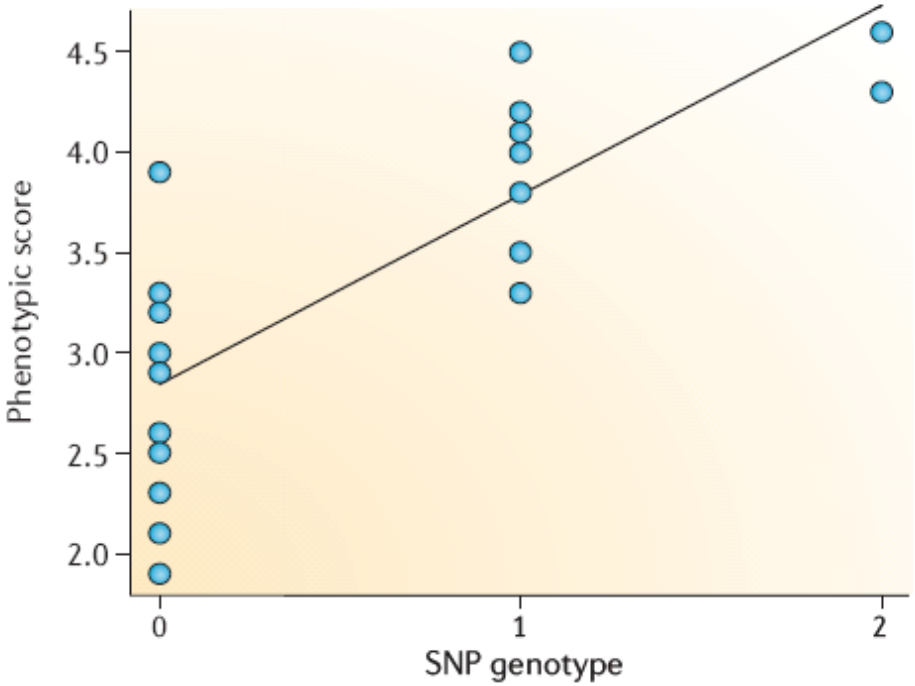
Genotype	Case	Control
A	$G_{case,A}$	$G_{control,A}$
a	$G_{case,a}$	$G_{control,a}$
Total	$2xN_{case}$	$2xN_{control}$

- χ^2 test with 1df

Single SNP Association Analysis: Continuous-valued Traits

- Continuous-valued traits
  - Also called quantitative traits
  - Cholesterol level, blood pressure etc.

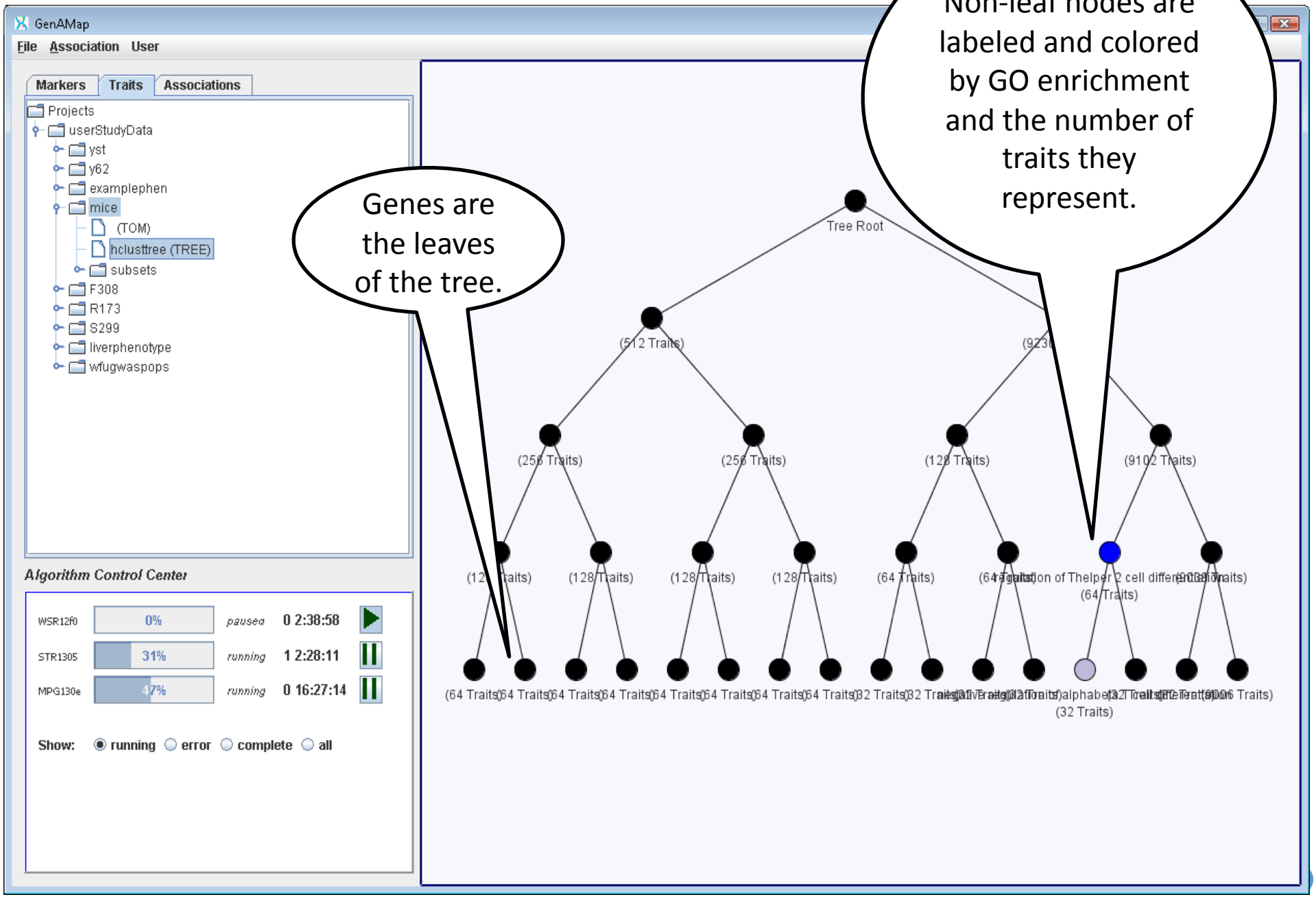
- For each locus, fit a linear regression using the number of minor alleles at the given locus of the individual as covariate



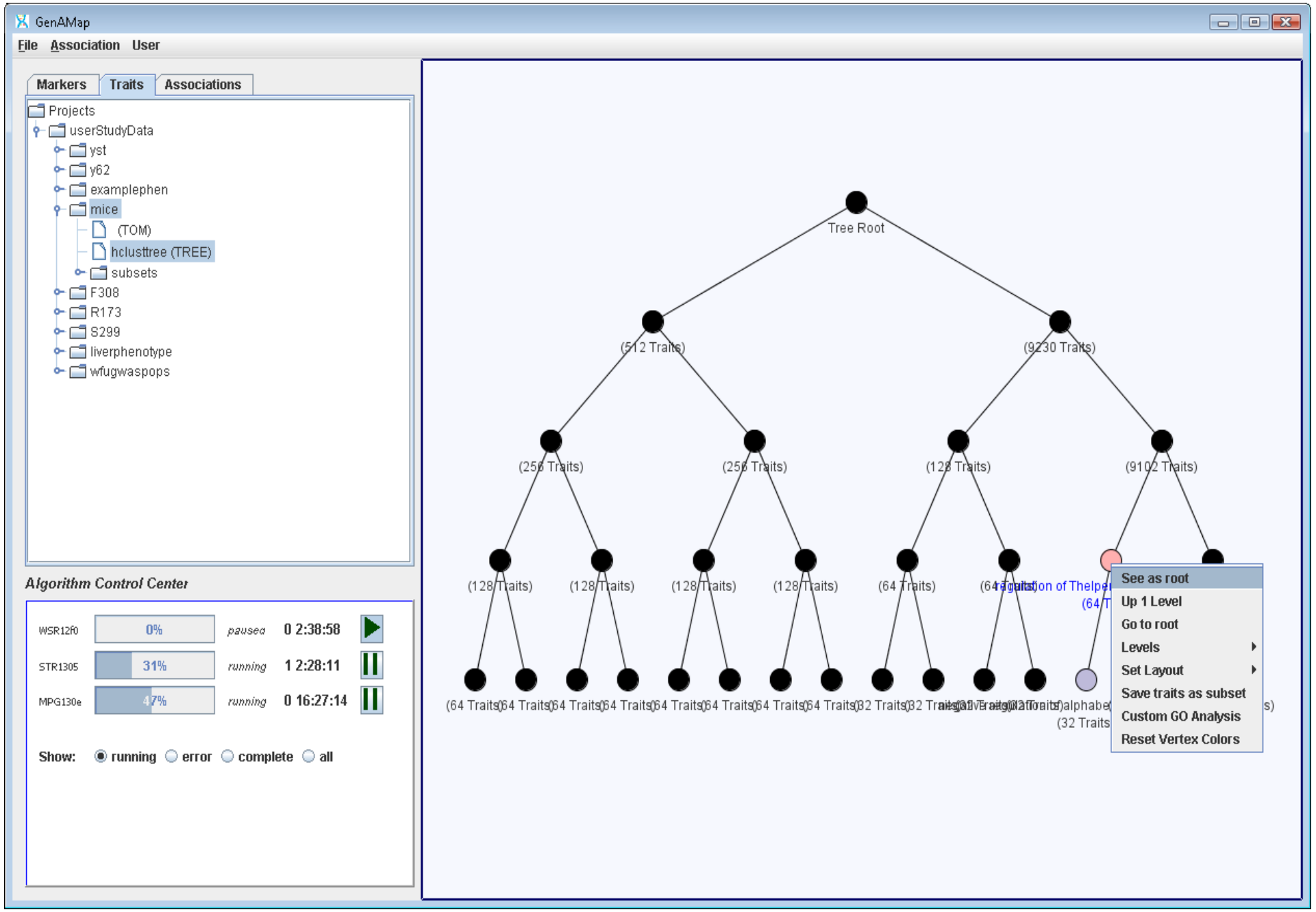
A Tree Analysis of Mouse eQTL Dataset

- NIH heterogeneous stock of mice (Johannesson et al., Genome Research 2009)
  - 259 mice from 7 inbred strains (A/J, AKR/J, BALBc/J, CBA/J, C3H/HeJ, C57BL/6J, DBA/2J and LP/J)
  - 9742 gene expression
  - 12545 SNPs

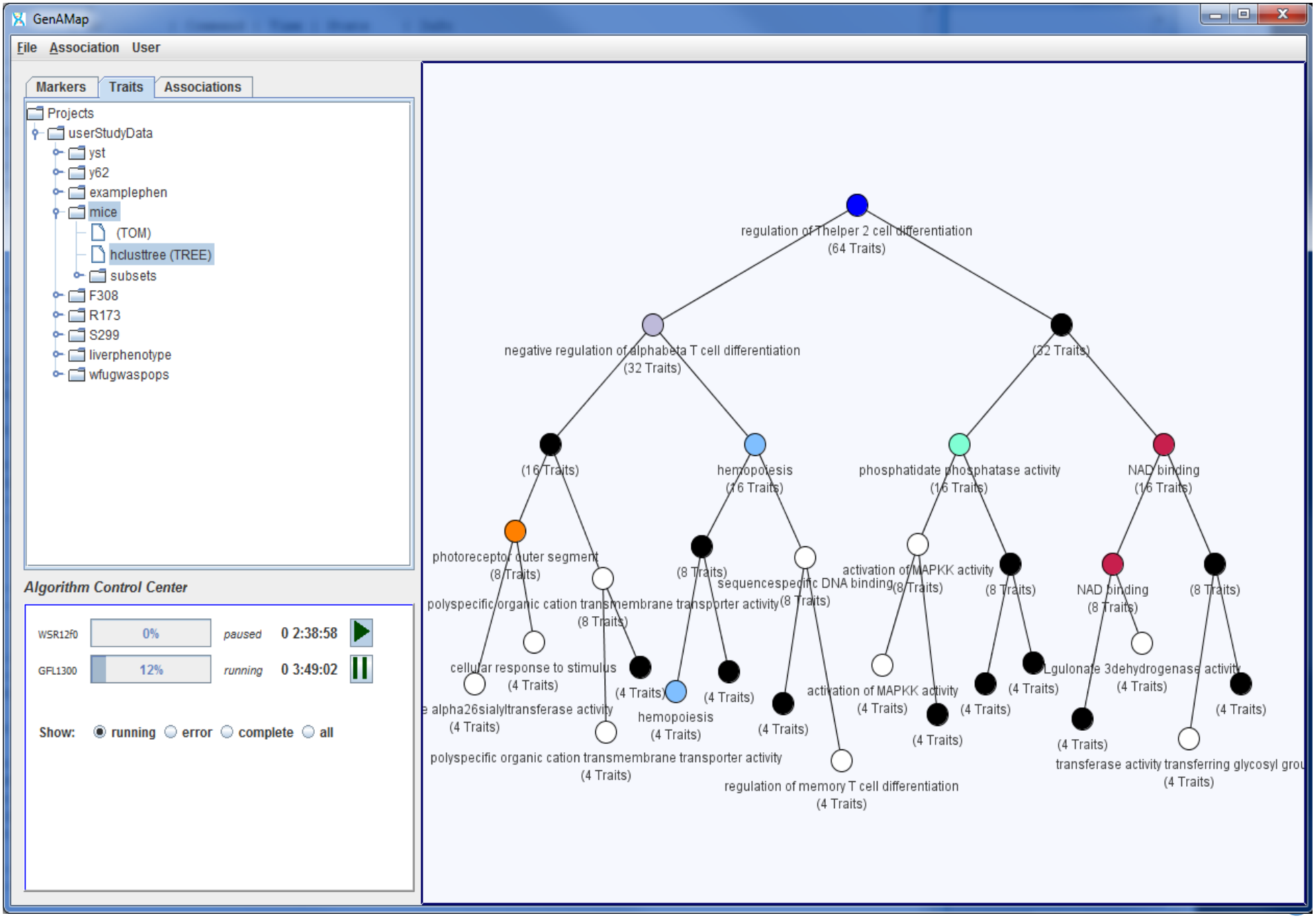
Genes displayed as a hierarchical tree



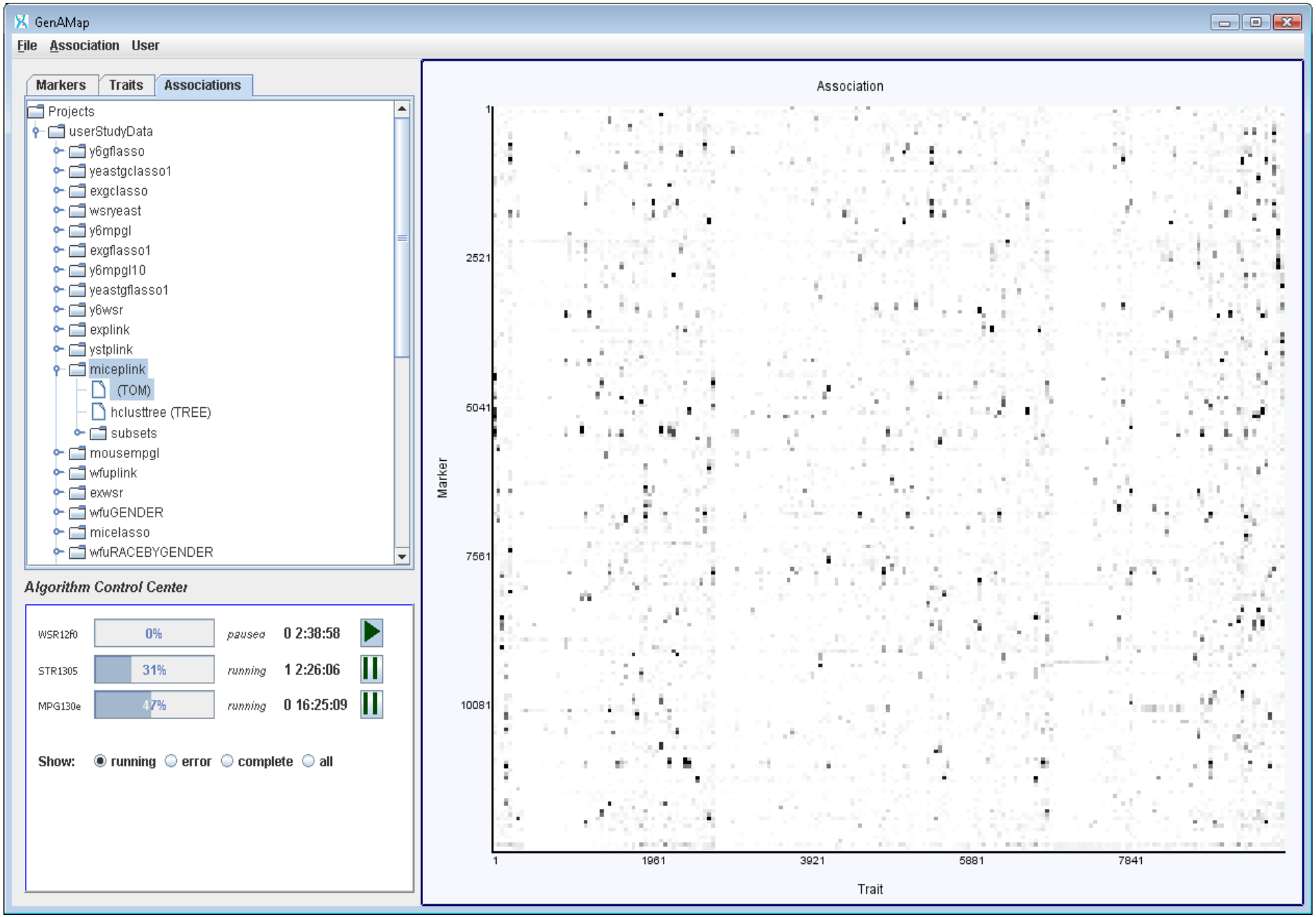
Browsing through the tree



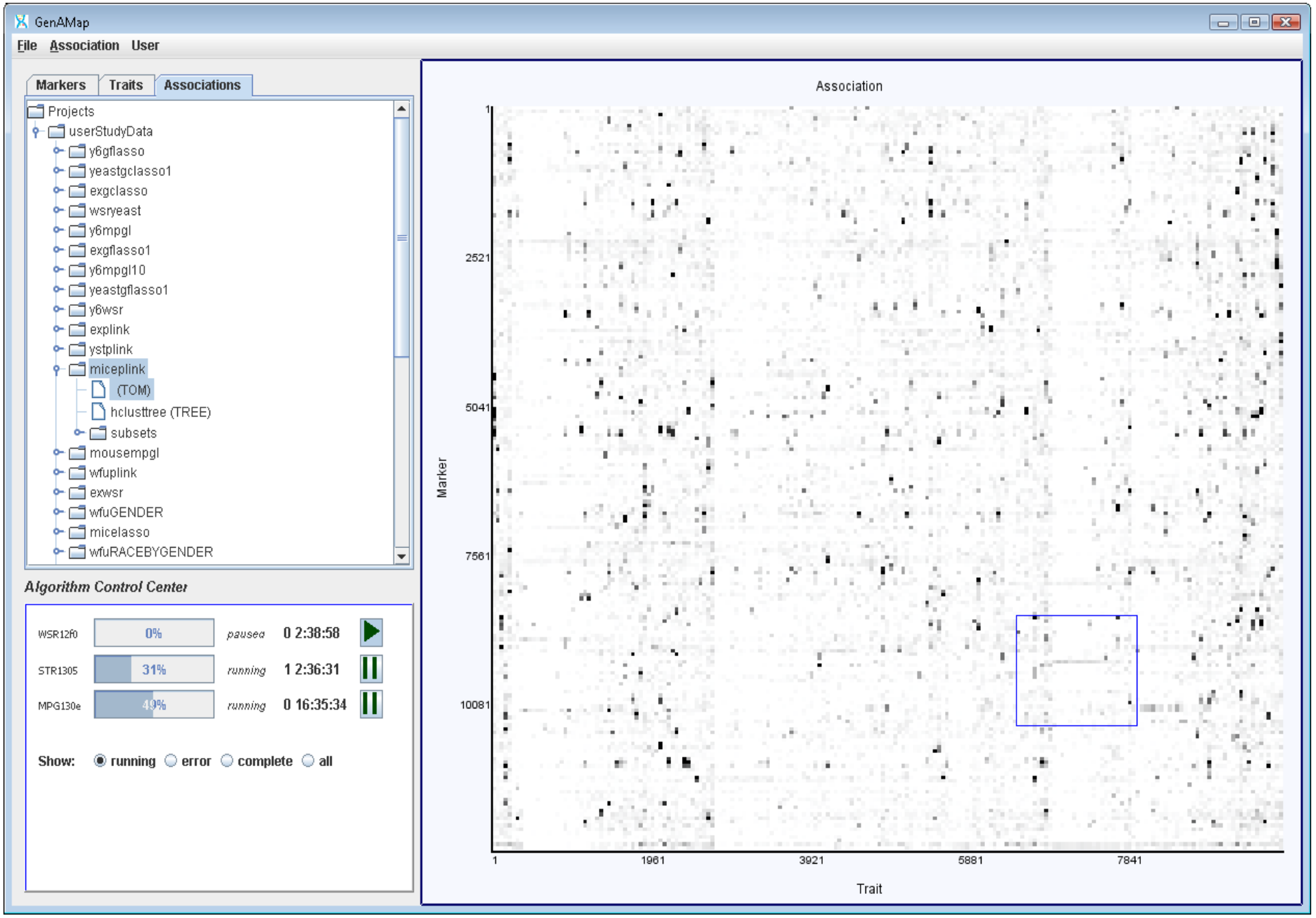
Branches of the tree are enriched for a common GO category



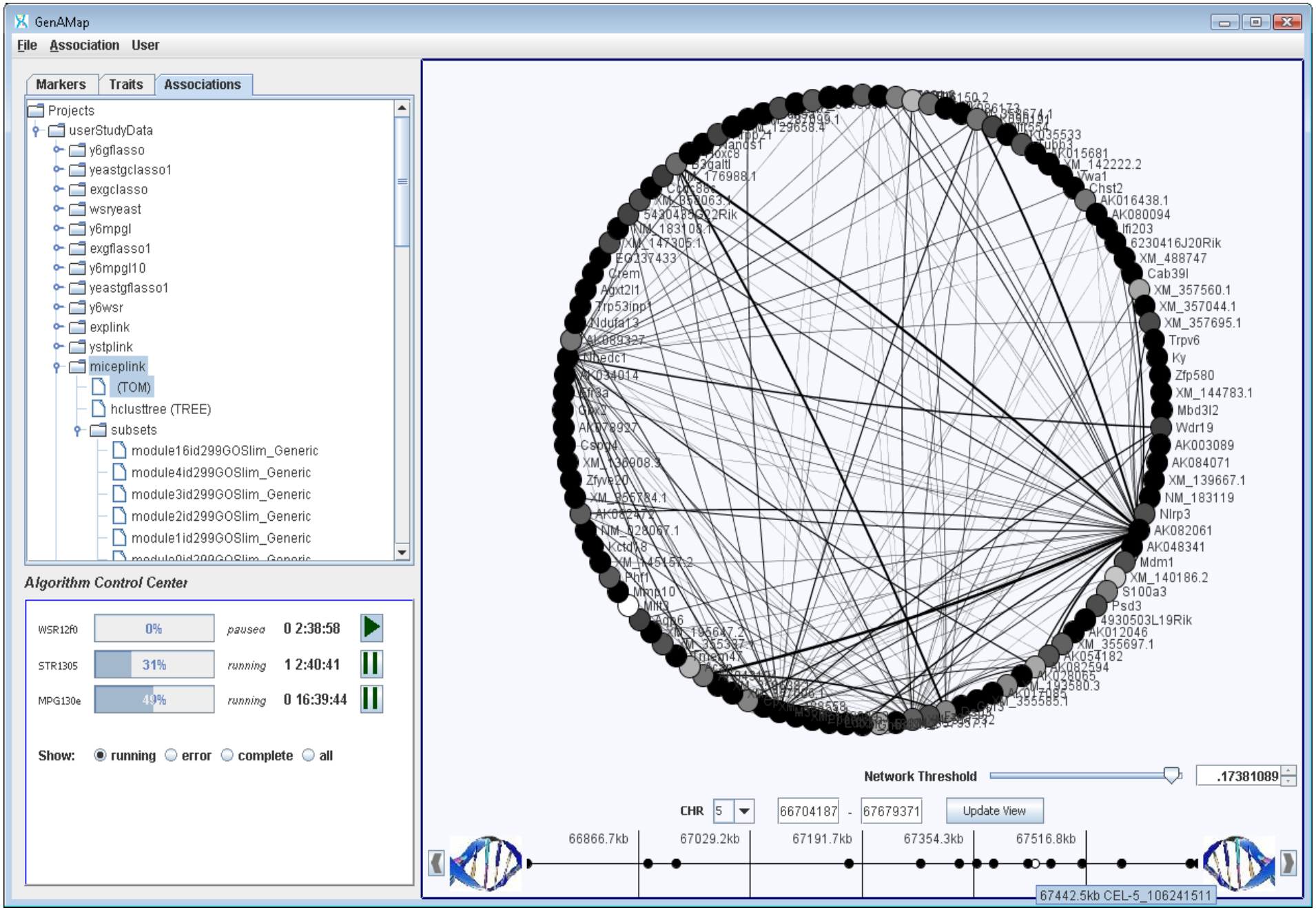
Association results (- log *p*-value)



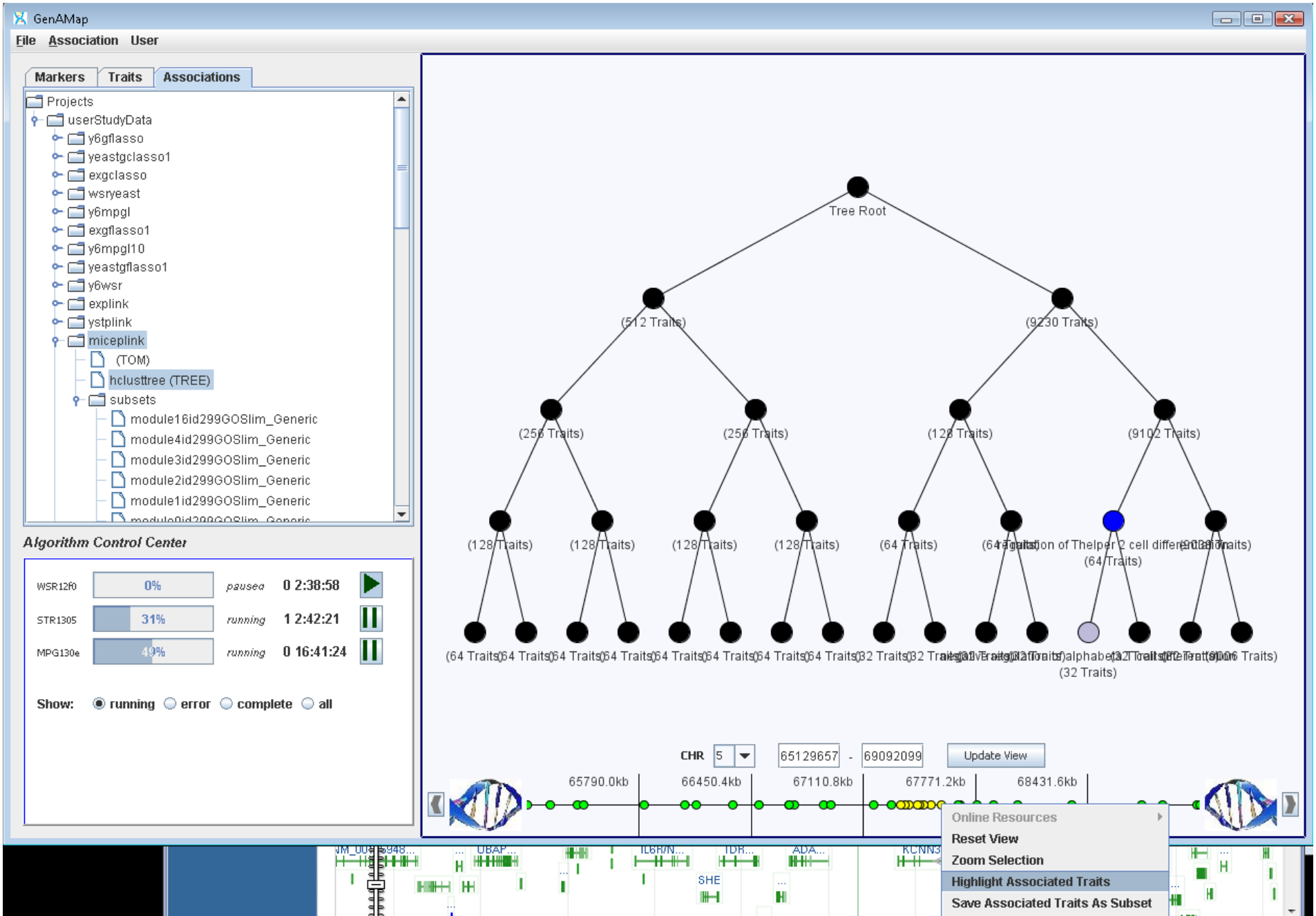
eQTL hotspot

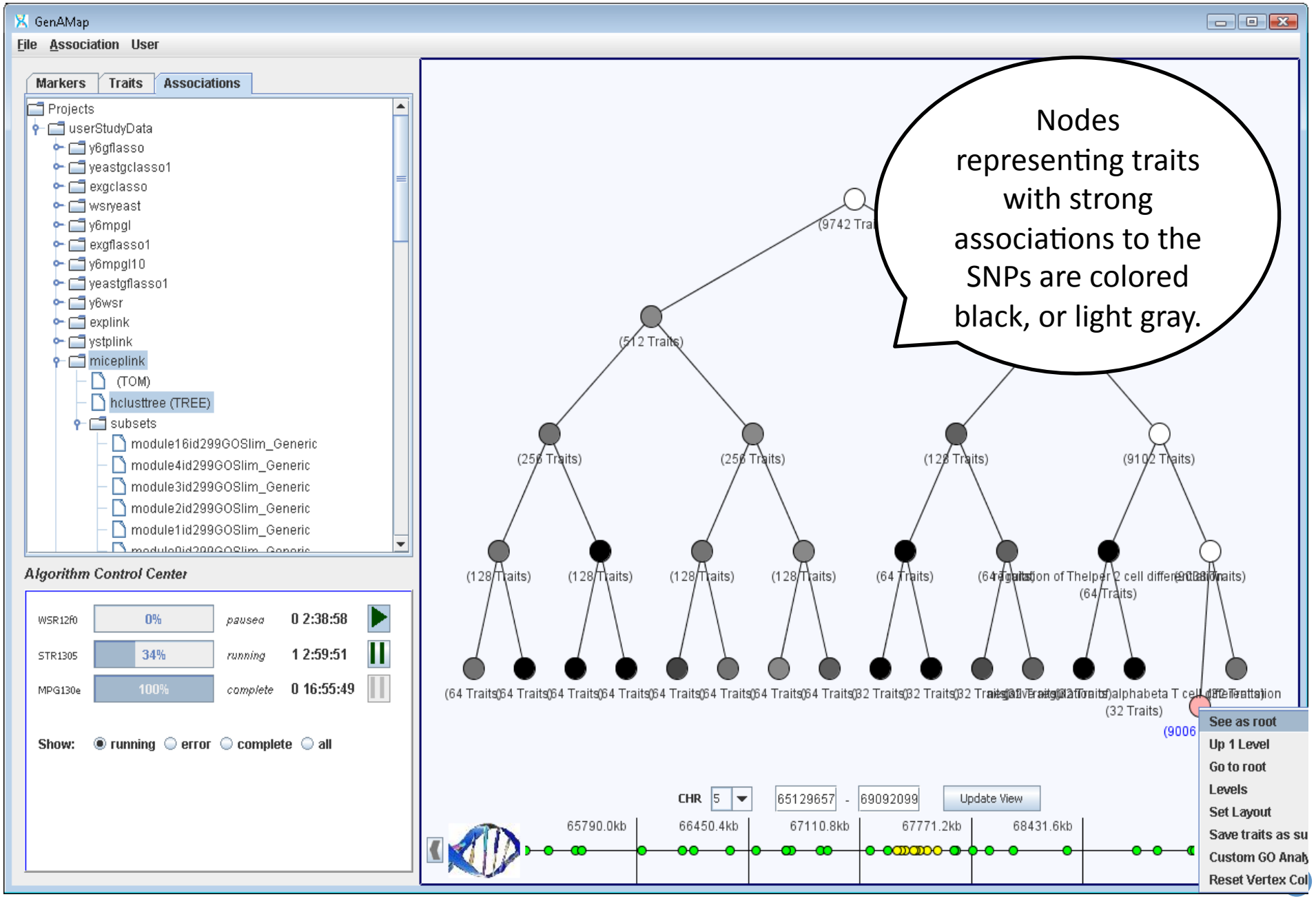


Select region to investigate on chromosome 5

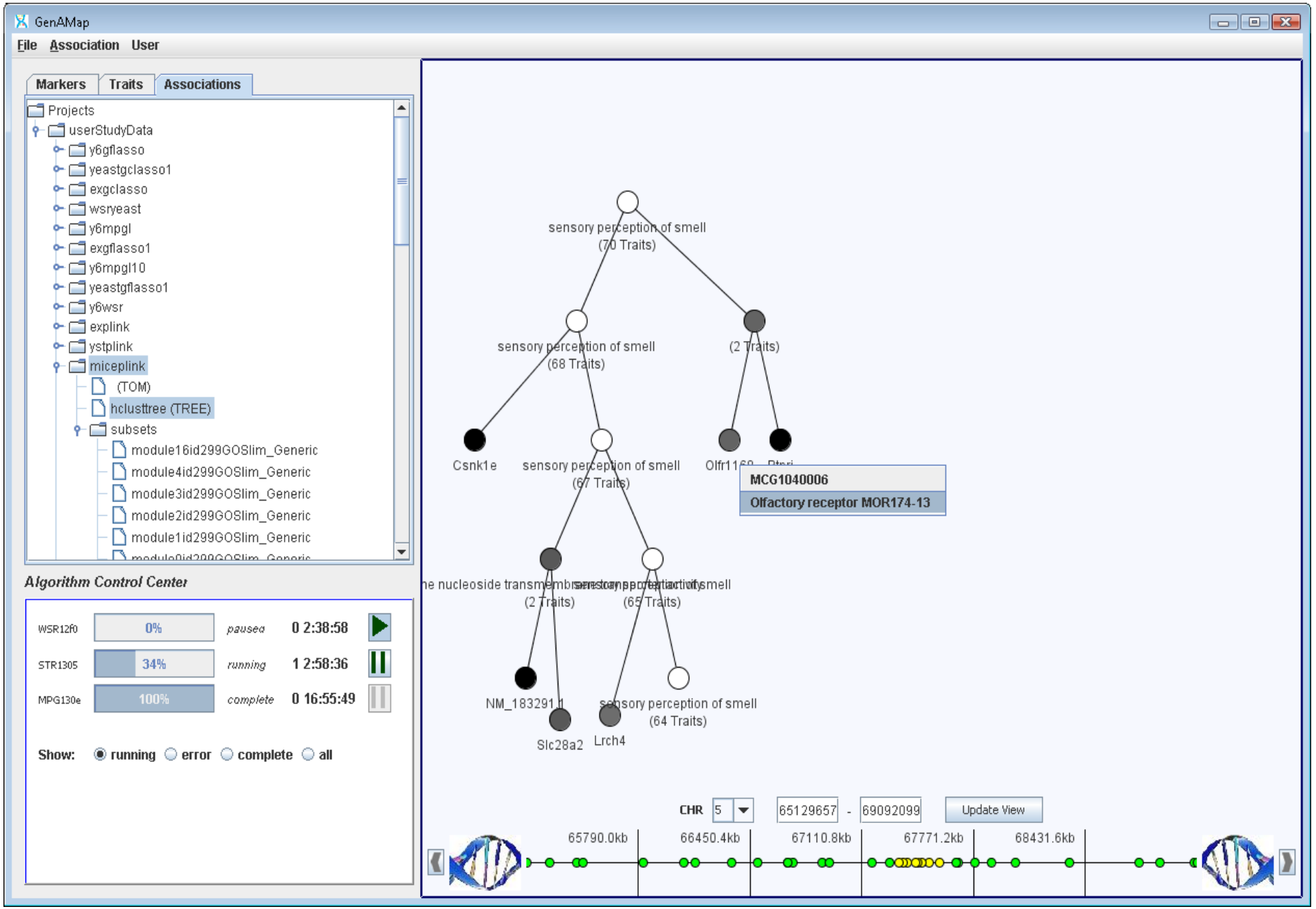


Switch to tree visualization

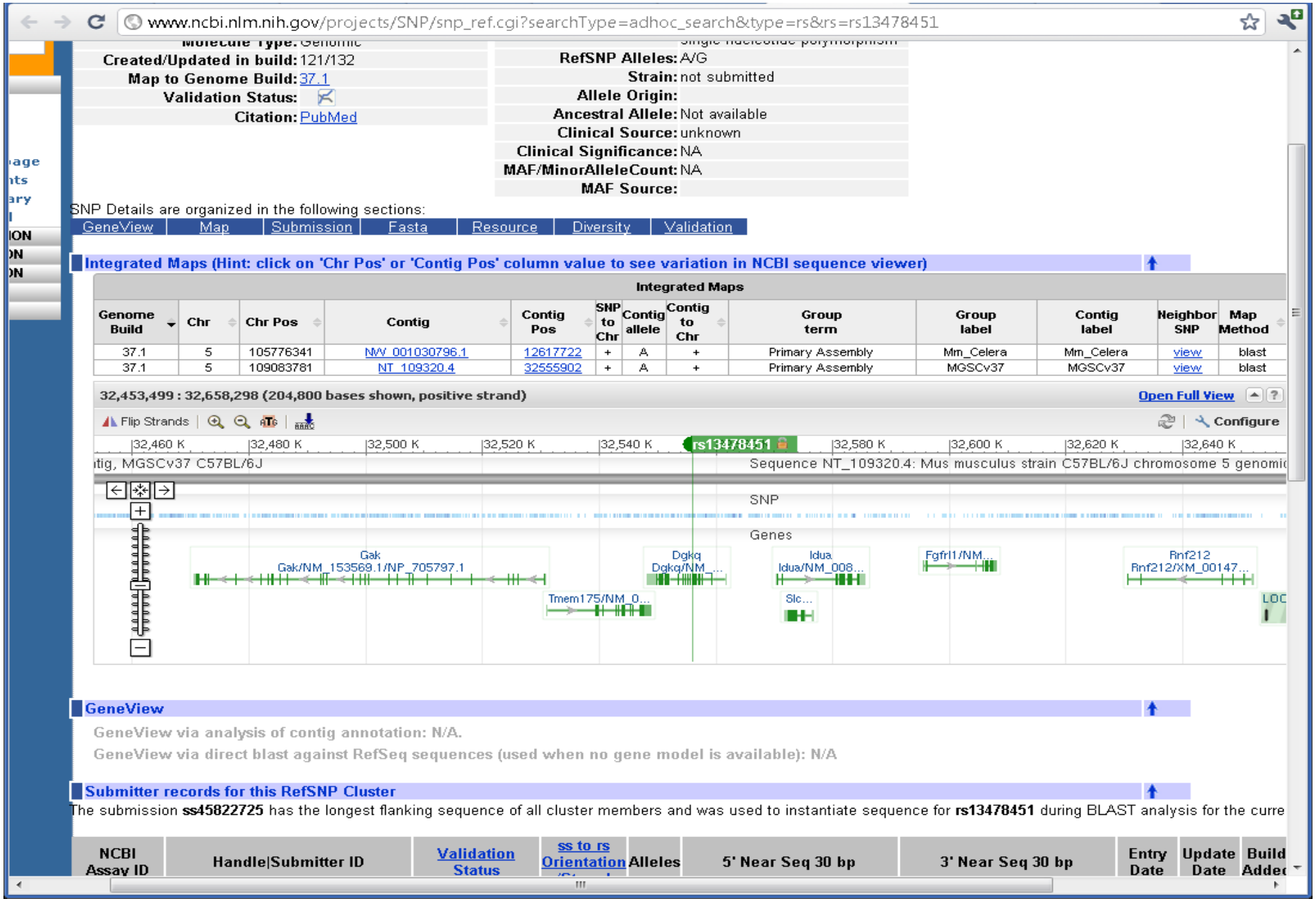



GenAMap
File Association User
Markers Traits Associations
Projects
userStudyData
y6gflasso
yeastgclasso1
exgclasso
wsryeast
y6mpgl
exgflasso1
y6mpgl10
yeastgflasso1
y6wsr
explink
ystplink
miceplink
(TOM)
hclusttree (TREE)
subsets
module16id299GOSlim_Generic
module4id299GOSlim_Generic
module3id299GOSlim_Generic
module2id299GOSlim_Generic
module1id299GOSlim_Generic
Algorithm Control Center
WSR12f0 0% paused 0 2:38:58
STR1305 34% running 1 2:59:51
MPG130e 100% complete 0 16:55:49
Show: running error complete all
Nodes representing traits with strong associations to the SNPs are colored black, or light gray.
(512 Traits)
(256 Traits)
(256 Traits)
(128 Traits)
(9102 Traits)
(128 Traits)
(128 Traits)
(128 Traits)
(128 Traits)
(64 Traits)
(64 Traits)
(64 Traits)
(32 Traits)
CHR 5 65129657 - 69092099 Update View
65790.0kb
66450.4kb
67110.8kb
67771.2kb
68431.6kb
See as root
Up 1 Level
Go to root
Levels
Set Layout
Save traits as su
Custom GO Anal
Reset Vertex Col

This region is associated with sensory perception of smell



These are our candidate genes near the SNP



Correcting for Multiple Testing

- What happens when we scan the genome of 1 million markers for association with $\alpha = 0.05$?
  - 50,000 (=1 millionx0.05) SNPs are expected to be found significant just by chance
  - We need to be more conservative when we decide a given marker is significantly associated with the trait.

- Correction methods
  - Bonferroni correction
  - Permutation test

Bonferroni Correction

- If N markers are tested, we correct the significance level as $\alpha' = \alpha/N$
  - Assumes the N tests are independent, although this is not true because of the linkage disequilibrium.
  - Overly conservative for tightly linked markers

Permutation Procedure

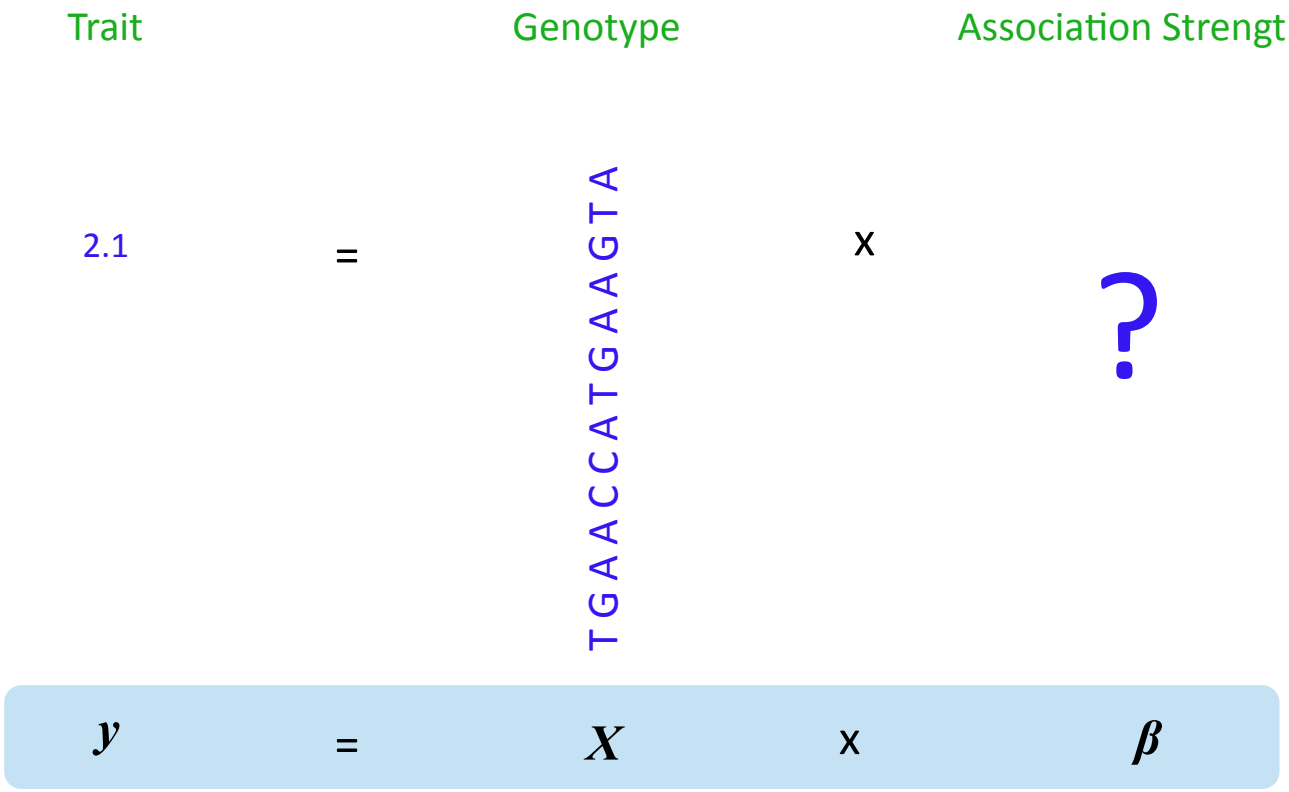
- Step 1: Compute the test statistic T using the original dataset
- Step 2: Set $N_{sig} = 0$
- Step 3: Repeat 1:N_{perm}
  - Step 3a: Randomly permute the individuals in the phenotype data to generate datasets with no association (retain the original genotype)
  - Step 3b: Find the test statistics T_{perm} of SNPs using the permuted dataset
  - Step 3c: if $T > T_{perm}$, $N_{sig} = N_{sig}+1$
- Step 4: Compute p-value as $(1-N_{sig}/N_{perm})$

This approach is computationally demanding because often a large N_{perm} is required.

Considering All SNPs in a Single Association Model

- Sparse multivariate regression
  - Estimates the effect of each SNP on the phenotype in the presence of all the other SNPs
  - High-dimensional data
    - Association strengths should be estimated for a very large number of SNPs
    - Penalized regression methods can be used to set the association strengths of many irrelevant SNPs to zero
  - Estimating the parameters (association strengths)
    - Convex optimization methods

Multivariate Regression for Single-Trait Association Analysis



Multivariate Regression for Single-Trait Association Analysis

Trait | Genotype | Association Strength

2.1 = TGAACCATGAAGTA x

$$\underset{\beta}{\operatorname{argmin}} \; (y - X\beta)' \cdot (y - X\beta)$$

Many non-zero associations:
Which SNPs are truly significant?

Sparsity

- One common assumption to make is **sparsity.**
- **Makes statistical sense:** Learning is now feasible in high dimensions with small sample size
- **Makes biological sense:** each phenotype is likely to be associated with a small number of SNPs, rather than all the SNPs.

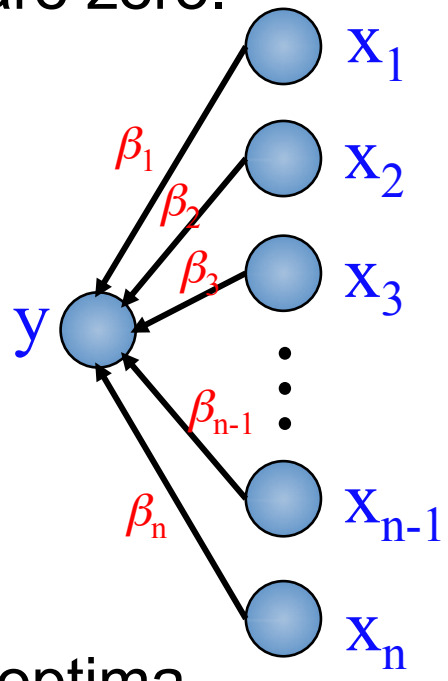
Sparsity: In a mathematical sense

- Consider least squares linear regression problem:
- Sparsity means most of the beta's are zero.

$$\hat{\boldsymbol{\beta}} = \text{argmin}_{\beta} \|\mathbf{Y} - \mathbf{X}\boldsymbol{\beta}\|^2$$

$$\text{subject to:}$$

$$\sum_{j=1}^{p} \mathbb{I}[|\beta_j| > 0] \leq C$$



- But this is not convex!!! Many local optima, computationally intractable.

L1 Regularization (LASSO)

- A convex relaxation.

Constrained Form

$$\hat{\boldsymbol{\beta}} = \text{argmin}_{\beta} \|\mathbf{Y} - \mathbf{X}\boldsymbol{\beta}\|^2$$

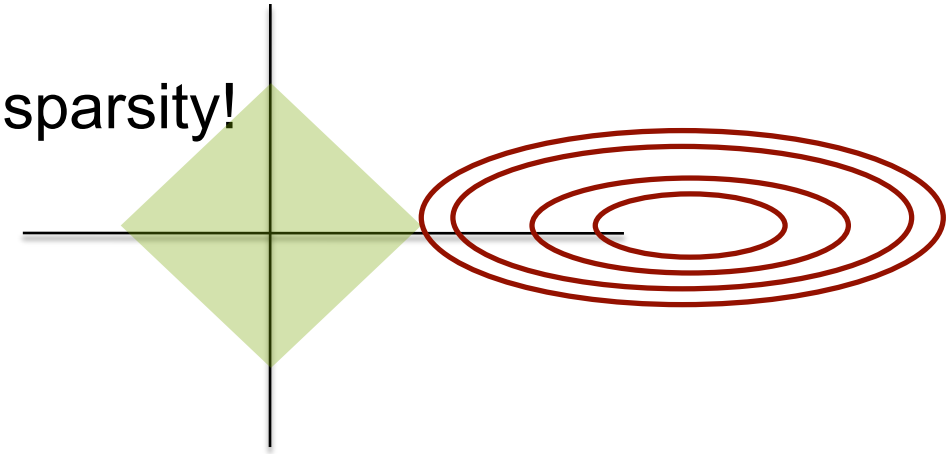
subject to:

$$\sum_{j=1}^{p} |\beta_j| \leq C$$

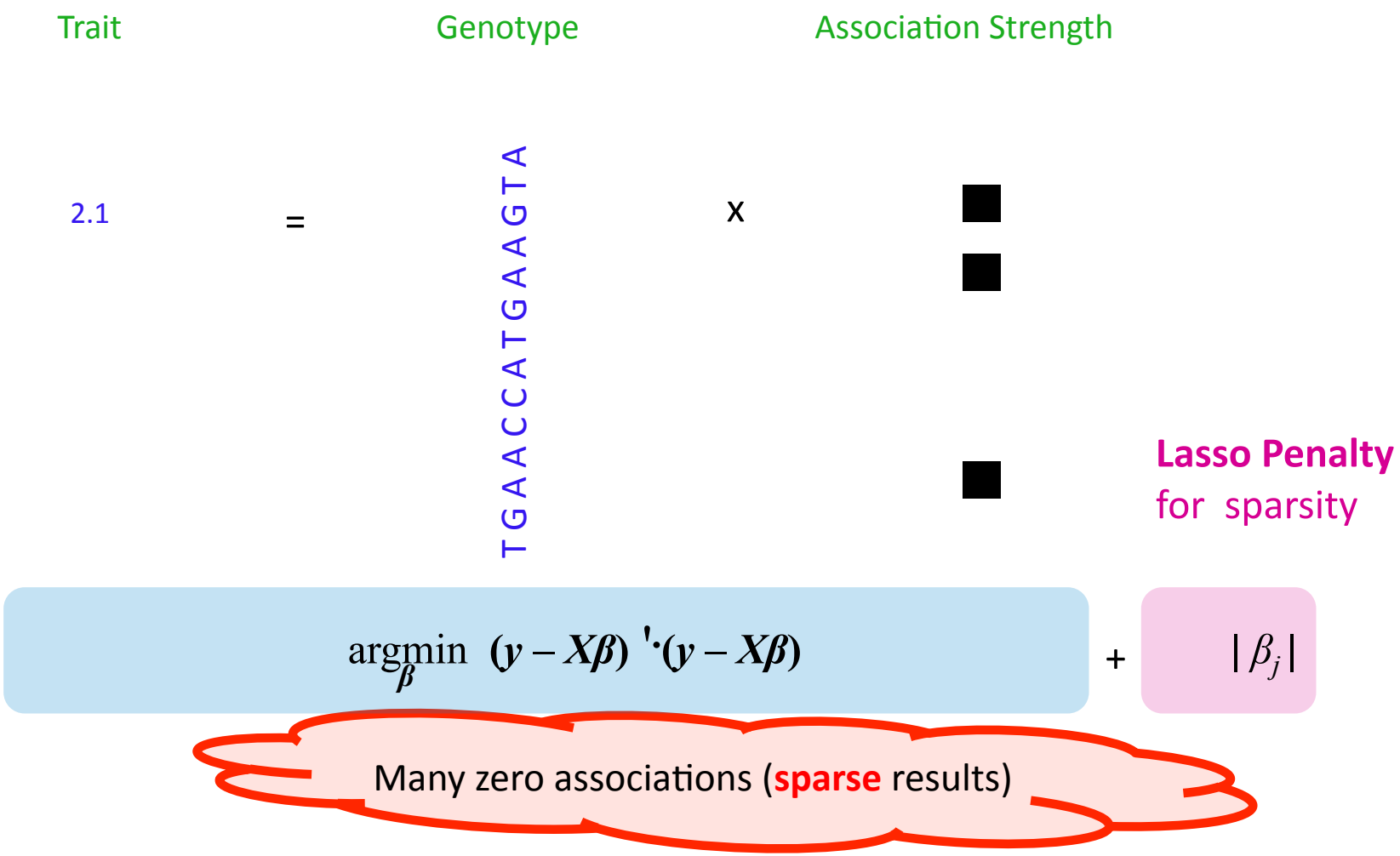
Lagrangian Form

$$\hat{\boldsymbol{\beta}} = \text{argmin}_{\beta} \|\mathbf{Y} - \mathbf{X}\boldsymbol{\beta}\|^2 + \lambda \|\boldsymbol{\beta}\|_1$$

- Still enforces sparsity!



Lasso for Reducing False Positives



Tibshirani, Journal of Royal Statistical Society 1996
Wu et al., Bioinformatics 2009

Estimating Parameters in Lasso (Association Strengths)

- Pathwise coordinate descent algorithm

  (Friedman et al., Annals of Applied Statistics 2007)

  – Compute the subgradient of the objective function with respect to each β_j to find the update equation

  – In each iteration, update each β_j, and iterate until convergence

- A fast implementation available at

  http://cran.r-project.org/web/packages/glmnet/index.html

Logistic Regression for Multiple SNPs in Case/control Association

	Case(1)/Control(0)	Genotype
Individual 1	0	..C.....T..C.....T... ..C.....A..C.....T...
Individual 2	1	..G.....A..G.....A... ..C.....T..C.....T...
⋮		
Individual N	1	..C.....A..G.....T... ..C.....T..C.....T...

$$p(y_i=\text{case})=f\left(\sum_{k=1}^{K} x_{ik}\beta_k\right)$$

- f : logistic function
- β_k : weight (association strength) for the kth SNP
- x_{ik} : genotype of the kth SNP for the ith individual (0,1, or 2 depending on the number of minor alleles)

Part III

Structured Genome-Phenome-Transcriptome Association Analysis

Structured Association: a New Paradigm

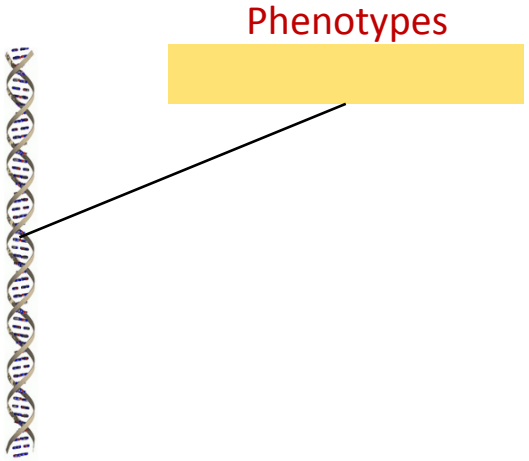
Standard Approach

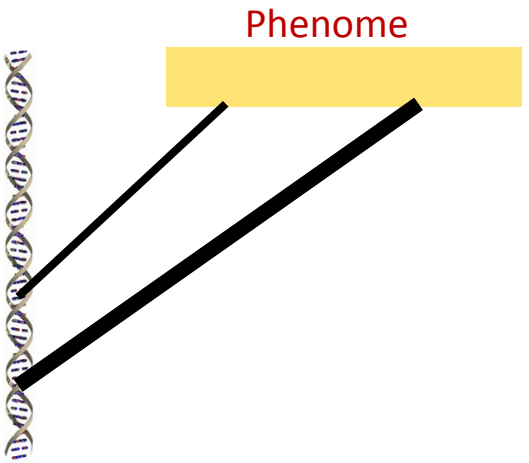
Consider **one phenotype** at a time

vs.

New Approach

Consider **multiple correlated phenotypes (phenome) and genotypes (genome) jointly**





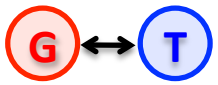
Overview

- Genome structure in association analysis
  - Linkage disequilibrium
  - Population structure
  - Epistasis

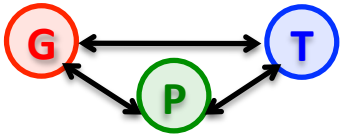
- Transcriptome structure in association analysis
  - Pleiotropy
    - Pathway-based statistical tests
    - Leveraging gene expression network
    - Leveraging gene expression tree

- Phenome structure in association analysis
  - Pleiotropy
  - Dynamic trait

- Two-way structured association



- Three-way structured association



- Visualization software

Multi-marker Association Test

- Idea: a haplotype of multiple SNPs is a better proxy for a true causal SNP than a single SNP
  - Exploit the linkage disequilibrium structure in genome

- Form a new allele by combining multiple SNPs for a haplotype

SNP A	SNP B
0	0
0	1
1	0
1	1

Auxiliary Markers for Haplotypes			
1	0	0	0
0	1	0	0
0	0	1	0
0	0	0	1

- Test the haplotype allele for association

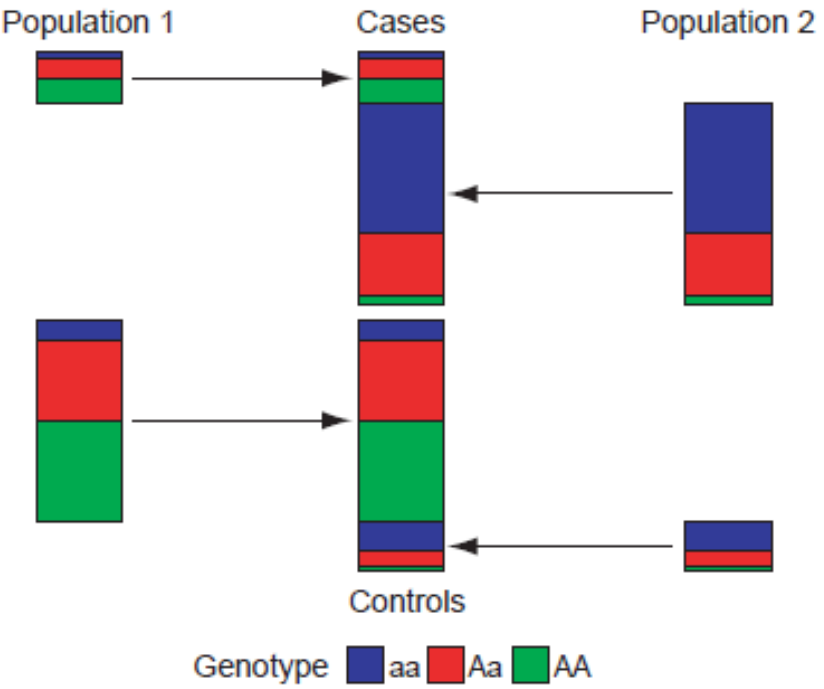
Multi-marker Association Test

- Multi-marker approach can capture dependencies across multiple markers
  - SNPs in LD form a haplotype that can be tested as a single allele
  - Can achieve the same power with data collected for fewer samples

- Challenge as the size of haplotype increases
  - Haplotype of K SNPs results in 2^K different haplotypes, but the number of samples corresponding to each haplotype decreases quickly as we increase K
  - Large K requires a large sample size

Population Structure and Association Analysis

- Population structure in data causes false positives
  - Samples in the case population are usually more related
  - Any SNPs more prevalent in the case population will be found significantly associated with the trait.



Accounting for Population Structure in Association Analysis

- Needs to account for population structure in association mapping
  - Genomic control (Devlin & Roeder, Biometrics 1999)
  - Structured association (Pritchard et al., AJHG 2000)
  - EigenStrat: principal component analysis (Price et al., Nature Genetics 2006)
  - Multi-population lasso (Puniyani et al., ISMB 2010)

Genomic Control (GC)

- Idea: Use the SNPs that are not associated with the trait to remove the effect of population stratification

- Genotype data consist of
  - Candidate genes to be tested
  - *L* supplementary loci (null loci) for estimating the inflation factor λ

- GC uses the inflation factor λ to correct the association statistic of the SNP in the candidate gene

- Limitation: the inflation factor λ is assumed to be the same across the genome, ignoring population admixture

Devlin & Roeder, Biometrics 1999

Structured Association

- Idea: Within each subpopulation, an association between a genetic marker and the trait is a true association.

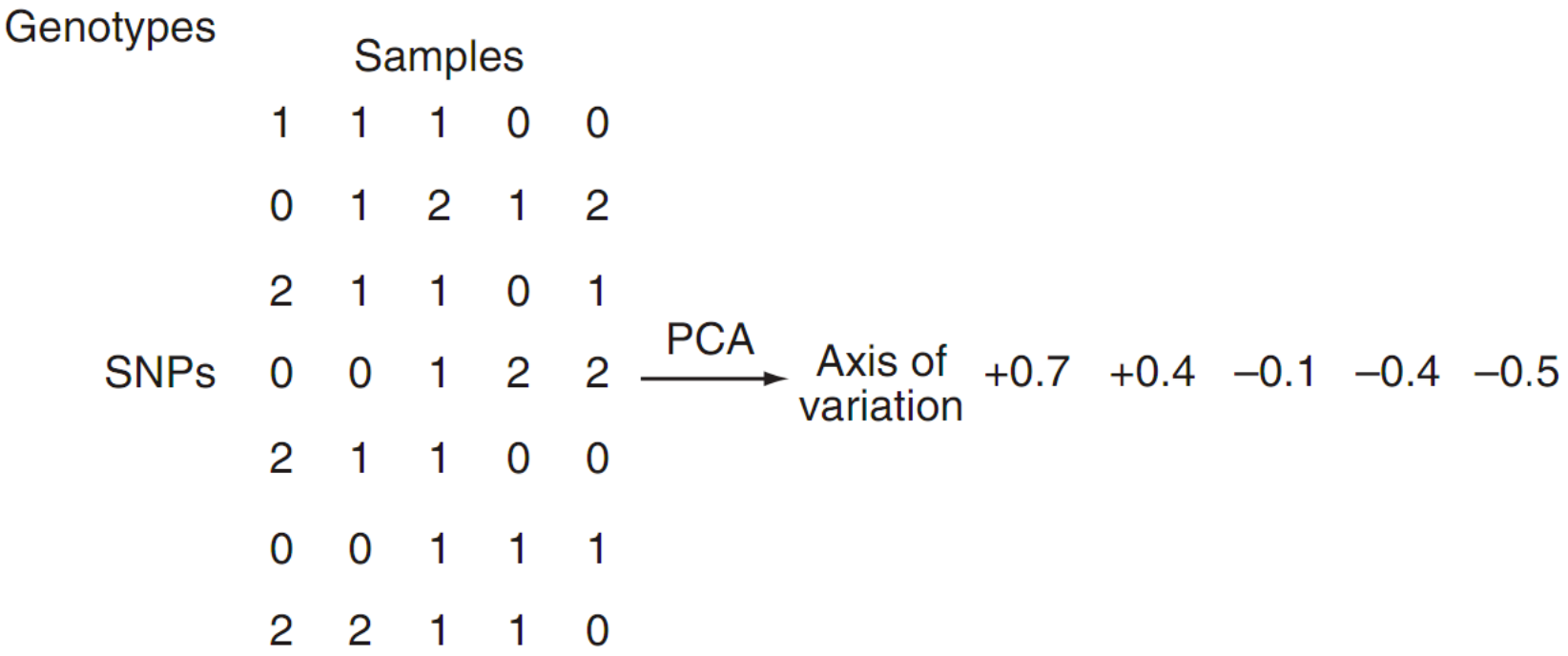
- Two-stage method
  - Step 1: Using Structure (Pritchard et al., Genetics 2000) and unlinked genetic markers,
    - estimate the population structure
    - assign sampled individuals to putative subpopulations
  - Step 2:
    - Test for association within the subpopulations inferred in Step 1

- Limitation
  - Running Structure is computationally demanding

Pritchard et al., AJHG 2000

EigenStrat: Structured Association with PCA

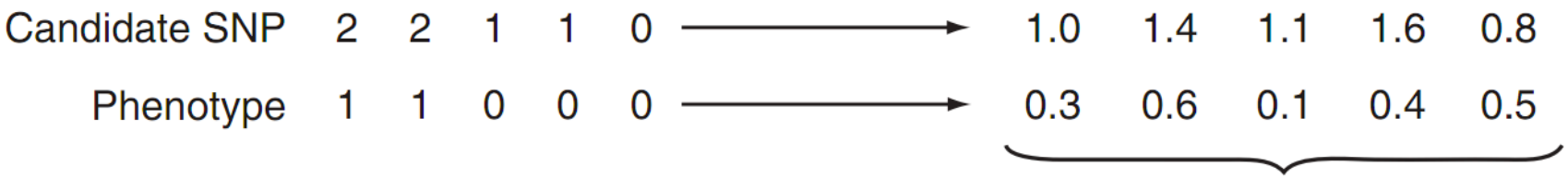
- Step 1: (Inferring Ancestry) PCA is applied to genotype data to infer continuous axes of genetic variation



Price et al., Nature Genetics 2006

EigenStrat: Structured Association with PCA

- Step 2: (Removing Ancestry Effects) Genotype at a candidate SNP and phenotype are continuously adjusted by amounts attributable to ancestry along each axis



- Step 3: (Association test) $\chi^2 = 0.07 \Longrightarrow$ no association

Multi-Population Group Lasso (MPGL)

- Idea: instead of correcting for the population structure (as in GC, structured association, and EigenStrat), let's exploit the population structure to detect true associations

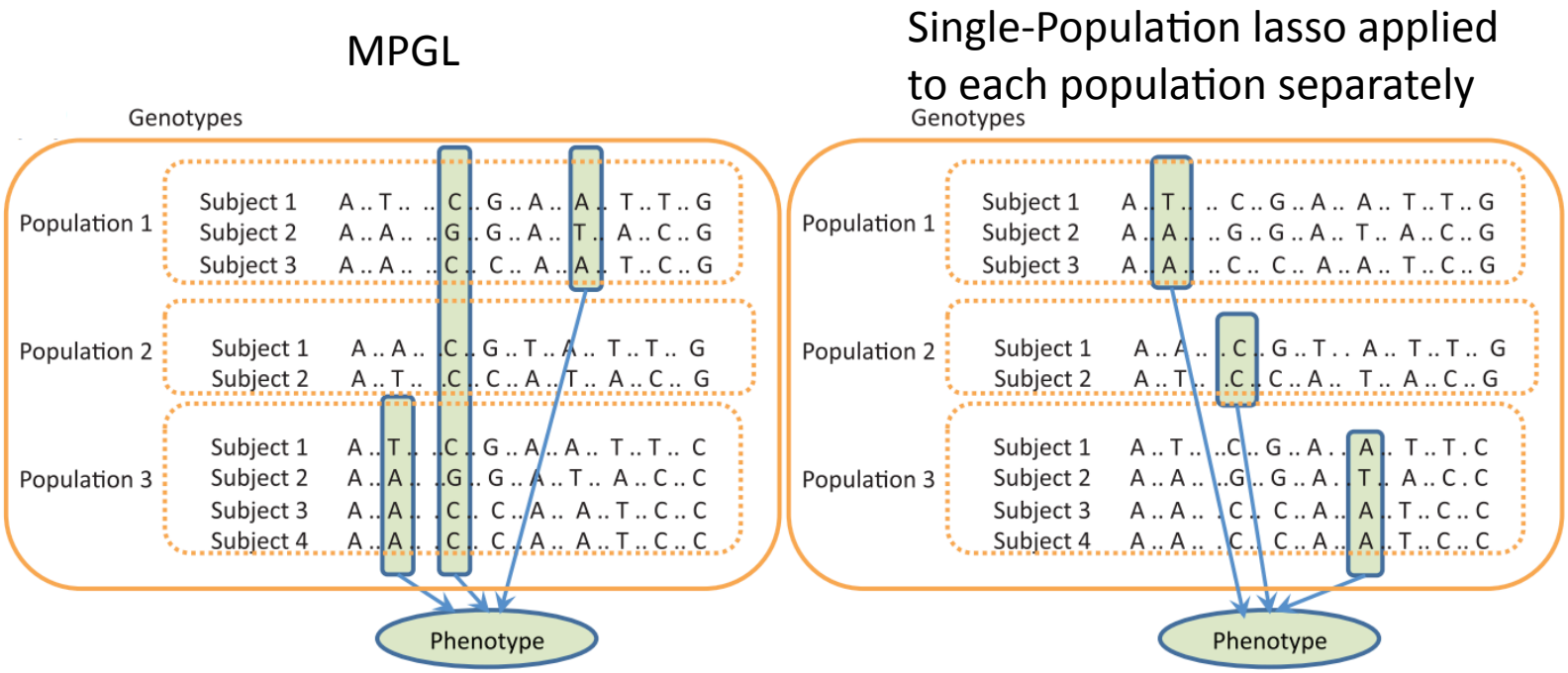
- Assume that the population structure is known
  - If not, use existing algorithms such as Structure to infer population structure

- Sparse multivariate regression with group-lasso penalization

Puniyani et al., ISMB 2010

Multi-Population Group Lasso (MPGL)

- MPGL combines information across multiple populations to detect
  - SNPs with associations in all of the populations
  - SNPs with associations in each population



Multi-Population Group Lasso (MPGL)

- Joint estimation of shared and population-specific associations

$$\min_B \frac{1}{2} \sum_{i=1}^{k} (Y^{(i)} - X^{(i)} \beta^{(i)})^2 + \lambda ||B||_{l_1/l_2}$$

For Each Population i

Least Square Error

Encourages Joint Sparsity

$$||B||_{l_1/l_2} = \sum_{i=1}^{p} ||B_i||_2$$

Sum over SNPs

Experiments: Lactose Persistence

- Data : 1400 individuals from the control group of the WTCCC dataset, all of European descent.
  (The Wellcome Trust Case Control Consortium, Nature 2007)

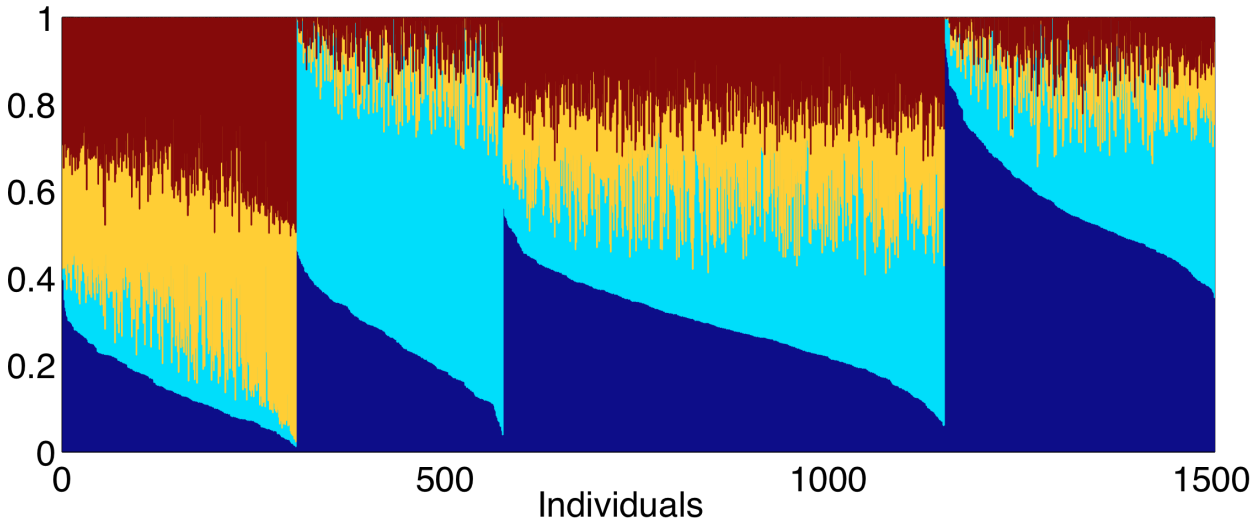
- Genotype : 135.16-136.82Mb region on chromosome 2 (known to show geographical variation).

- Phenotype : Lactose persistence, fully determined by a particular mutation near the LCT gene (Enattah et al., 2002)

- Associated marker : SNP rs4988243 lies in a high linkage disequilibrium region (r^2 >0.9) with this known genetic variant.

Analysis of Population Structure

- Results from *Structure* (Pritchard et al., Genetics 2000) on genotype data with four populations

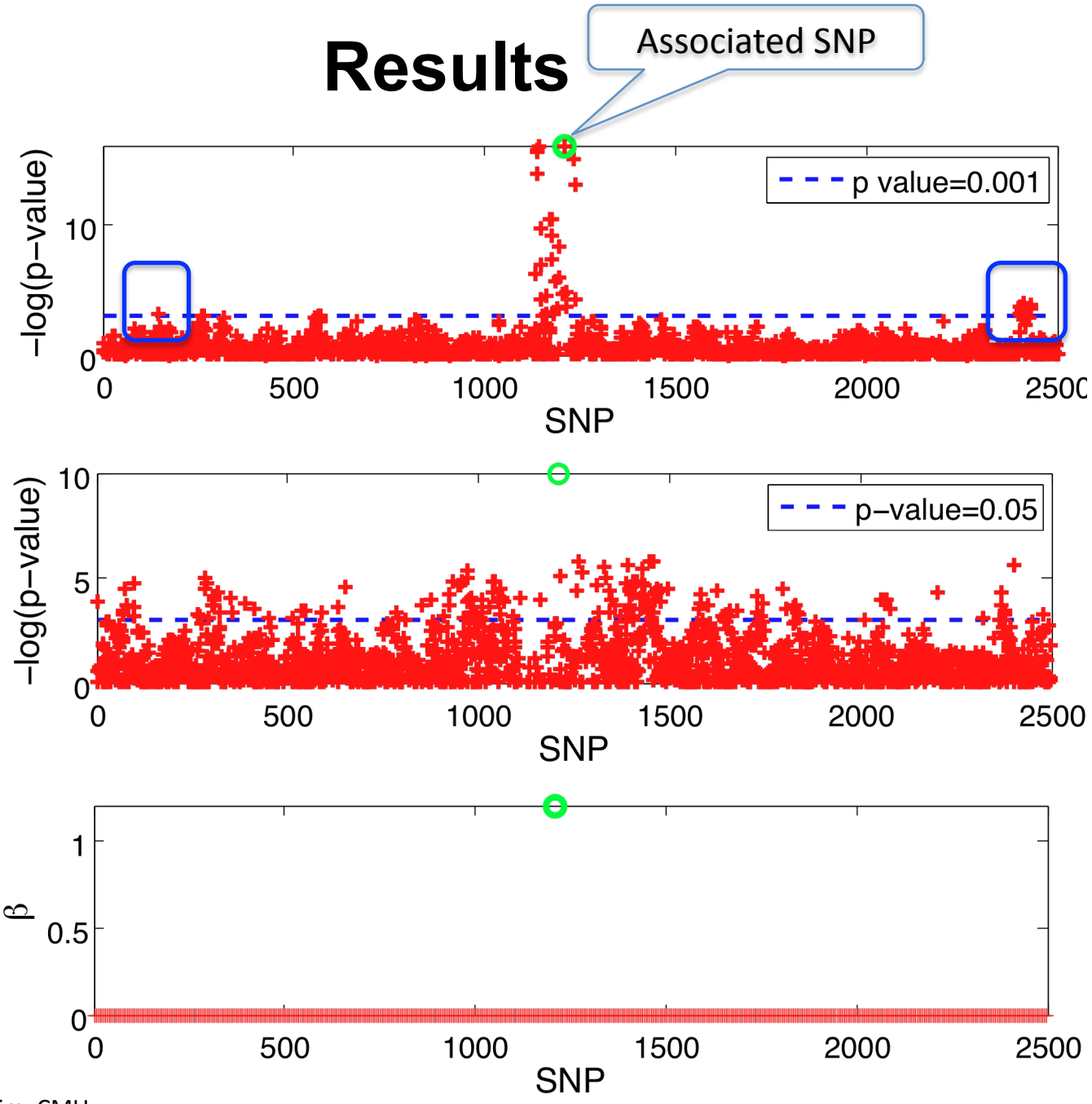


Results

Eigenstrat

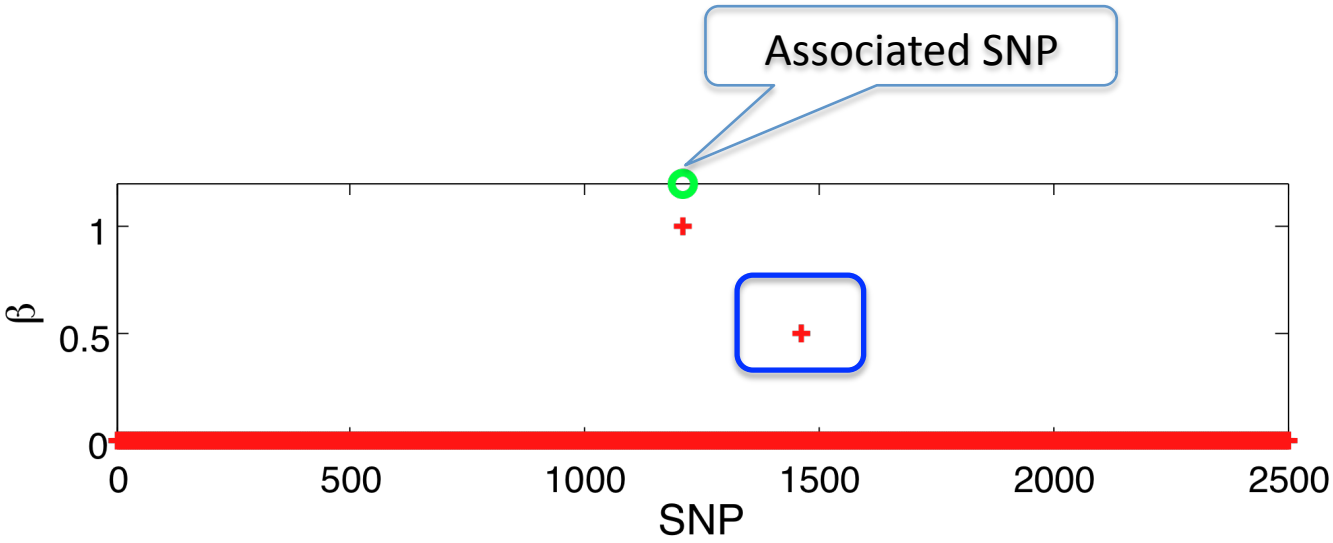
Genomic Control

Lasso

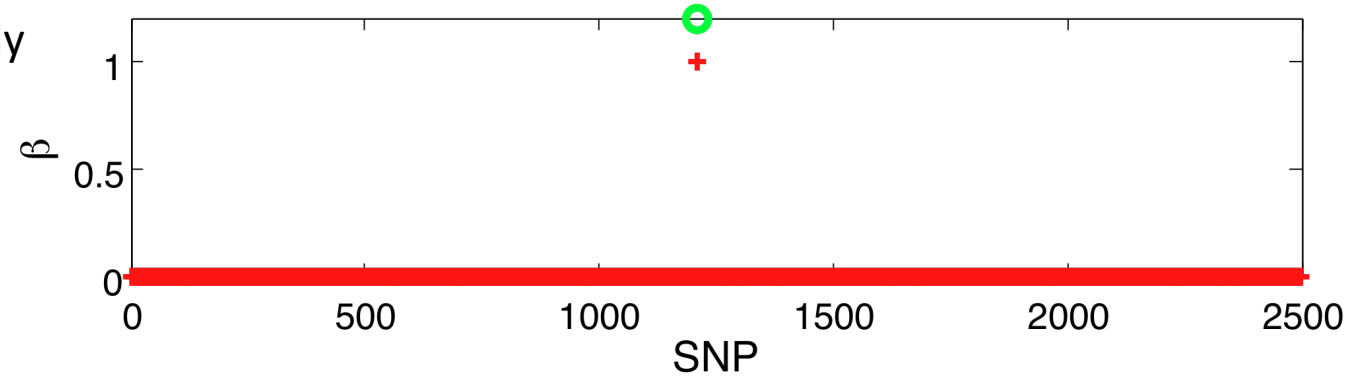


Results

Lasso for structured association



MPGL identifies only the correct SNP

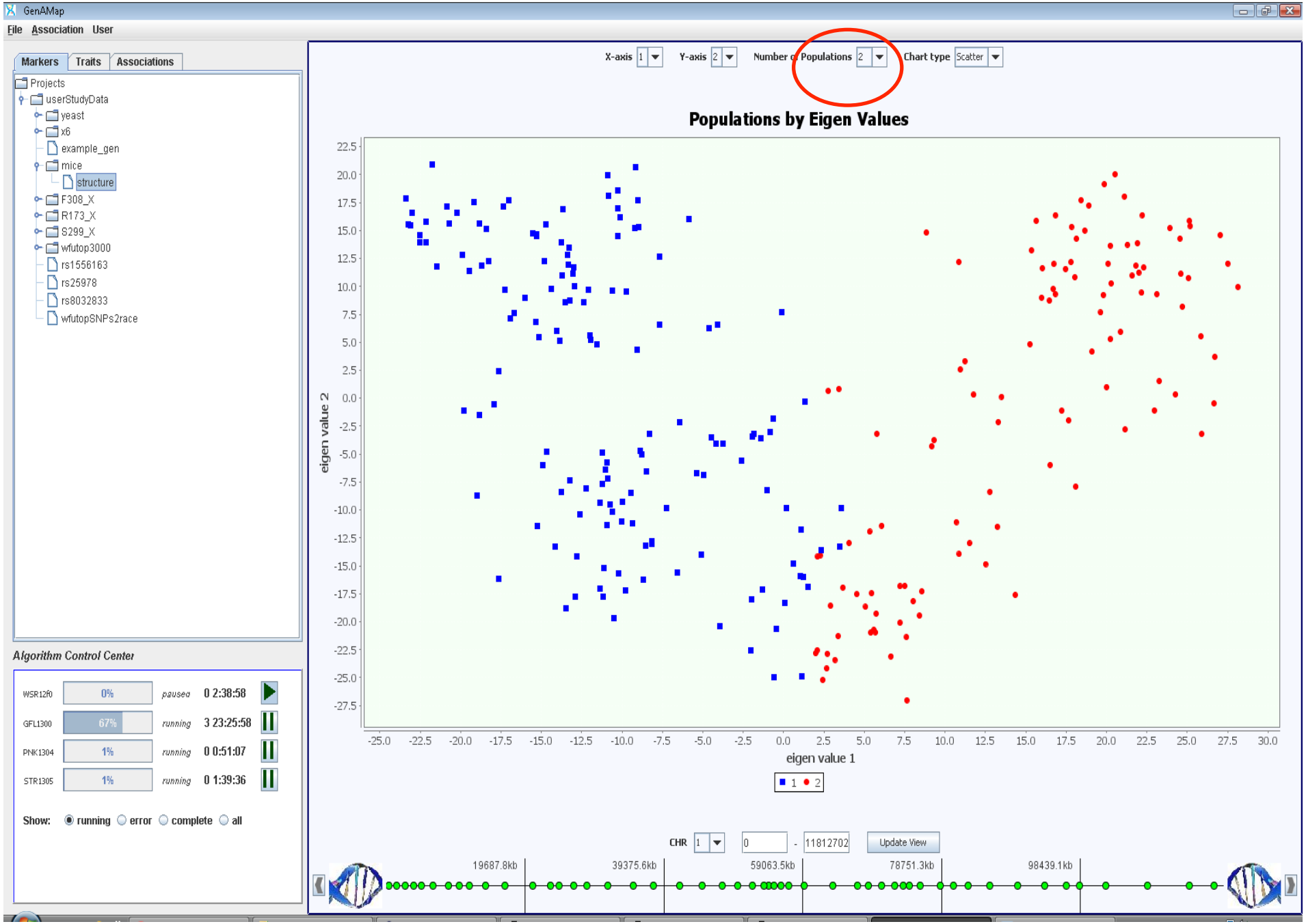


Association Analysis of Mouse Data: Considering Population Structure

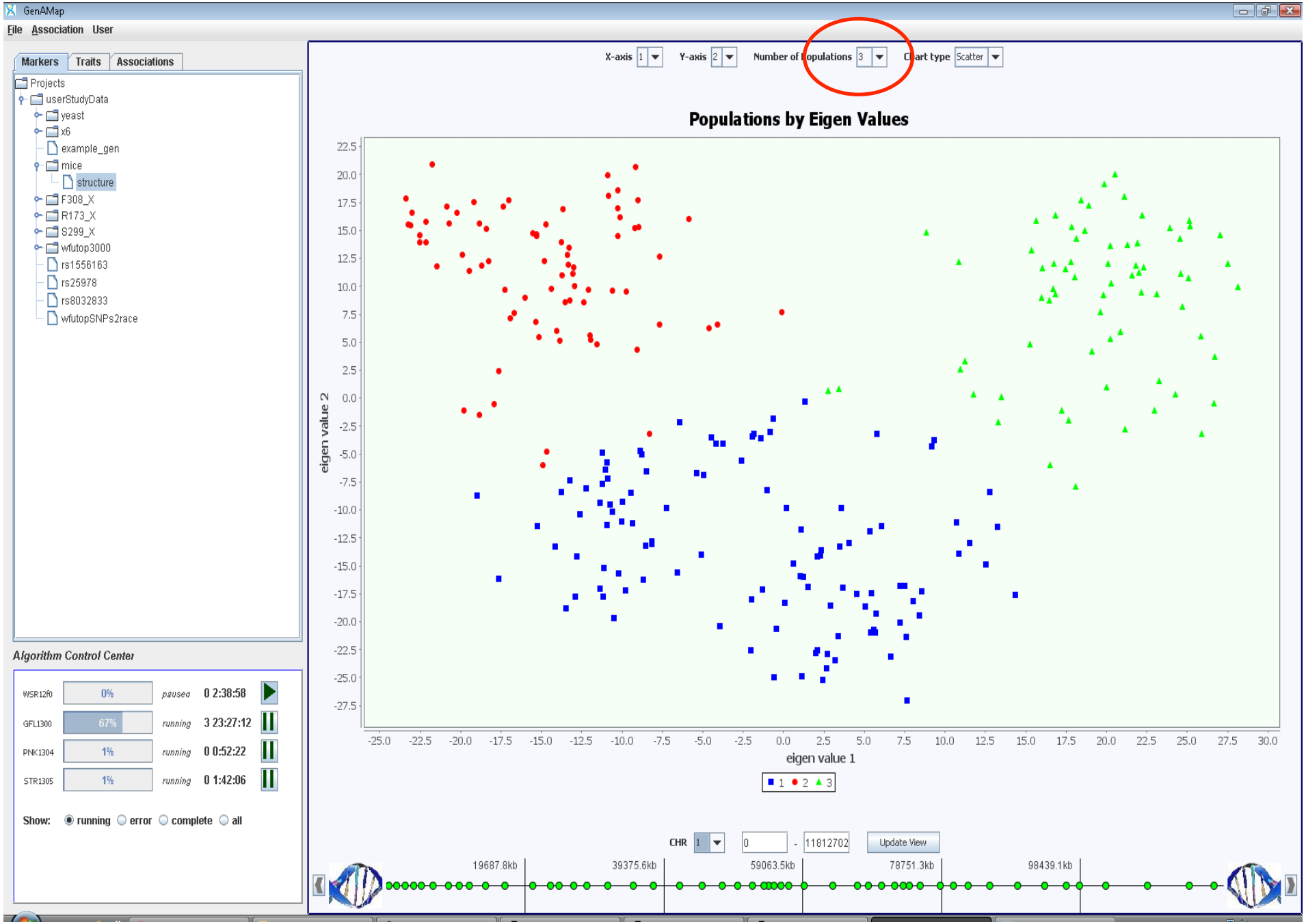
- NIH heterogeneous stock of mice (Johannesson et al., Genome Research 2009)
  - 259 mice descended from 7 inbred strains (A/J, AKR/J, BALBc/J, CBA/J, C3H/HeJ, C57BL/6J, DBA/2J and LP/J)
  - 176 phenotype measurements
  - 12,545 SNPs

- Specifically look at 7 asthma-related traits
  - Respiratory rate, tidal volume, minute volume, expiratory time, inspiratory time, enhanced pause

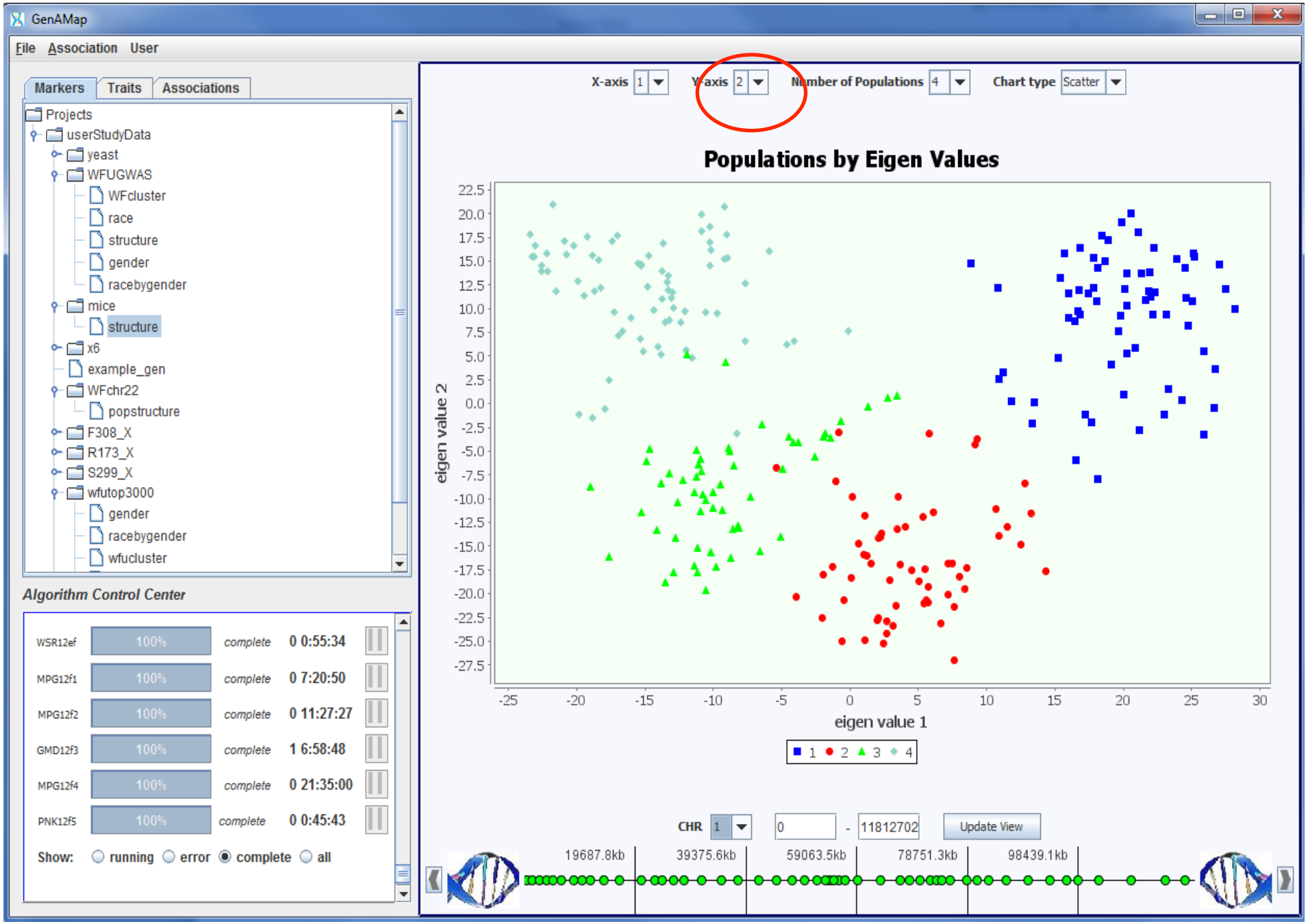
Mouse results from structure – 2 populations



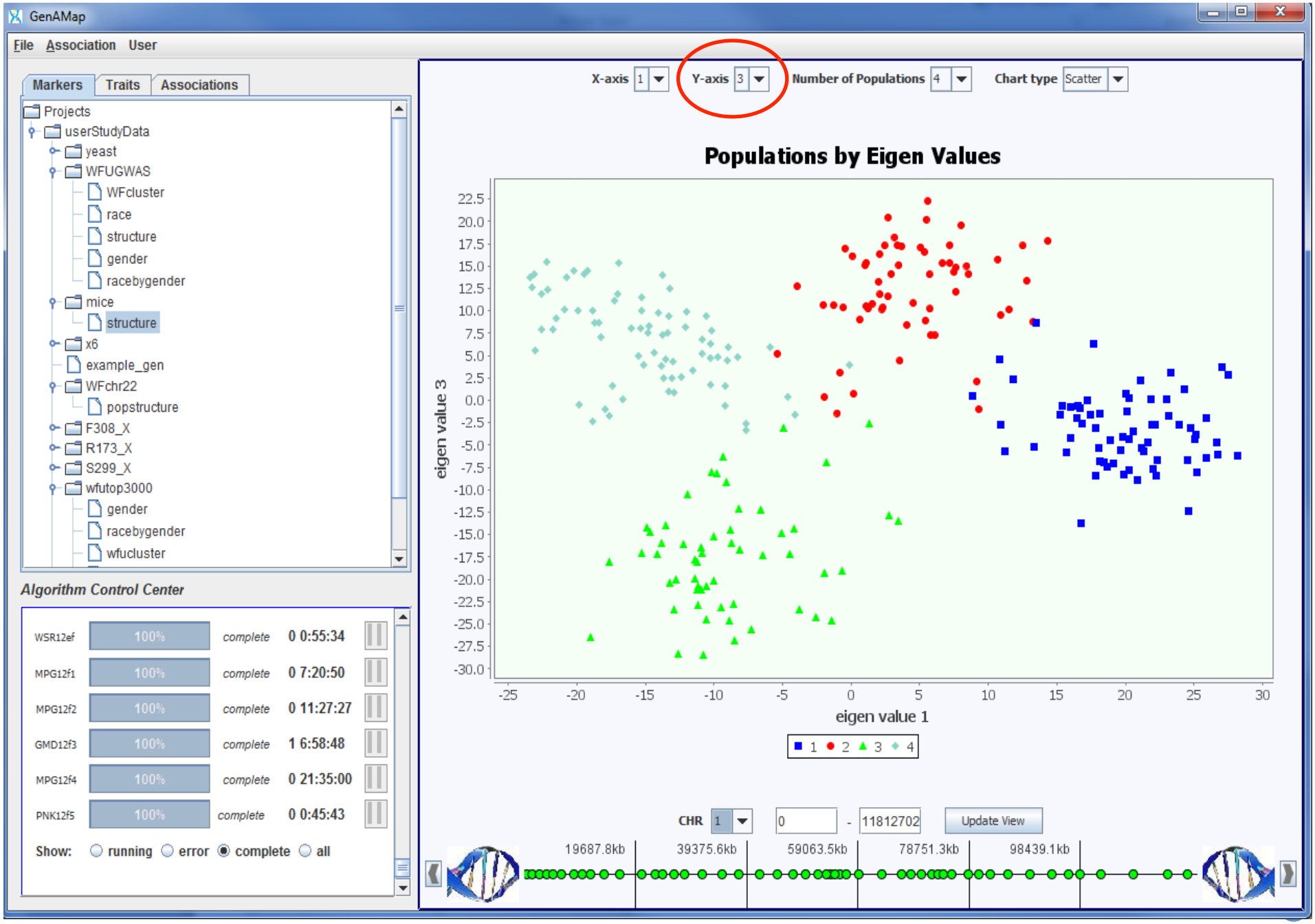
Mouse results from structure – 3 populations



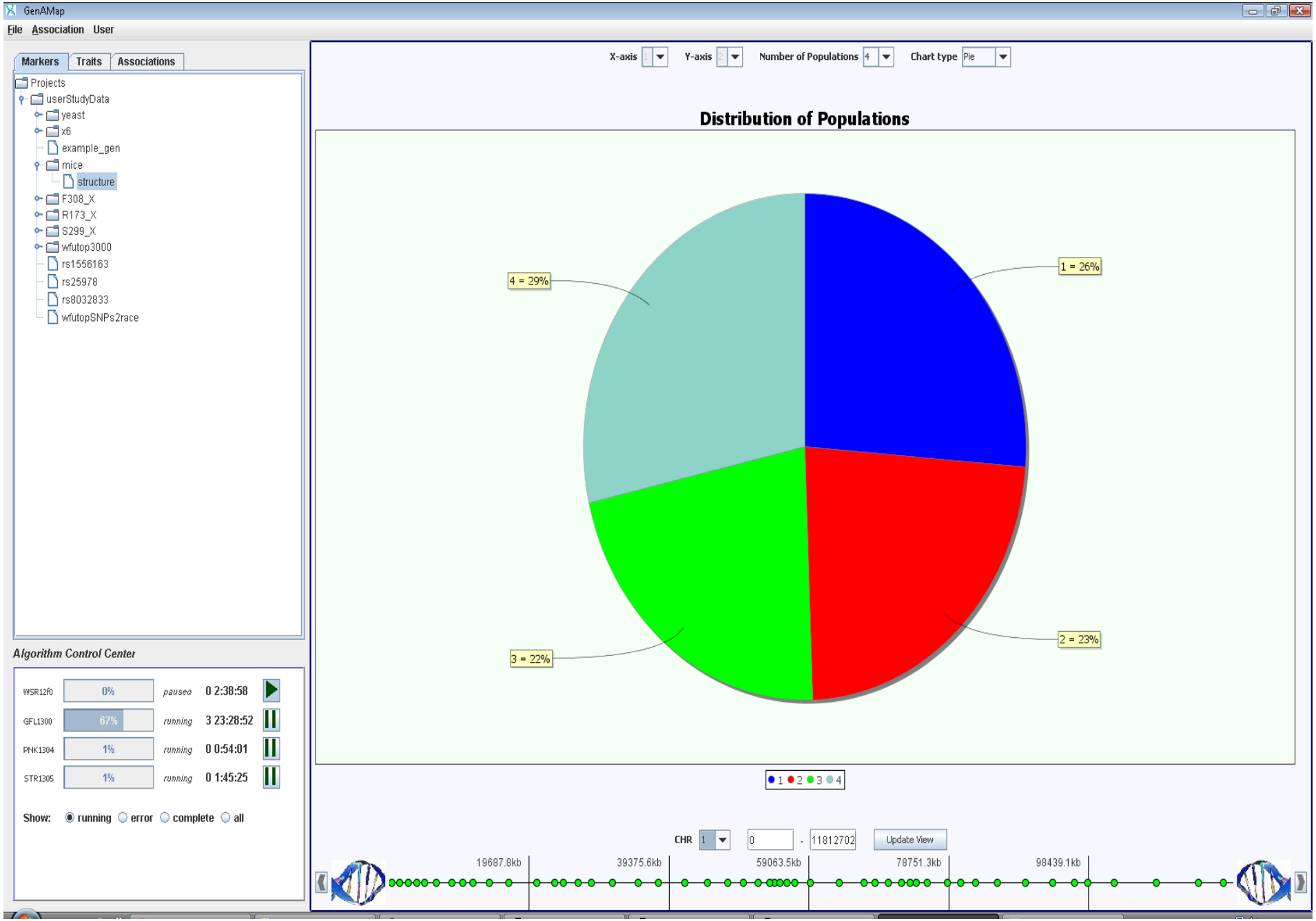
Mouse results from structure – 4 populations



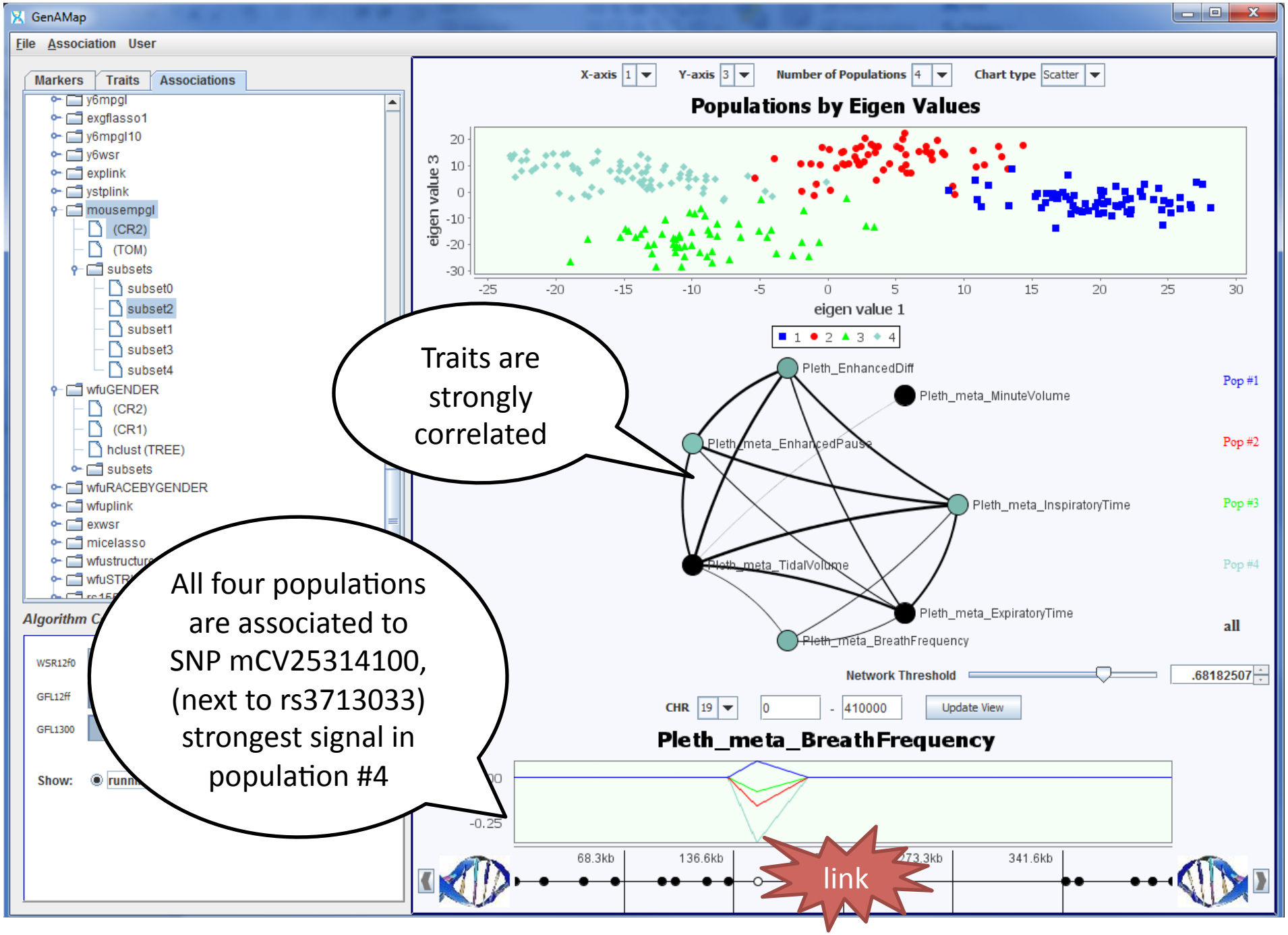
Mouse results from structure – 4 populations



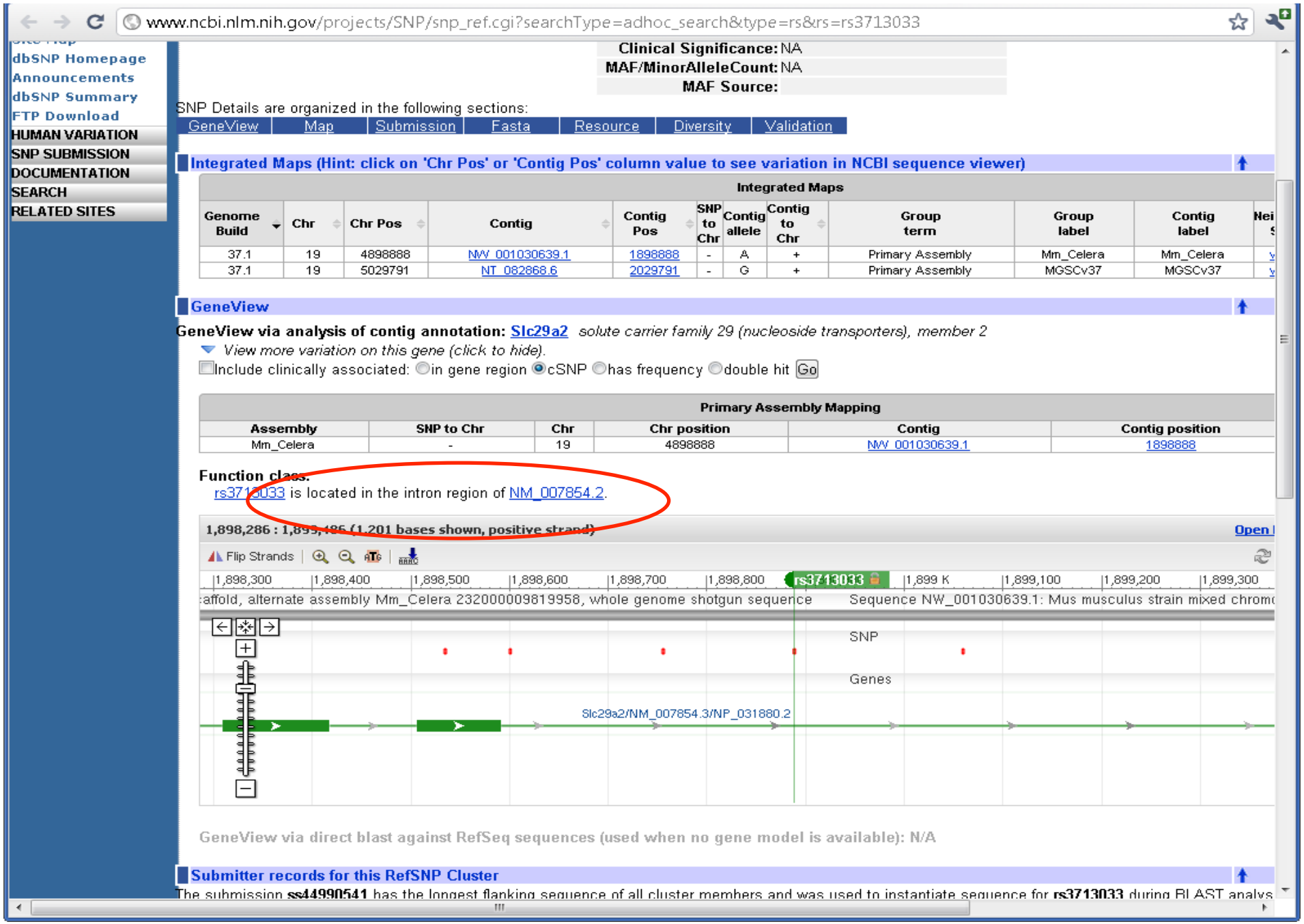
Mouse results from structure – 4 populations

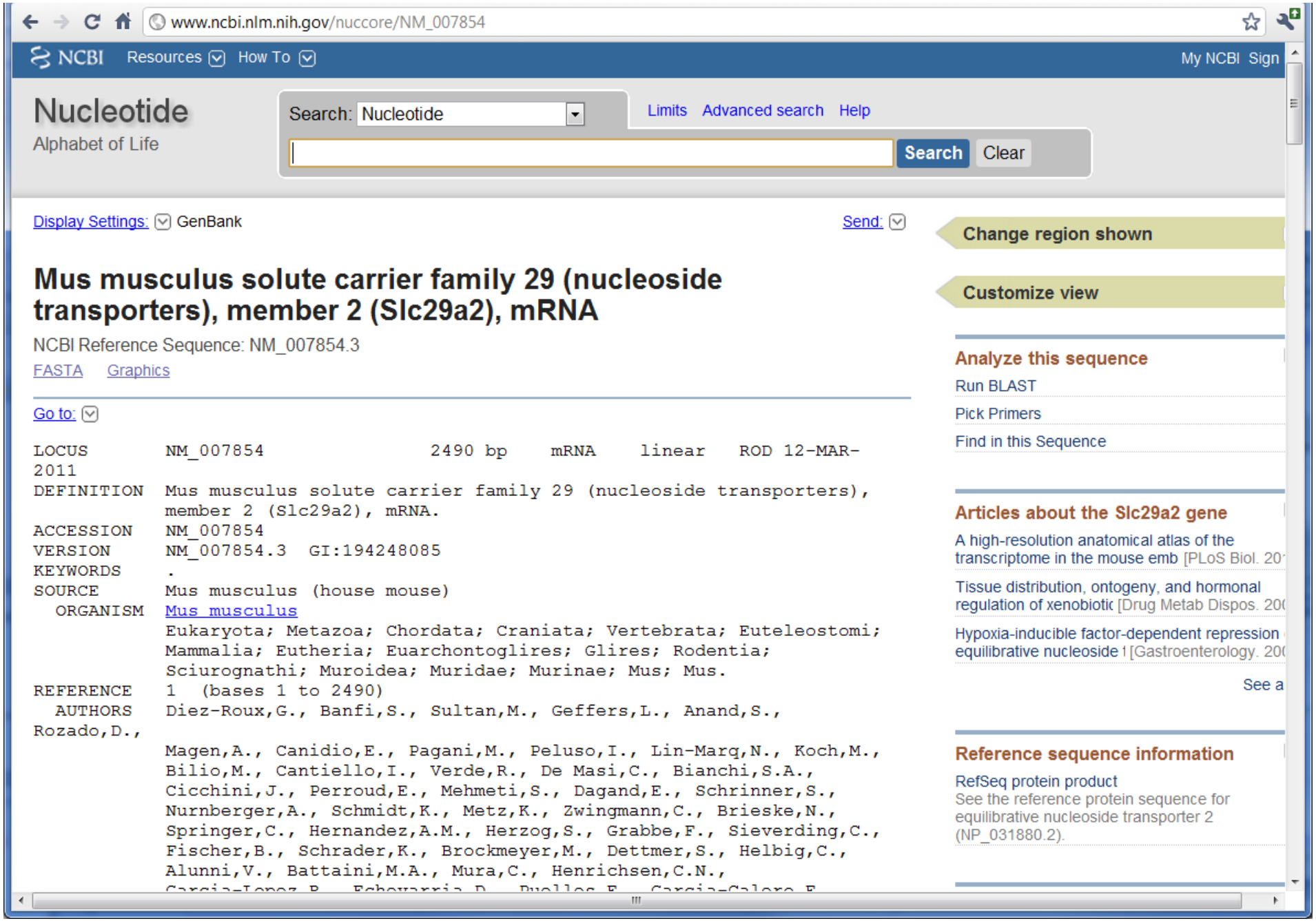


Mouse results from MPGL



dbSNP


www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?searchType=adhoc_search&type=rs&rs=rs3713033
dbSNP Homepage
Announcements
dbSNP Summary
FTP Download
HUMAN VARIATION
SNP SUBMISSION
DOCUMENTATION
SEARCH
RELATED SITES
Clinical Significance: NA
MAF/MinorAlleleCount: NA
MAF Source:
SNP Details are organized in the following sections:
GeneView | Map | Submission | Fasta | Resource | Diversity | Validation
Integrated Maps (Hint: click on 'Chr Pos' or 'Contig Pos' column value to see variation in NCBI sequence viewer)
Integrated Maps
Genome Build | Chr | Chr Pos | Contig | Contig Pos | SNP to Chr | Contig allele | Contig to Chr | Group term | Group label | Contig label
37.1 | 19 | 4898888 | NW_001030639.1 | 1898888 | - | A | + | Primary Assembly | Mm_Celera | Mm_Celera
37.1 | 19 | 5029791 | NT_082868.6 | 2029791 | - | G | + | Primary Assembly | MGSCv37 | MGSCv37
GeneView
GeneView via analysis of contig annotation: Slc29a2 solute carrier family 29 (nucleoside transporters), member 2
View more variation on this gene (click to hide).
Include clinically associated: in gene region cSNP has frequency double hit Go
Primary Assembly Mapping
Assembly | SNP to Chr | Chr | Chr position | Contig | Contig position
Mm_Celera | - | 19 | 4898888 | NW_001030639.1 | 1898888
Function class:
rs3713033 is located in the intron region of NM_007854.2.
1,898,286 : 1,899,486 (1,201 bases shown, positive strand)
Open
Flip Strands
1,898,300 | 1,898,400 | 1,898,500 | 1,898,600 | 1,898,700 | 1,898,800 | rs3713033 | 1,899 K | 1,899,100 | 1,899,200 | 1,899,300
affold, alternate assembly Mm_Celera 232000009819958, whole genome shotgun sequence
Sequence NW_001030639.1: Mus musculus strain mixed chromo
SNP
Genes
Slc29a2/NM_007854.3/NP_031880.2
GeneView via direct blast against RefSeq sequences (used when no gene model is available): N/A
Submitter records for this RefSNP Cluster
The submission ss44990541 has the longest flanking sequence of all cluster members and was used to instantiate sequence for rs3713033 during BLAST analys


www.ncbi.nlm.nih.gov/nuccore/NM_007854
NCBI
Resources
How To
My NCBI
Sign
Nucleotide
Alphabet of Life
Search: Nucleotide
Limits
Advanced search
Help
Search
Clear
Display Settings: GenBank
Send:
Change region shown
Customize view
Mus musculus solute carrier family 29 (nucleoside transporters), member 2 (Slc29a2), mRNA
NCBI Reference Sequence: NM_007854.3
FASTA
Graphics
Go to:
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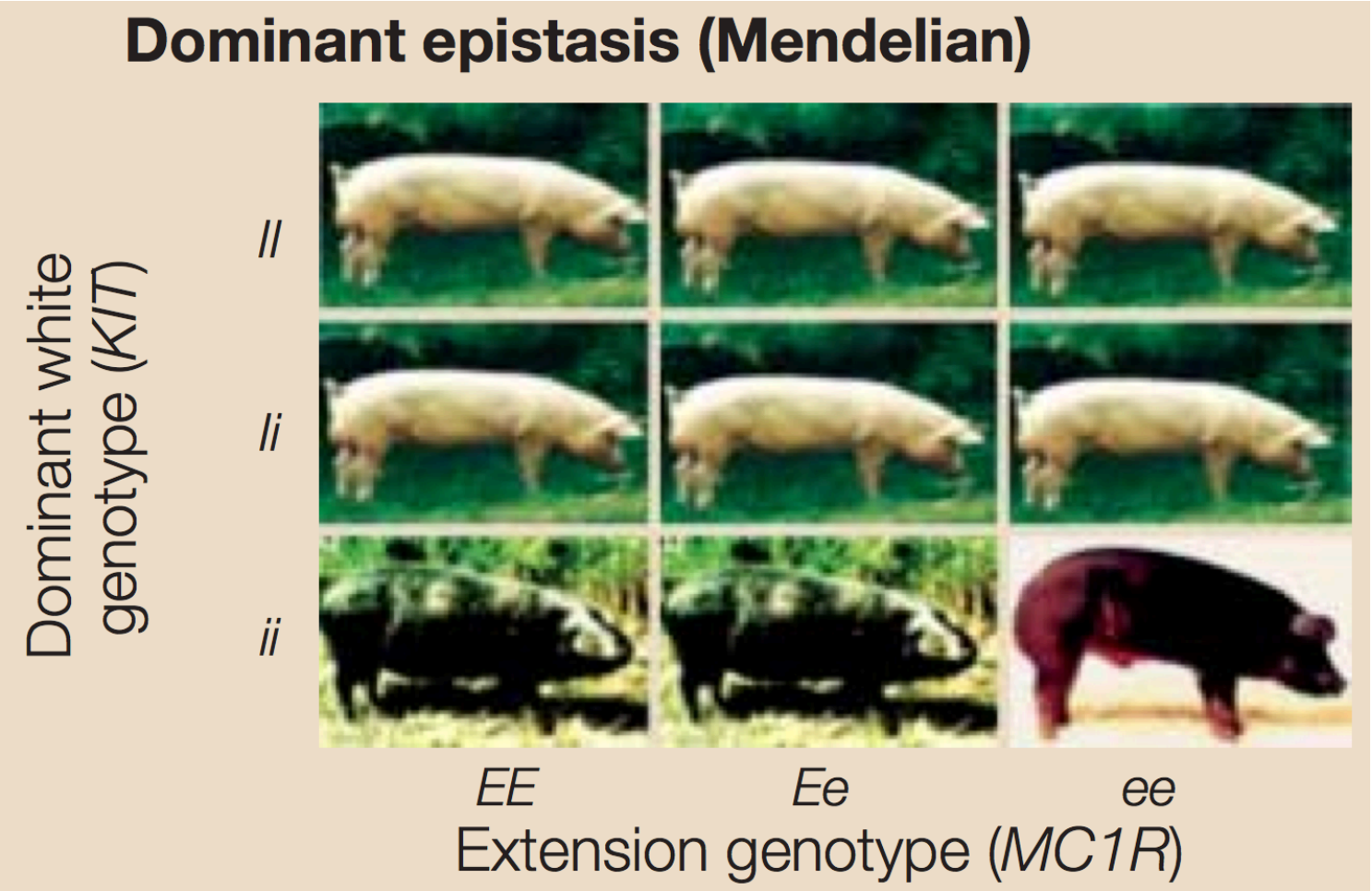
DEFINITION Mus musculus solute carrier family 29 (nucleoside transporters), member 2 (Slc29a2), mRNA.
ACCESSION NM_007854
VERSION NM_007854.3 GI:194248085
KEYWORDS .
SOURCE Mus musculus (house mouse)
ORGANISM Mus musculus
Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Glires; Rodentia; Sciurognathi; Muroidea; Muridae; Murinae; Mus; Mus.
REFERENCE 1 (bases 1 to 2490)
AUTHORS Diez-Roux,G., Banfi,S., Sultan,M., Geffers,L., Anand,S., Rozado,D.,
Magen,A., Canidio,E., Pagani,M., Peluso,I., Lin-Marq,N., Koch,M., Bilio,M., Cantiello,I., Verde,R., De Masi,C., Bianchi,S.A., Cicchini,J., Perroud,E., Mehmeti,S., Dagand,E., Schrinner,S., Nurnberger,A., Schmidt,K., Metz,K., Zwingmann,C., Brieske,N., Springer,C., Hernandez,A.M., Herzog,S., Grabbe,F., Sieverding,C., Fischer,B., Schrader,K., Brockmeyer,M., Dettmer,S., Helbig,C., Alunni,V., Battaini,M.A., Mura,C., Henrichsen,C.N.,
Analyze this sequence
Run BLAST
Pick Primers
Find in this Sequence
Articles about the Slc29a2 gene
A high-resolution anatomical atlas of the transcriptome in the mouse emb [PLoS Biol. 20
Tissue distribution, ontogeny, and hormonal regulation of xenobiotic [Drug Metab Dispos. 20
Hypoxia-inducible factor-dependent repression equilibrative nucleoside [Gastroenterology. 20
See a
Reference sequence information
RefSeq protein product
See the reference protein sequence for equilibrative nucleoside transporter 2 (NP_031880.2).

Epistasis

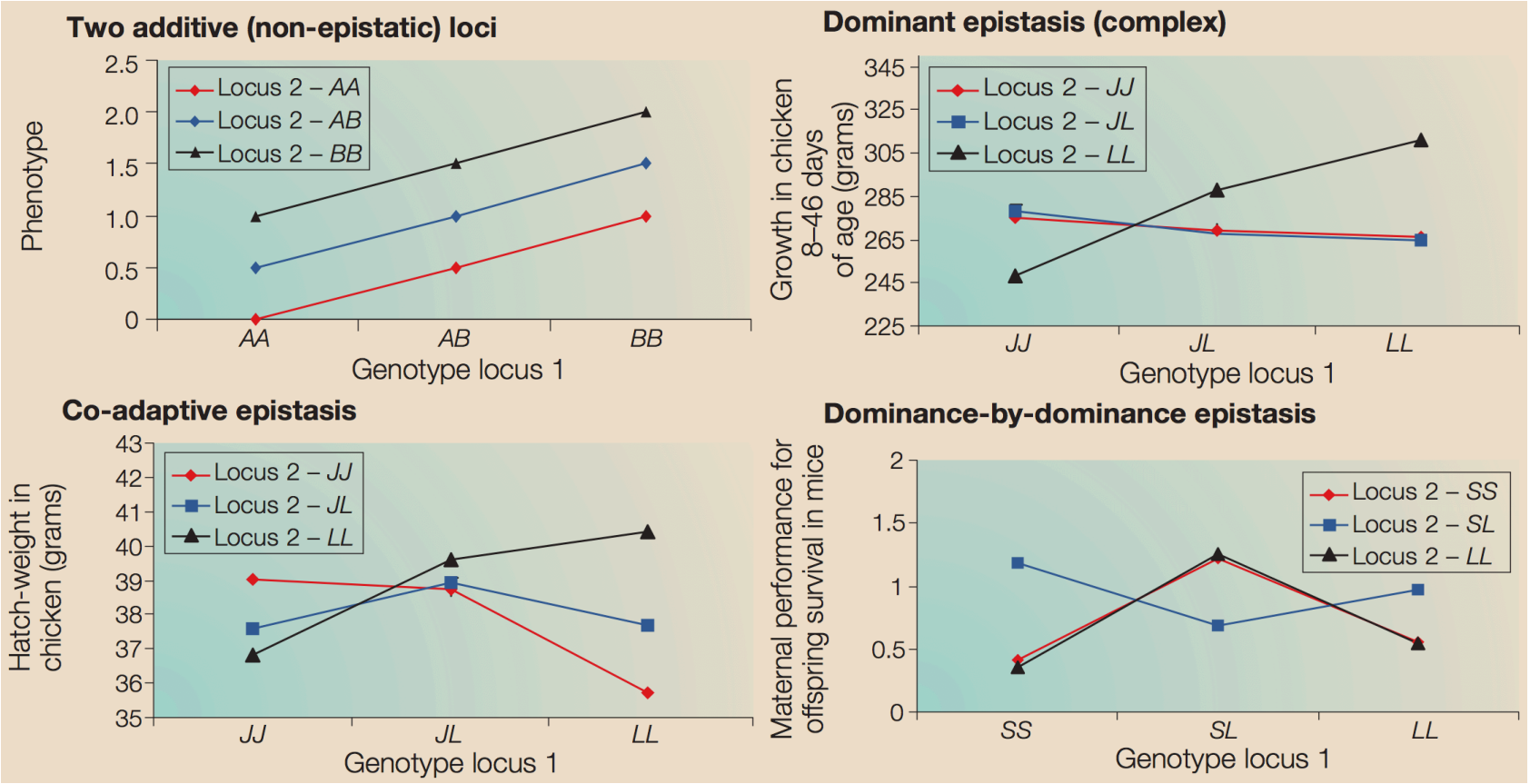
- Definition: The effect of one locus depends on the genotype of another locus

Epistasis for Mendelian Traits



Carlborg & Haley, Nature Reviews Genetics 2004

Epistasis for Complex Traits



Carlborg & Haley, Nature Reviews Genetics 2004

Epistasis

- Epistatic effects of SNPs can often be detected only if the interacting SNPs are considered jointly
  - The number of candidate SNP interactions is very large
    - For J SNPs, JxJ SNP pairs need to be considered for epistasis
    - In general for J SNPs and K-way interactions, there are $O(J^K)$ candidate interactions
    - Computationally expensive to consider all possible groups of interacting SNPs
    - For a reliable detection of K-way interactions, a large sample size is required
  - Multiple testing problem

Two-stage Lasso for Detecting Epistasis

(Wu et al. Genetic Epidemiology 2010)

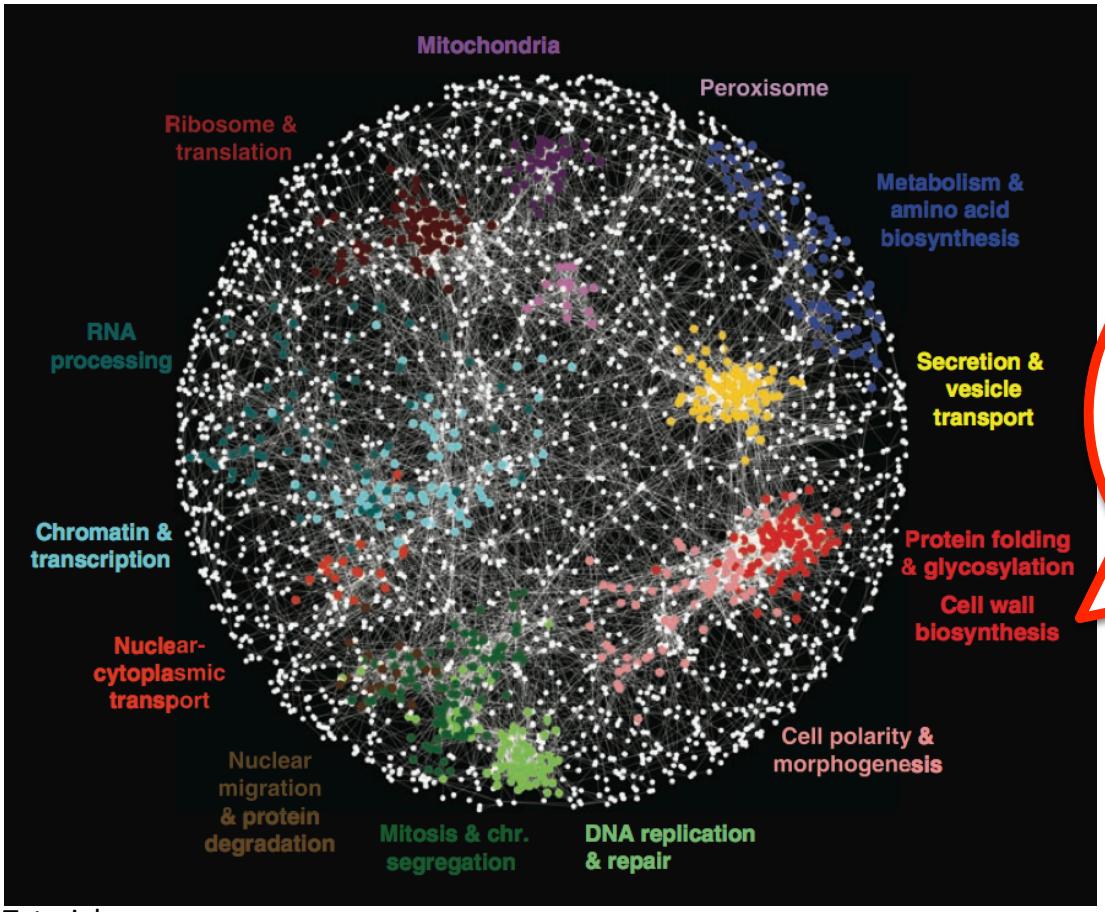
- Two-stage lasso
  - Stage 1: Apply lasso with no consideration of epistasis to detect SNPs with significant individual effects
  - Stage 2: Apply lasso with pairs of only those SNPs selected in Stage 1

- Reduces the computational burden

- Limitation: SNPs with epistatic effects often do not have detectable individual (marginal) effects, and many of these association signals will be missed.

Epistasis: Exploiting Prior Knowledge

- Synthetic genetic interaction network from double-knockout experiments provide strong evidence of gene-gene interaction

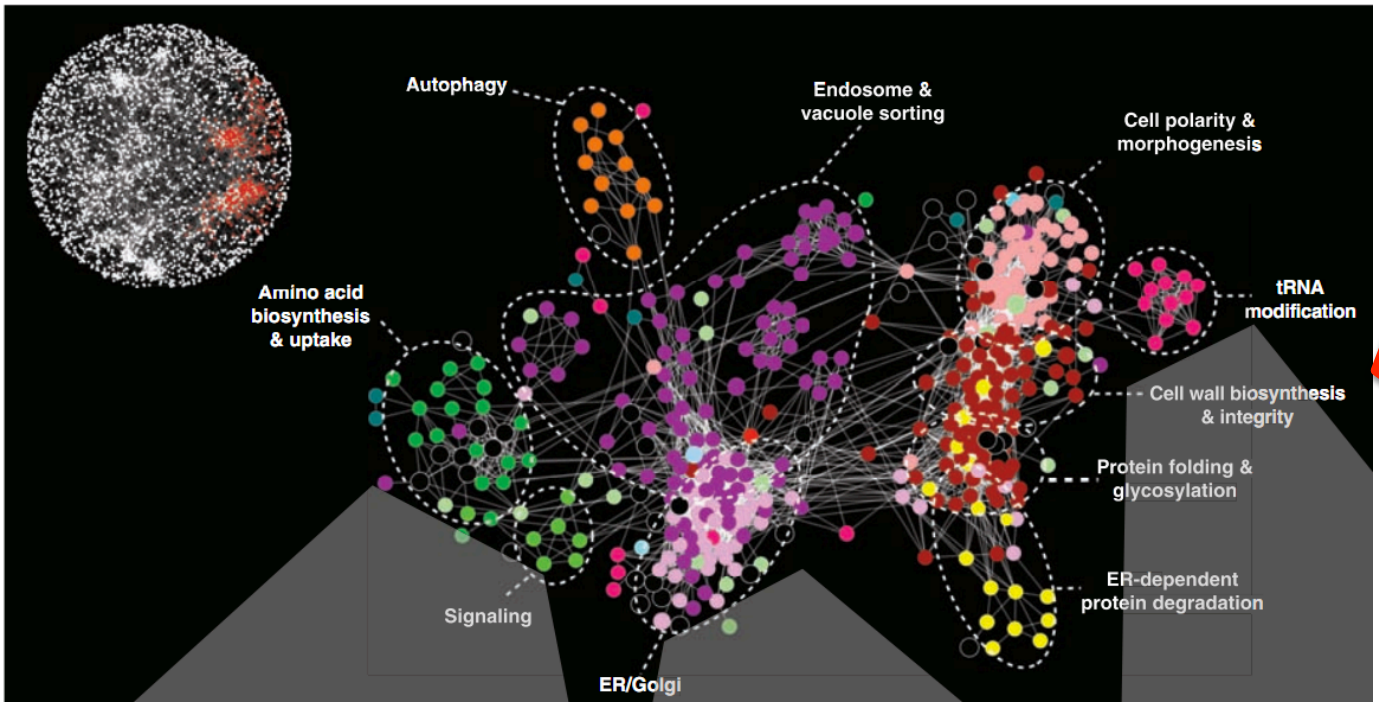


Idea I: Use the synthetic genetic interaction network to generate candidate SNP pairs with epistatic interaction

Costanzo et al., Science 2010

Epistasis: Exploiting Prior Knowledge

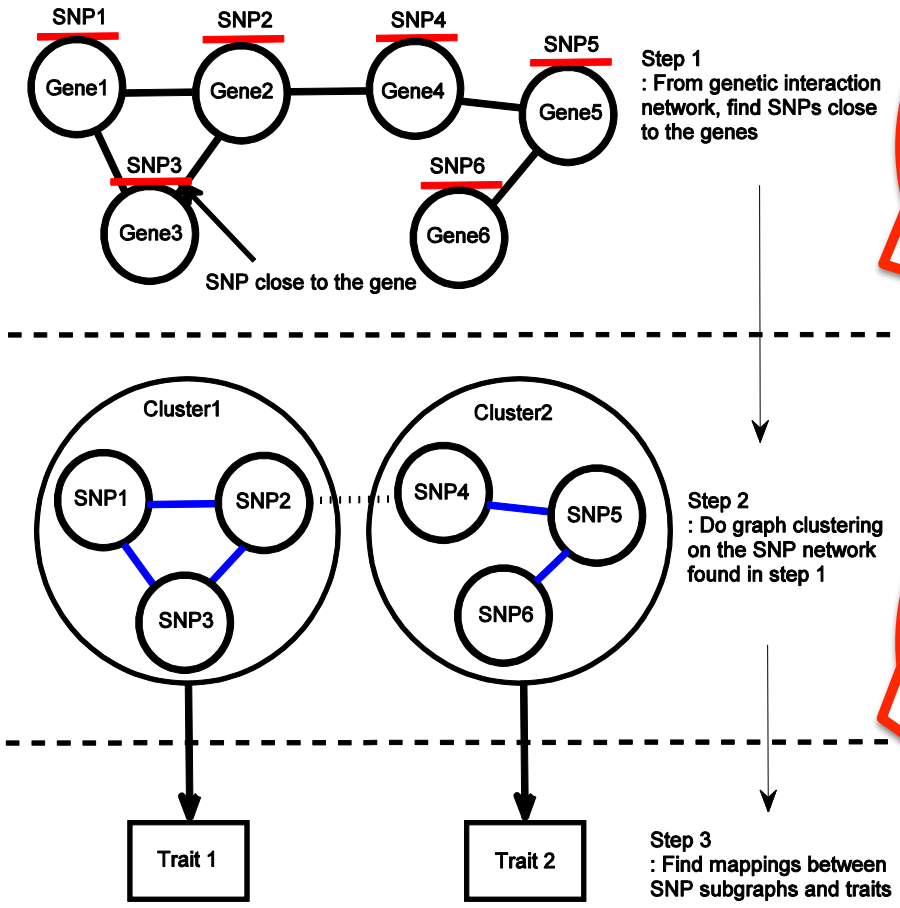
- Synthetic genetic interaction network from double-knockout experiments provide strong evidence of gene-gene interaction



Idea II: Combine information across related candidate SNP pairs to increase the power of detecting associations

Costanzo et al., Science 2010

Epistasis: Exploiting Prior Knowledge



Idea I: Use the synthetic genetic interaction network to generate candidate SNP pairs with epistatic interaction

Idea II: Combine information across related candidate SNP pairs to increase the power of detecting associations

Epistasis: Structured Input/Ouput (IO)-Lasso

$$\beta_{io-lasso} = \arg\min_{\beta} \sum_{k=1}^{K}\sum_{i=1}^{N}\left(Y_i^k - \sum_{j=1}^{p}\beta_j^k X_{ij} - \sum_{(r,s)\in U}\beta_{rs}^k Z_{i,rs}\right) + \lambda_1\sum_{j=1}^{p}\sum_{k=1}^{K}\left|\beta_j^k\right| + \lambda_2\sum_{k}\sum_{m}\sqrt{\sum_{(r,s)\in S_m}\beta_{rs}^{k\,2}} + \lambda_3\sum_{j}\sqrt{\sum_{k}\beta_j^{k\,2}} + \lambda_4\sum_{k}\sum_{(r.s)\in U}\left|\beta_{rs}^k\right|$$

Idea I: Use the synthetic genetic interaction network to generate candidate SNP pairs with epistatic interaction

Idea II: Combine information across related candidate SNP pairs to increase the power of detecting associations

U : genetic interaction networks

S_m : m^{th} cluster in SNP network

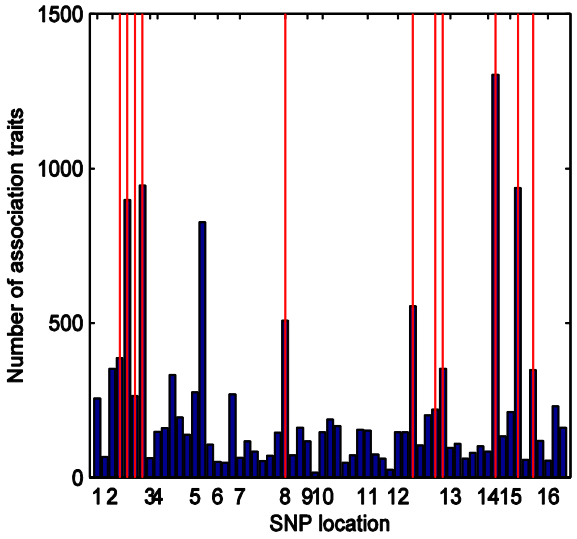
Lee, Kim, & Xing, Submitted 2011

Results on Yeast eQTL Dataset

- Yeast eQTL dataset (Brem & Kruglyak, PNAS 2005)
  - Genotypes: 114 yeast strains from the cross of laboratory strains and wild strains, 1260 non-redundant SNPs
  - Phenotypes: gene-expression levels for 5,637 genes
  - 2,219 clusters of the traits

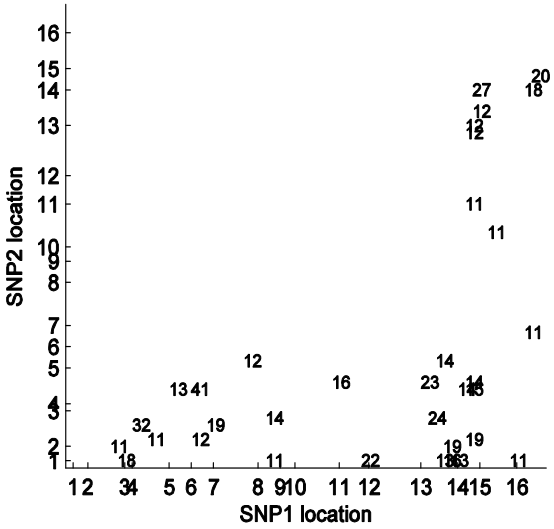
- Yeast genetic interactions (Costanzo et al., Science 2010)
  - Yeast contains ~6,000 genes
  - Synthetic genetic interactions for 5.4 million gene-gene pairs
  - We extracted 73,720 significant SNP pairs based on the results from synthetic lethal interaction experiment (0.09% of all SNP pairs)
    - We further selected 9,388 representative SNP pairs from these pairs of SNPs so that the correlation among the selected SNPs is low

eQTL hotspots of individual SNP effects



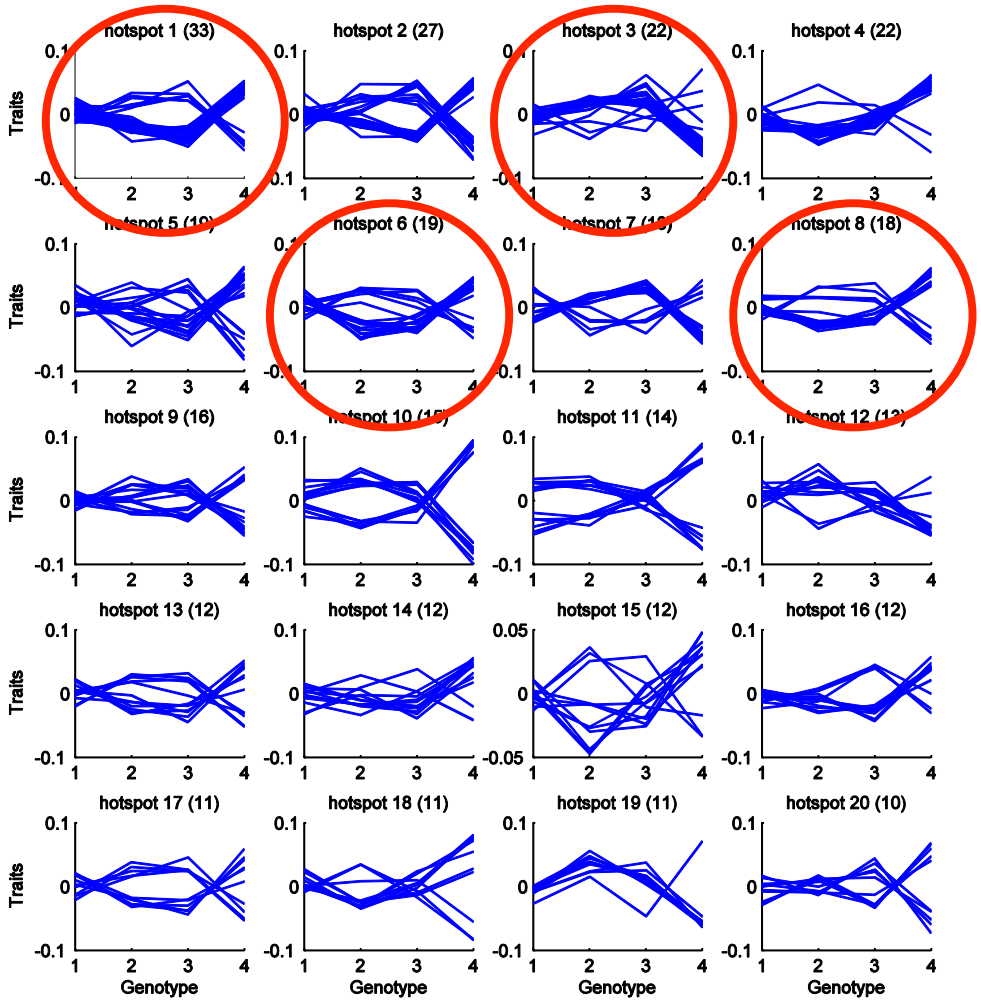
Red lines:
Previously reported eQTL hotspots
[Yvert et al. 2003]

eQTL hotspots of epistatically interacting SNPs



Lee, Kim, & Xing, Submitted 2011

Top 20 Epistatic Hotspots



Lee, Kim, & Xing, Submitted 2011

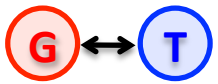
Overview

- Genome structure in association analysis
  - Linkage disequilibrium
  - Population structure
  - Epistasis

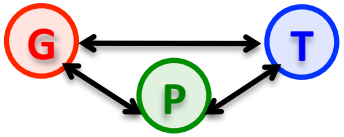
- Transcriptome structure in association analysis
  - Pleiotropy
    - Pathway-based statistical tests
    - Leveraging gene expression network
    - Leveraging gene expression tree

- Phenome structure in association analysis
  - Pleiotropy
  - Dynamic trait

- Two-way structured association



- Three-way structured association



- Visualization software

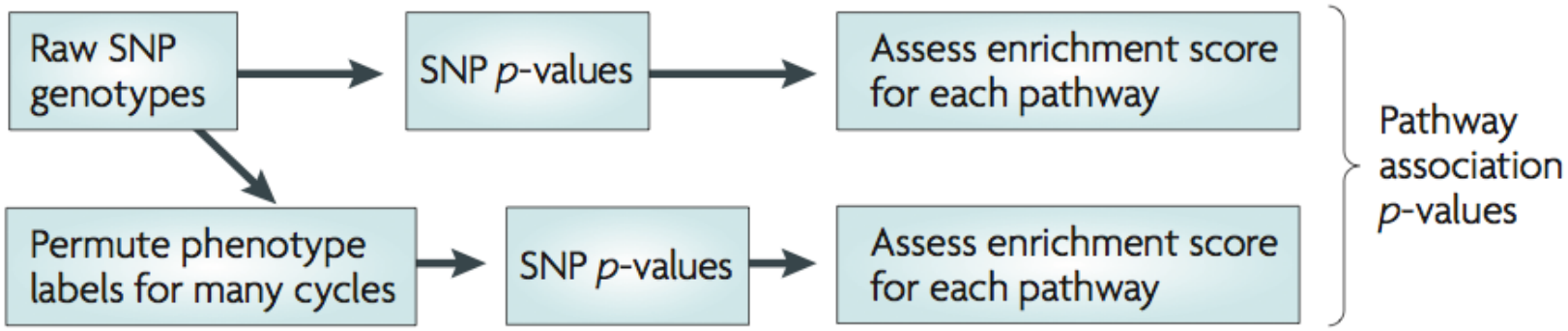
Association to the Transcriptome

- Expression quantitative trait locus (eQTL) analysis
  - Gene expression traits as phenotypes in association analysis
  - Typically involves more than 5000 genes
  - Univariate regression analysis and lasso could be applied to each gene expression trait

- Pleiotropic effects of SNPs
  - Definition: A genetic variation influences multiple phenotypes jointly
  - Instead of assessing the effect of genotype on a single phenotype, we consider multiple related phenotypes (e.g., genes in the same pathway) to detect pleiotropic effects

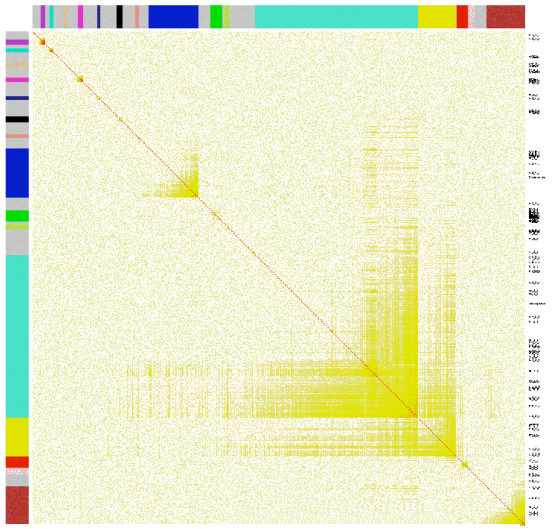
Computational Methods for Detecting Pleiotropy

- **Method 1**: Aggregating the results from a set of single-gene (trait) analyses



  - Limitation: It does not directly search for pleiotropic effects, but looks for pleiotropy as a post-processing step after single-trait analyses

Yeast eQTL Analysis: Association to a Gene Module



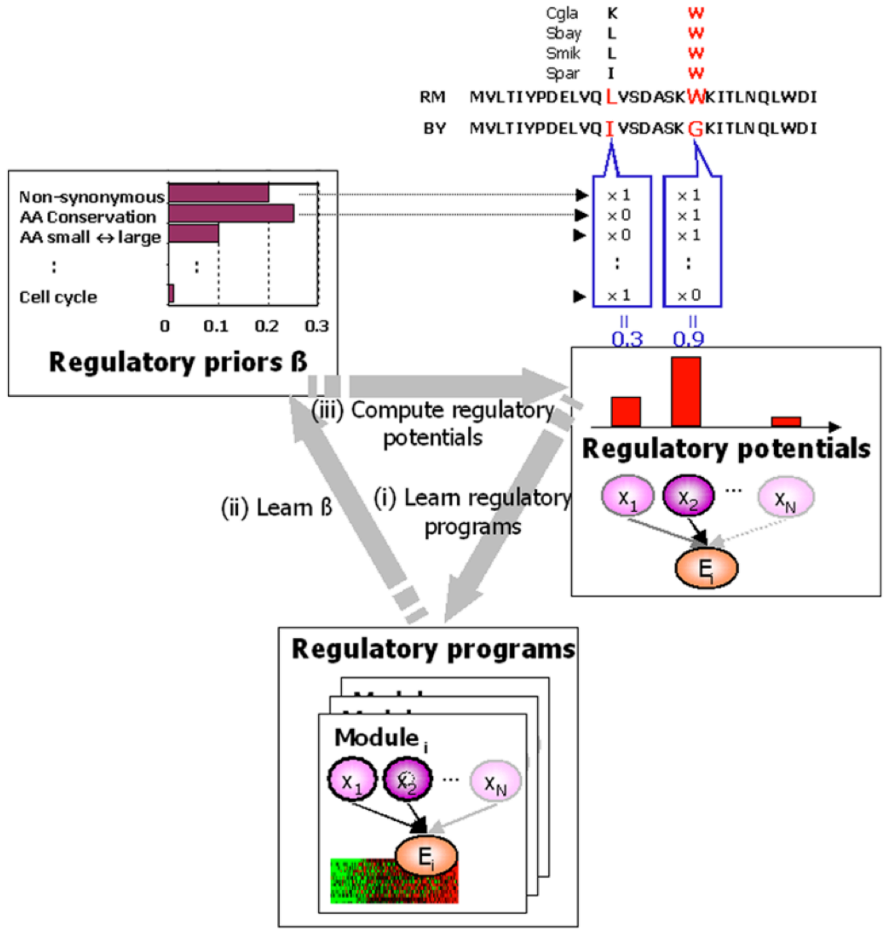
- Yeast eQTL dataset
  - Genotypes from 112 segregants from a yeast cross between BY and RM strains
  - Microarray gene-expression data

Module color[a]	Module size	GO category type[b]	GO category	GO category size (overlap)	GO enrichment nominal *P* value[c]	Chr.	Within-chr. genome coordinate	eQTL hot spot size (overlap)	eQTL enrichment nominal *P* value[c]
Turquoise	1,208	BP	Cytoplasm organization and biogenesis	169 (153)	7.47×10^{-58}	2	550,000	186 (144)	2.87×10^{-39}
Blue	369	BP	Organic acid metabolism	235 (94)	4.44×10^{-34}	3	70,000	50 (46)	1.61×10^{-42}
Brown	290	BP	Protein biosynthesis	292 (98)	2.63×10^{-41}	14	450,000	206 (107)	2.92×10^{-69}
Yellow	282	BP	Generation of precursor metabolites and energy	258 (46)	2.09×10^{-8}	15	170,000	182 (134)	6.06×10^{-122}
Green	84	MF	Transferase activity	428 (20)	0.0012	2	570,000	25 (5)	0.00021
Red	83	BP	Generation of precursor metabolites and energy	168 (44)	6.54×10^{-39}	15	570,000	25 (21)	2.28×10^{-32}
Black	44	BP	Lipid metabolism	149 (20)	3.31×10^{-17}	12	650,000	52 (34)	2.37×10^{-60}
Pink	43	BP	Intracellular transport	275 (14)	1.41×10^{-6}	14	450,000	206 (19)	1.92×10^{-13}
Magenta	39	MF	RNA binding	140 (18)	3.21×10^{-16}	8	90,000	31 (4)	0.00028
Purple	37	BP	Chromosome organization and biogenesis (sensu Eukaryota)	200 (7)	0.0033	12	1,050,000	38 (31)	9.07×10^{-64}
Green-yellow	31	CC	Endoplasmic reticulum	213 (15)	2.39×10^{-11}	12	670,000	68 (5)	0.00022
Tan	29	BP	Response to chemical stimulus	153 (3)	0.12	5	110,000	24 (13)	4.84×10^{-23}
Cyan	27	BP	Response to chemical stimulus	153 (9)	7.55×10^{-7}	3	210,000	33 (23)	5.26×10^{-56}
Salmon	27	BP	Biopolymer catabolism	140 (13)	2.71×10^{-12}	12	670,000	68 (2)	0.089
Midnight blue	23	BP	Reproduction	160 (15)	7.64×10^{-16}	8	110,000	38 (23)	4.66×10^{-50}

Zhu et al., Nature Genetics 2008

Computational Methods for Detecting Pleiotropy

- **Method 2**: *Lirnet* finds SNPs associated with average over phenotypes in each module
- Joint estimation of
  - Regulatory modules
  - SNPs associated with each regulatory module
  - Regulatory potentials for the importance weights of prior knowledge on SNPs
- Limitation: *Lirnet* uses averaged phenotypes rather than the raw phenotype values
  - Loss of information
  - What about anti-correlated phenotypes?



Lee et al., PLoS Genetics 2009

Computational Methods for Detecting Pleiotropy

- **Method 3**: Apply PCA to phenotype data and perform association analysis on the projected phenotype data

  (Weller et al., Theo. Appl. Gen. 1996, Mangin et al., Biometrics 1998)

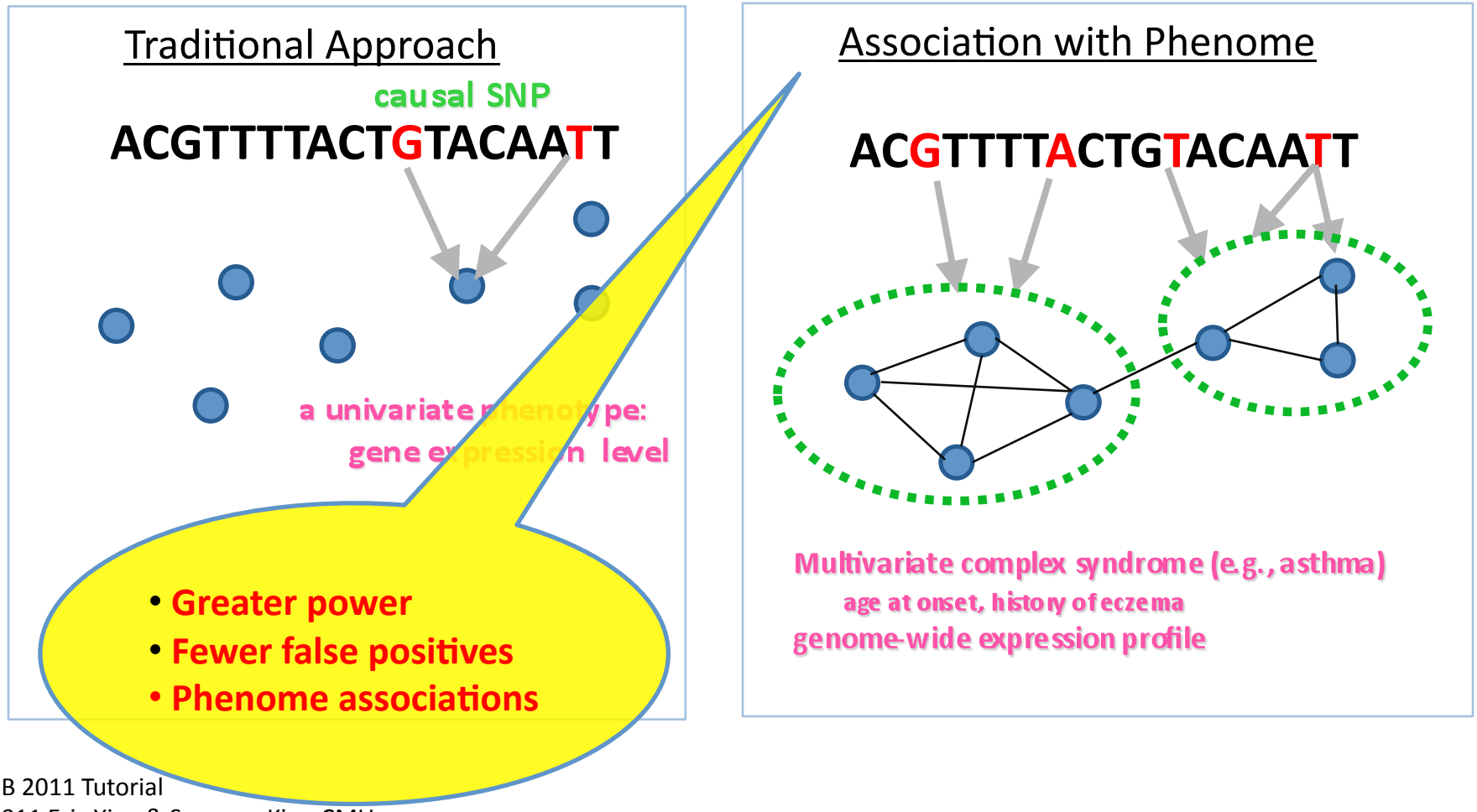
  - Limitation: It is not obvious how to interpret the projected phenotype values and their associations to genotypes

Computational Methods for Detecting Pleiotropy

- **Method 4**: Structured multi-task sparse regression that incorporate transcriptome structure as prior knowledge
  - Graph-guided fused lasso: gene-gene interaction as graph (Kim & Xing, PLoS Genetics 2009)
  - Tree-guided group lasso: gene modules as hierarchical clustering tree (Kim & Xing, ICML 2010)

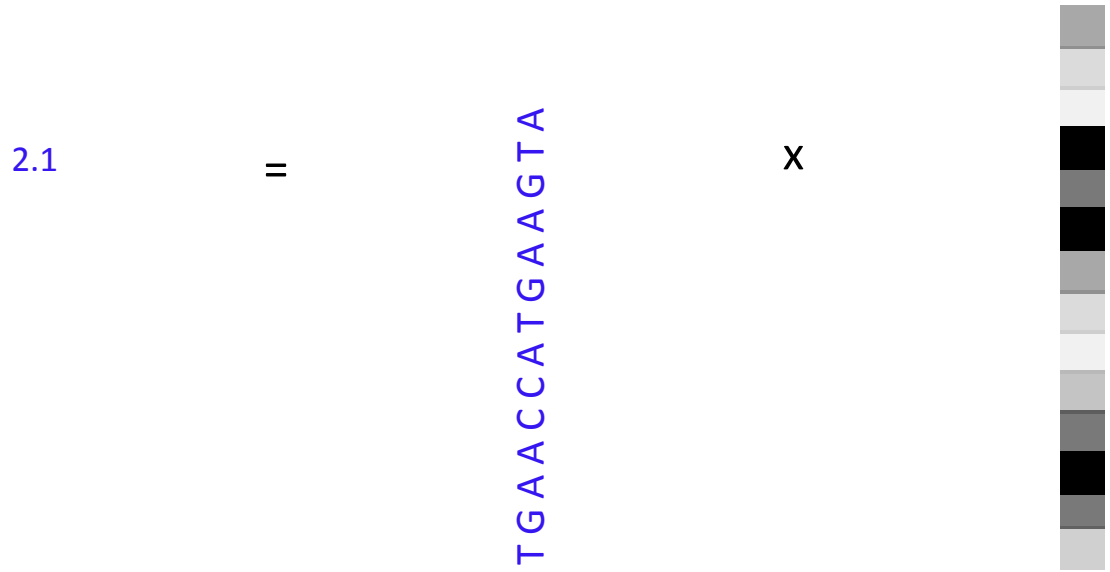
- Extending generic toolbox in statistics for association analysis
  - Convex optimization (Boyd and Vandenberghe, Cambridge University Press 2004)
    - Fast computation for complex algorithms
  - Penalized regression method for structured sparsity
    - Increase the power of detecting associations

Structured Association



Regression for Single-Trait Association Analysis

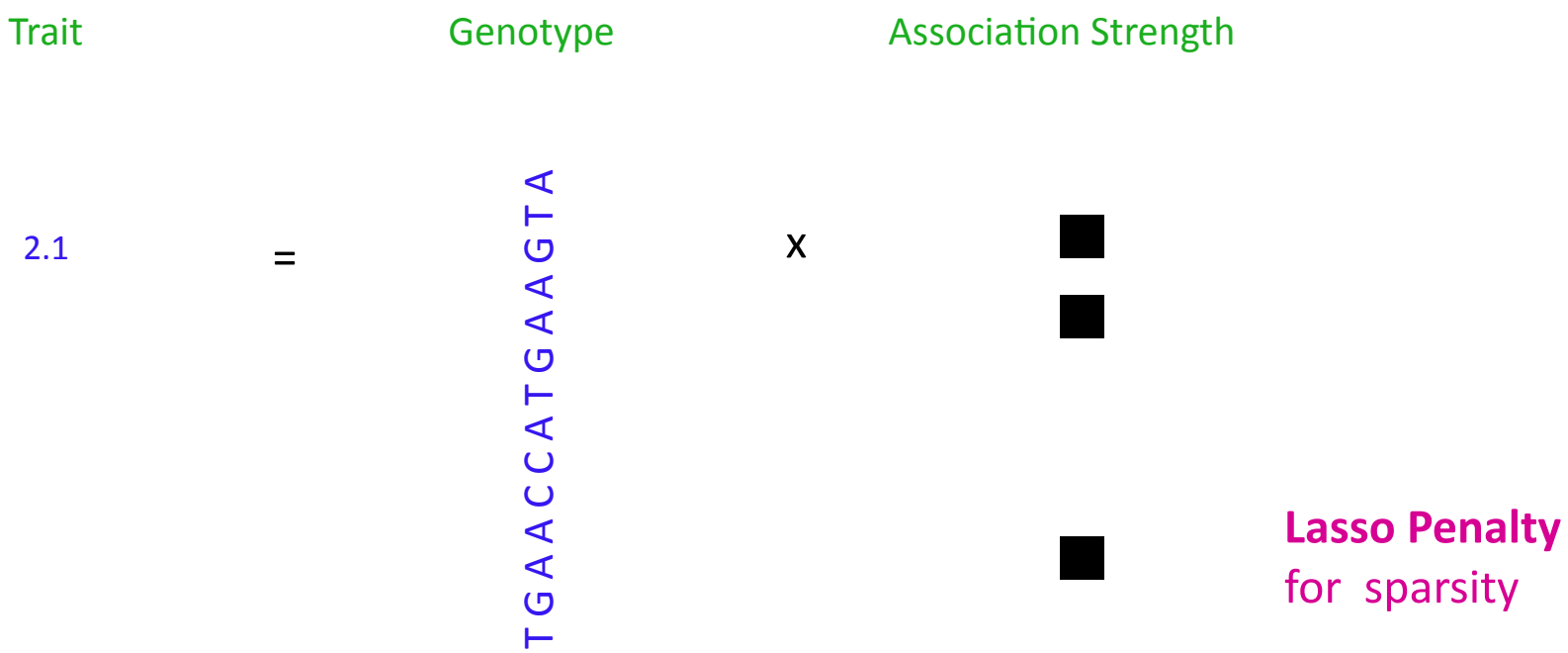
Trait | Genotype | Association Strength



$$\underset{\beta}{\operatorname{argmin}} \; (y - X\beta)' \cdot (y - X\beta)$$

Many non-zero associations:
Which SNPs are truly significant?

Lasso for Reducing False Positives

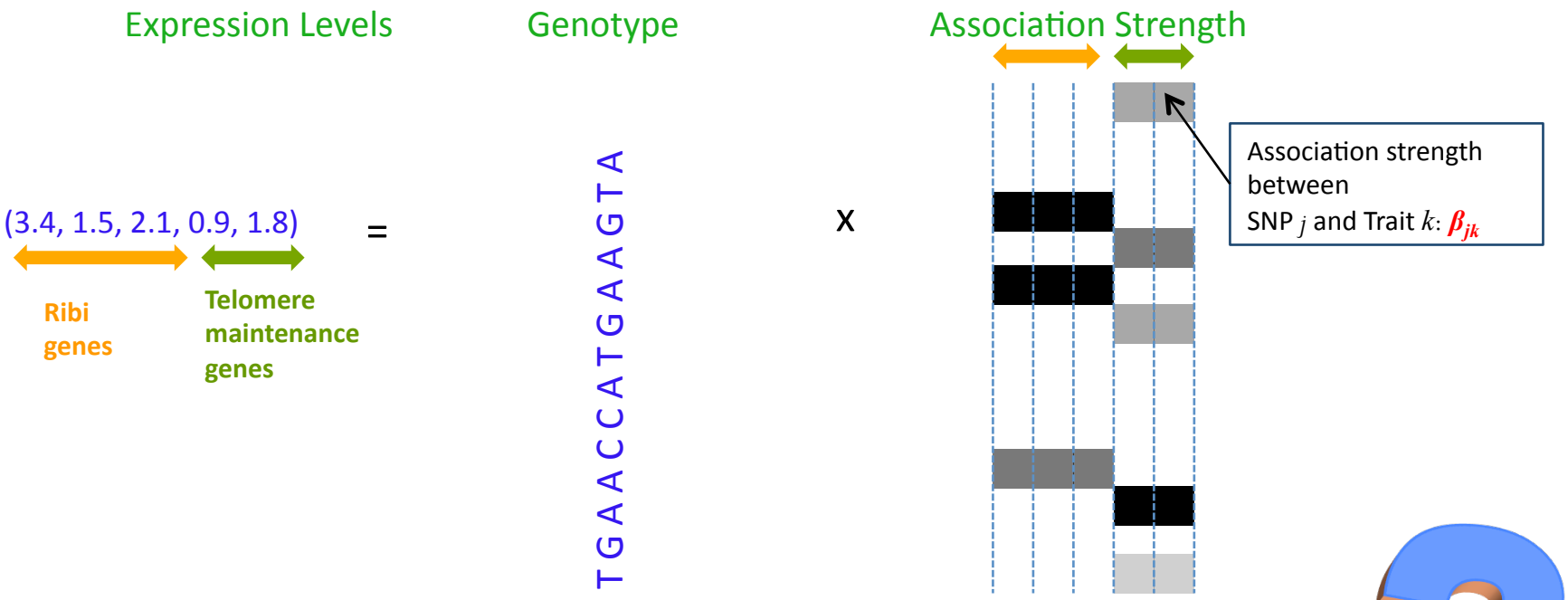


$$\underset{\beta}{\operatorname{argmin}} \; (y - X\beta)'(y - X\beta) + \sum_{j=1}^{J} |\beta_j|$$

Many zero associations (**sparse** results), but what if there are multiple related traits?

Tibshirani, Journal of Royal Statistical Society 1996
Wu et al., Bioinformatics 2009

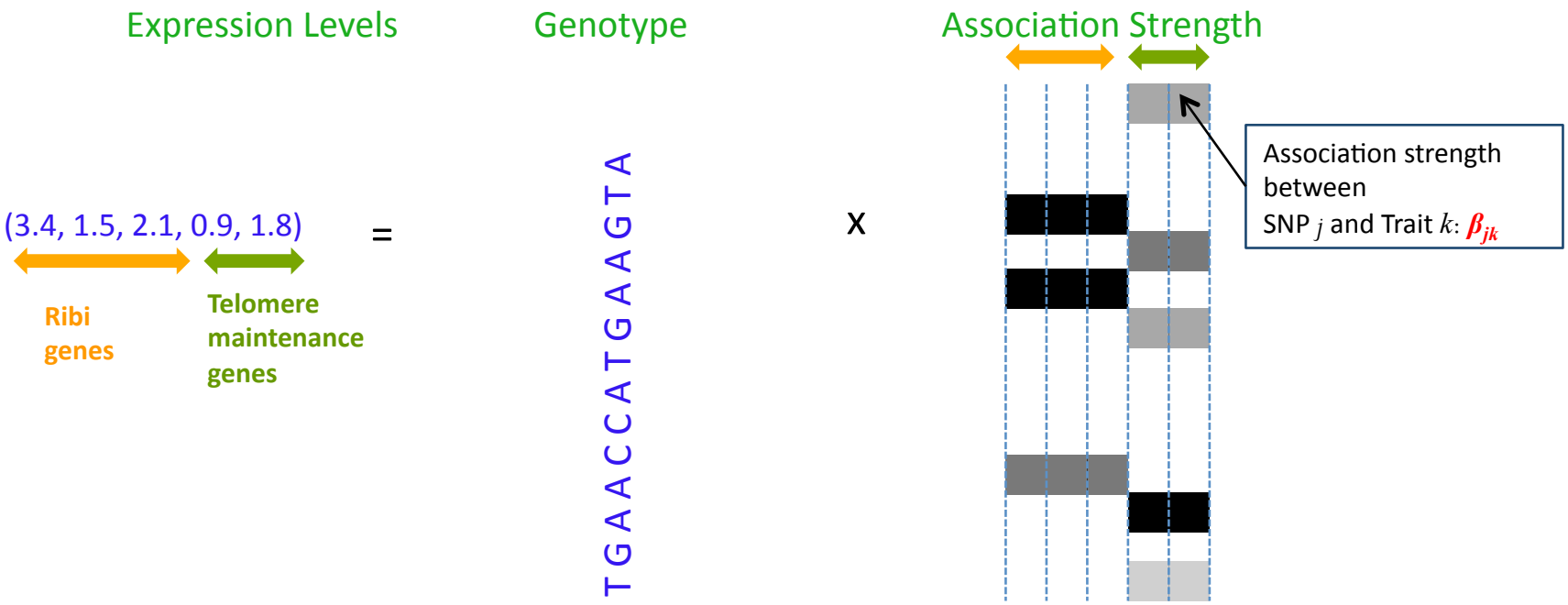
Multi-Task Regression for Transcriptome Association Analysis



$$\underset{\beta}{\operatorname{argmin}} \; (y - X\beta)'(y - X\beta) + \sum_{j=1}^{J} |\beta_j|$$

How to combine information across multiple traits to increase the power?

Multi-Task Regression for Transcriptome Association Analysis



$$\underset{\beta}{\operatorname{argmin}} \; (y - X\beta)' \cdot (y - X\beta) + \sum_{j=1}^{J} |\beta_j|$$

\+

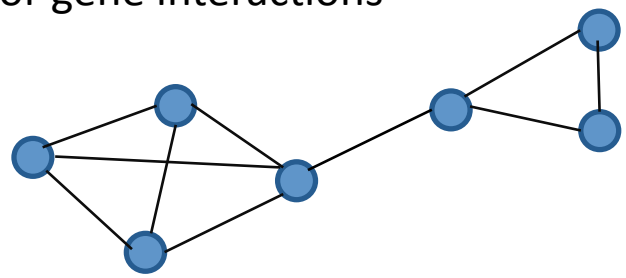
We introduce

graph-guided fusion penalty

Kim & Xing, PloS Genetics 2009

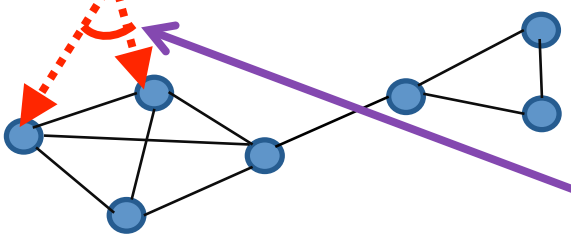
Graph-Constrained Fused Lasso

Step 1: Thresholded correlation graph for gene interactions



Step 2: Graph-constrained fused lasso

ACGTTTTACTGTACAATT



Fusion

$$\hat{\mathbf{B}}^{\mathrm{GC}} = \operatorname{argmin} \sum_k (\mathbf{y}_k - \mathbf{X}\boldsymbol{\beta}_k)^T \cdot (\mathbf{y}_k - \mathbf{X}\boldsymbol{\beta}_k)$$

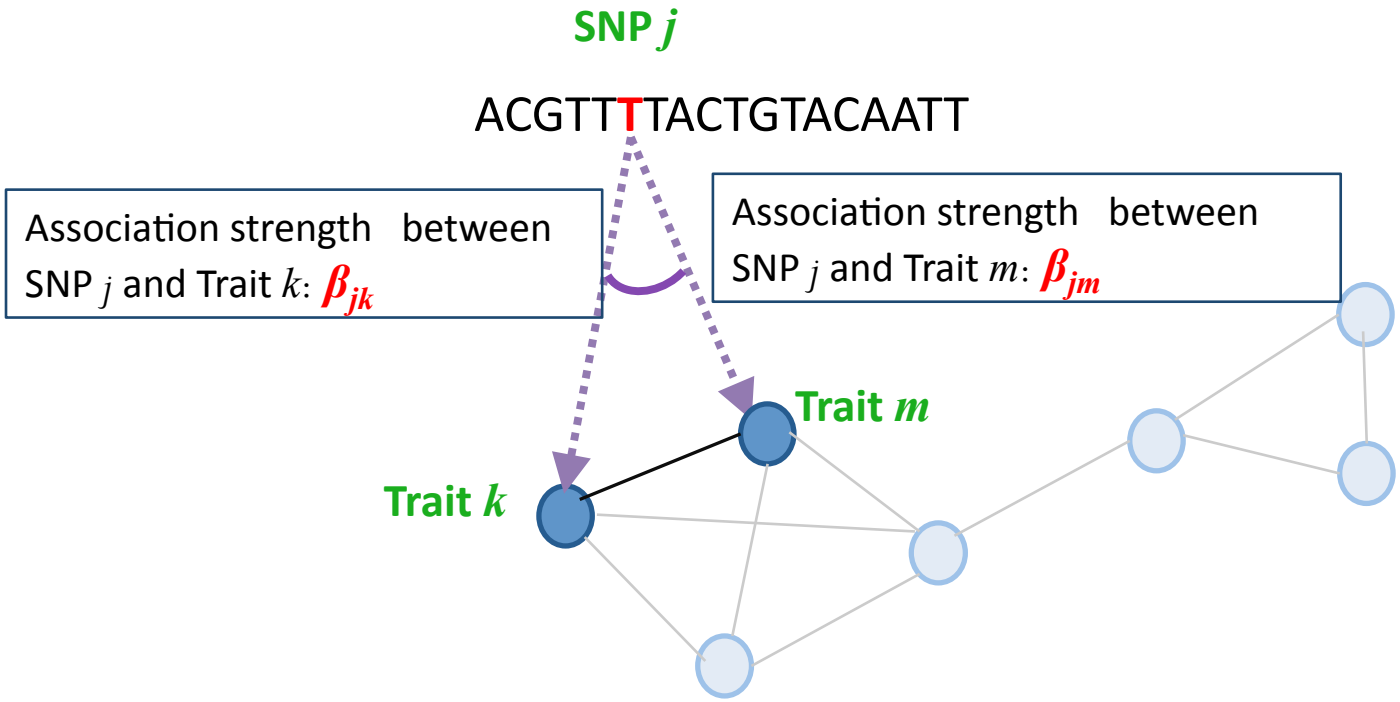
$$+\lambda \sum_k \sum_j |\beta_{jk}| + \gamma \sum_{(m,l)\in E} \sum_j |\beta_{jm} - \operatorname{sign}(r_{ml})\beta_{jl}|$$

Lasso Penalty

Graph-constrained fusion penalty

Kim & Xing, PloS Genetics 2009

Fusion Penalty

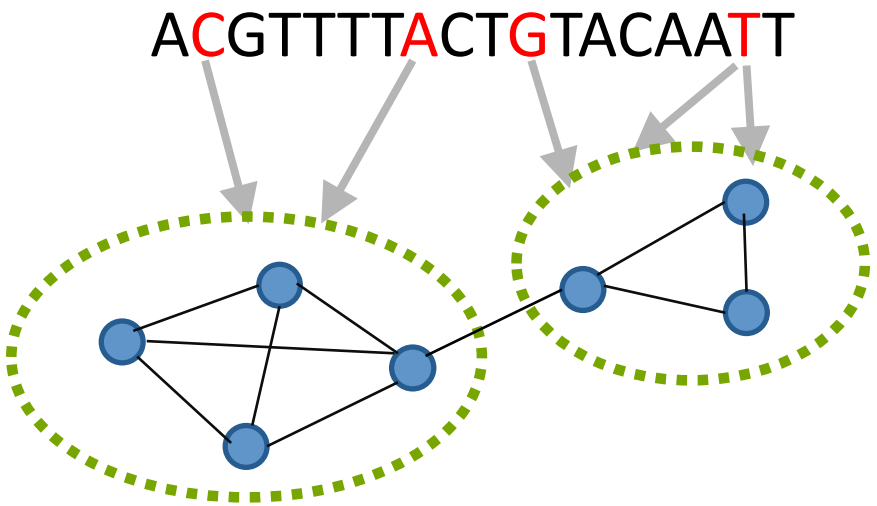


- Fusion Penalty: $|\beta_{jk} - \beta_{jm}|$
- For two correlated traits (connected in the network), the association strengths may have similar values.

Kim & Xing, PloS Genetics 2009

Transcriptome Association: Graph-Constrained Fused Lasso

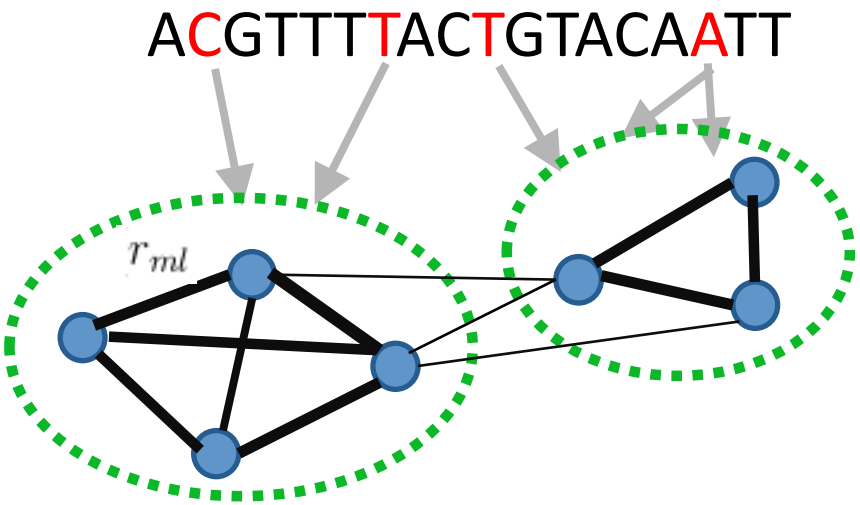
Overall effect



- Fusion effect propagates to the entire network
- Association between SNPs and subnetworks of traits

Transcriptome Association: Graph-Weighted Fused Lasso

Overall effect



- Subnetwork structure is embedded as a densely connected nodes with large edge weights
- Edges with small weights are effectively ignored

Kim & Xing, PloS Genetics 2009

Estimating Parameters

- Quadratic programming formulation

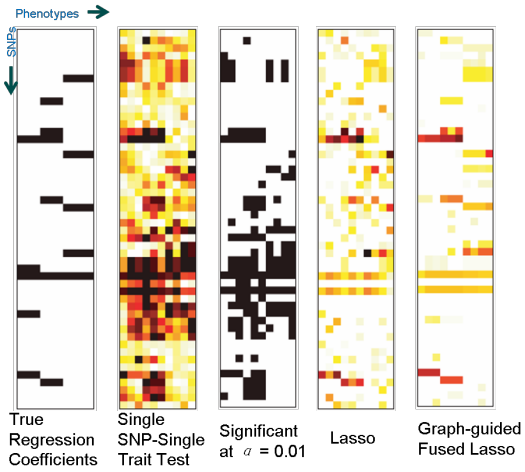
$$\hat{\mathbf{B}}^{\mathrm{GW}} = \operatorname{argmin} \sum_k (\mathbf{y}_k - \mathbf{X}\boldsymbol{\beta}_k)^T \cdot (\mathbf{y}_k - \mathbf{X}\boldsymbol{\beta}_k)$$

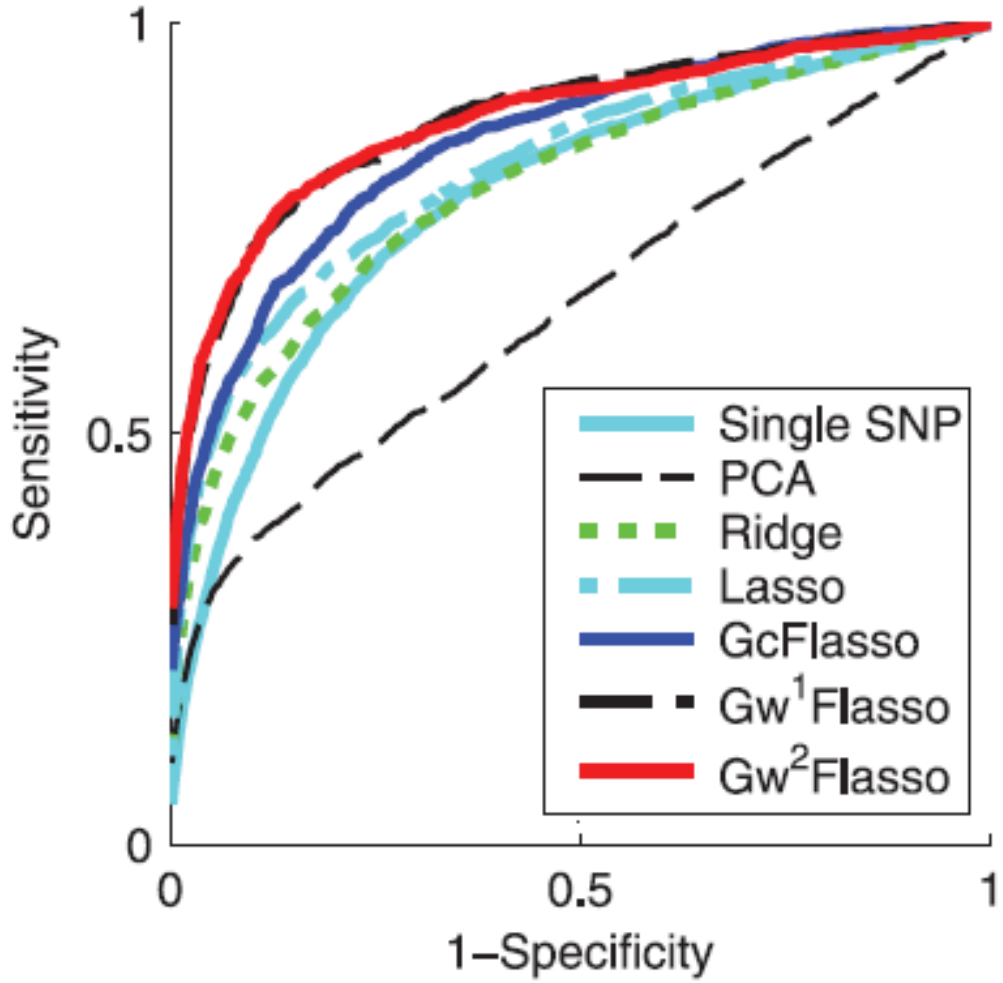
$$\text{s. t.} \quad \sum_k \sum_j |\beta_{jk}| \le s_1 \text{ and } \sum_{(m,l)\in E} f(r_{ml}) \sum_j |\beta_{jm} - \operatorname{sign}(r_{ml})\beta_{jl}| \le s_2$$

  - Important properties:
    - Convex optimization --- therefore global optimum exist
    - Sparse --- therefore results are parsimonious and interpretable
    - Theoretical Guarantee --- proof of consistency exist

- Many publicly available software packages for solving convex optimization problems can be used
- A new proximal gradient method can handle tens of thousands of SNPs and thousands of traits (later)

Simulation Results



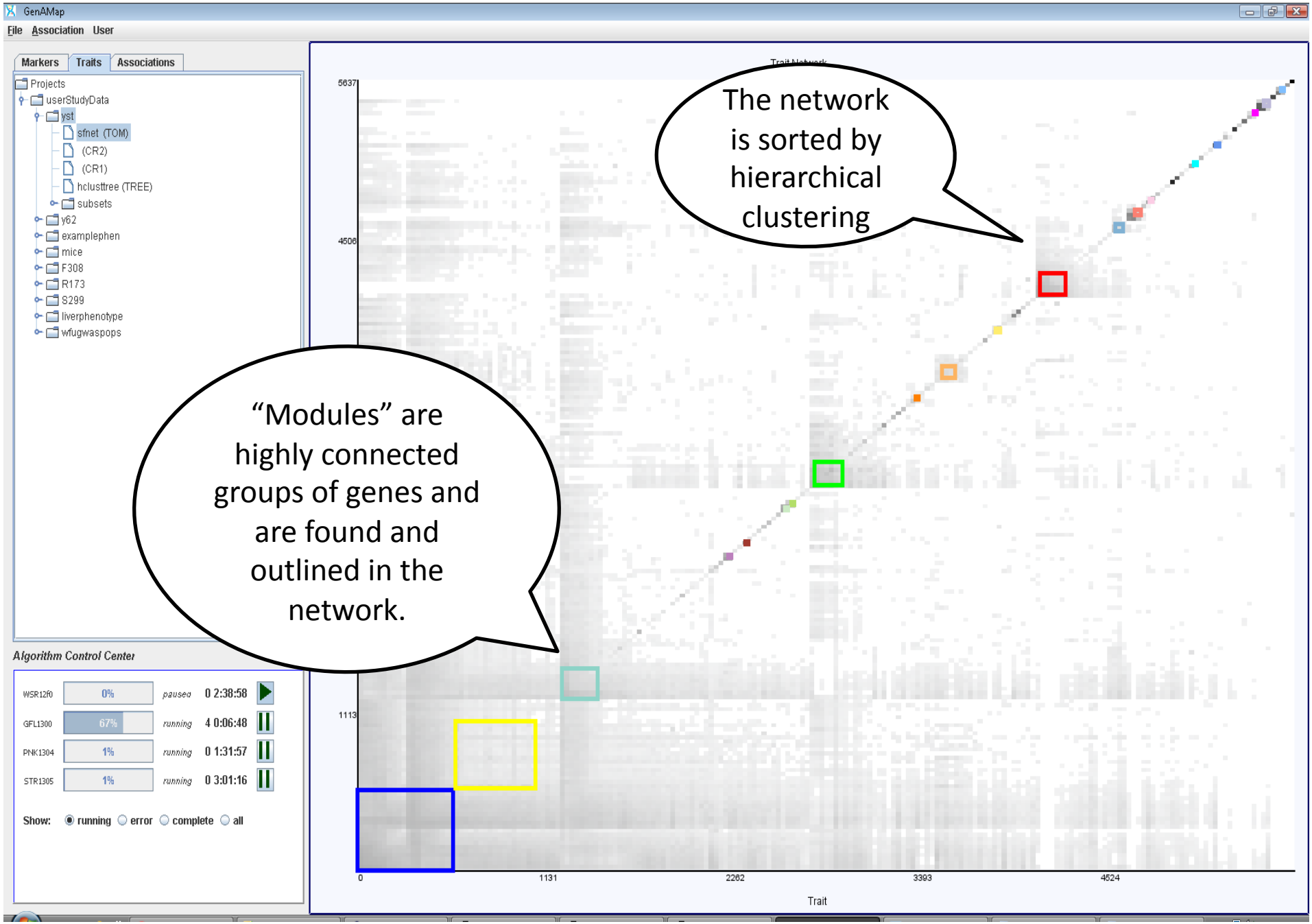


Yeast eQTL Dataset

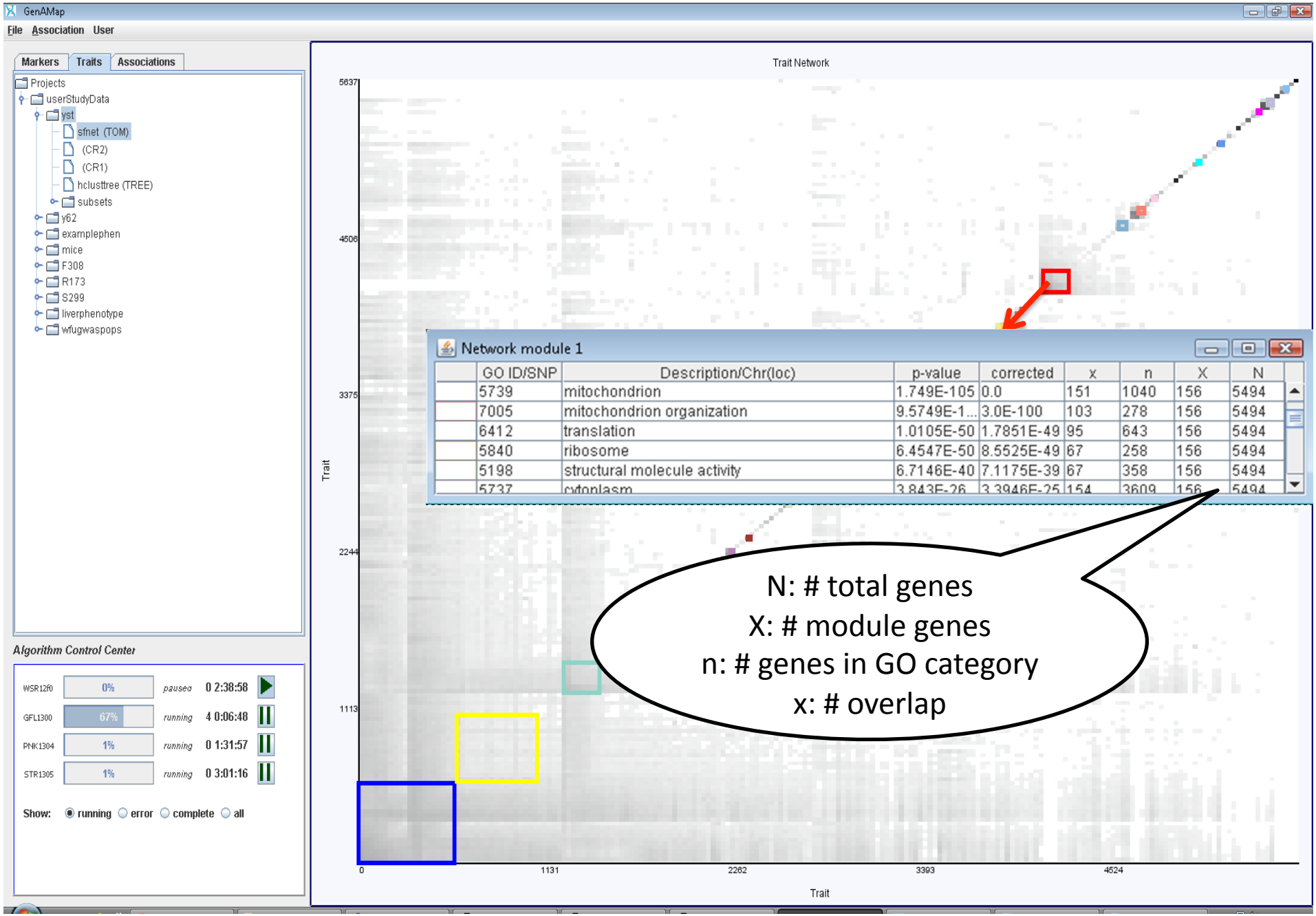
(Brem and Kruglyak, PNAS 2005)

- Genotype: 1260 SNPs
- Phenotype: expression measurements for 3684 genes
- 114 strains
- Goal: are there any SNPs that influence expression levels of genes?
  - Scale-free network construction and module finding
  - GFlasso analysis to find associations

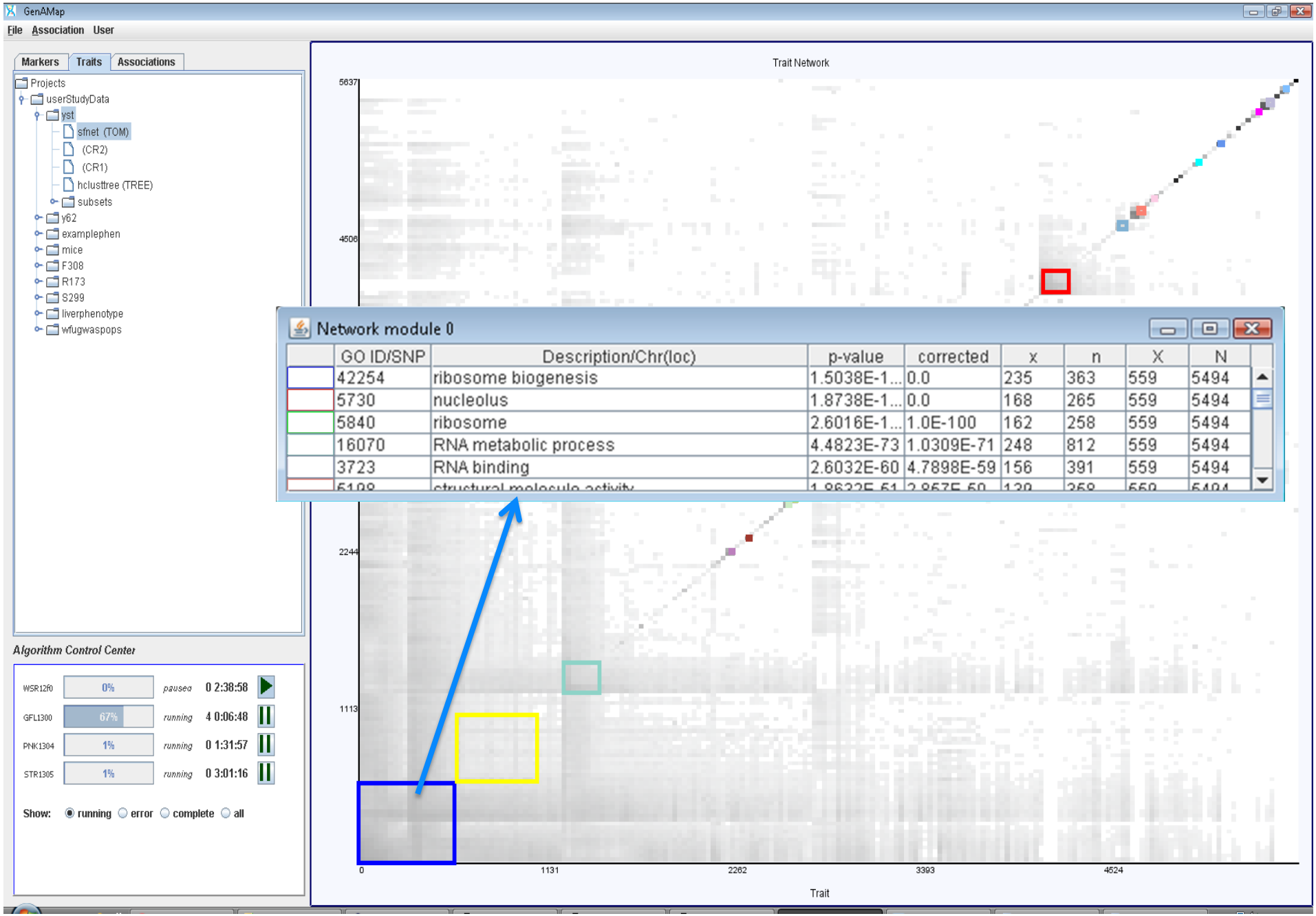
Gene-gene network exploration



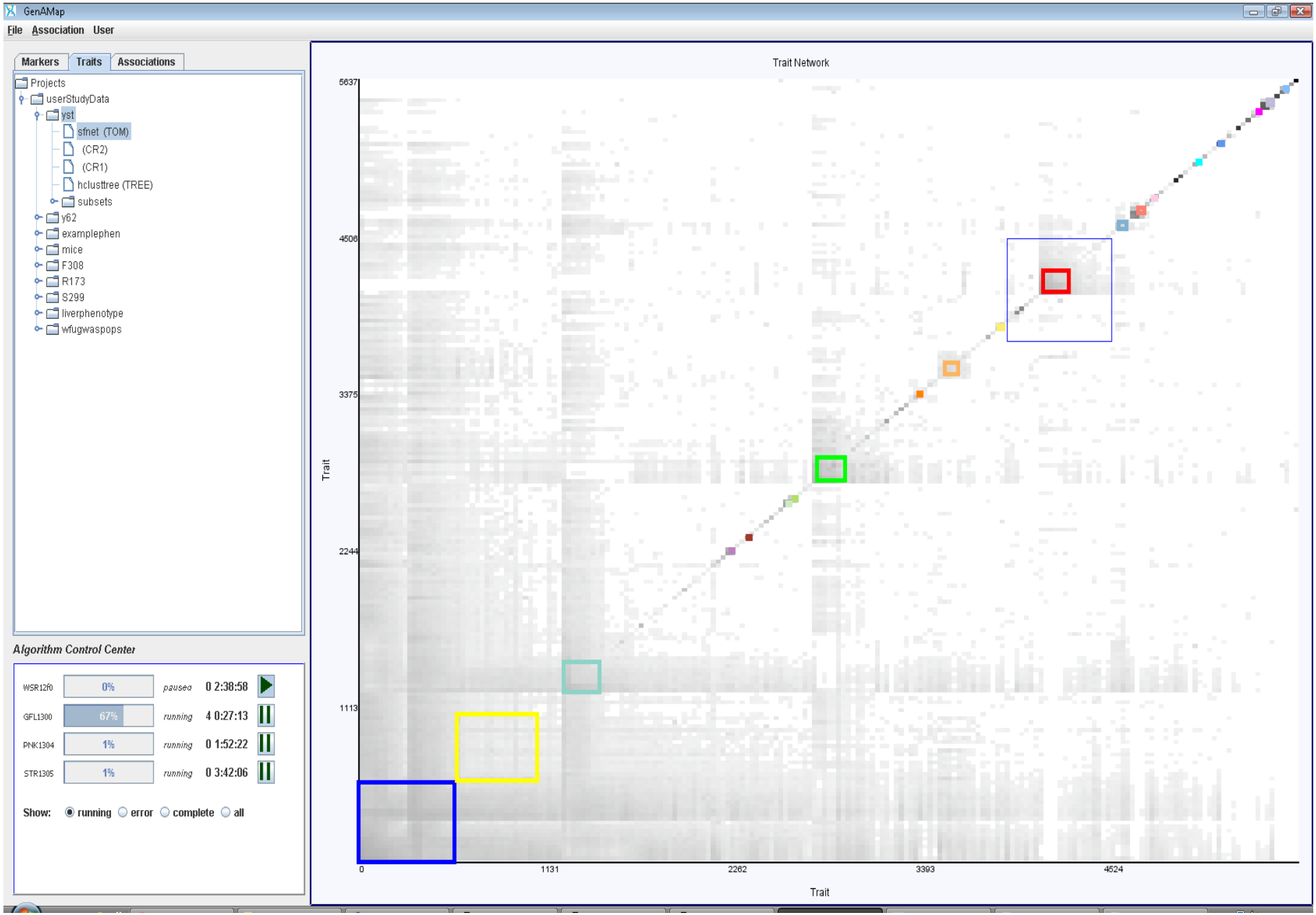
Gene-gene network exploration : Mitochondrion module

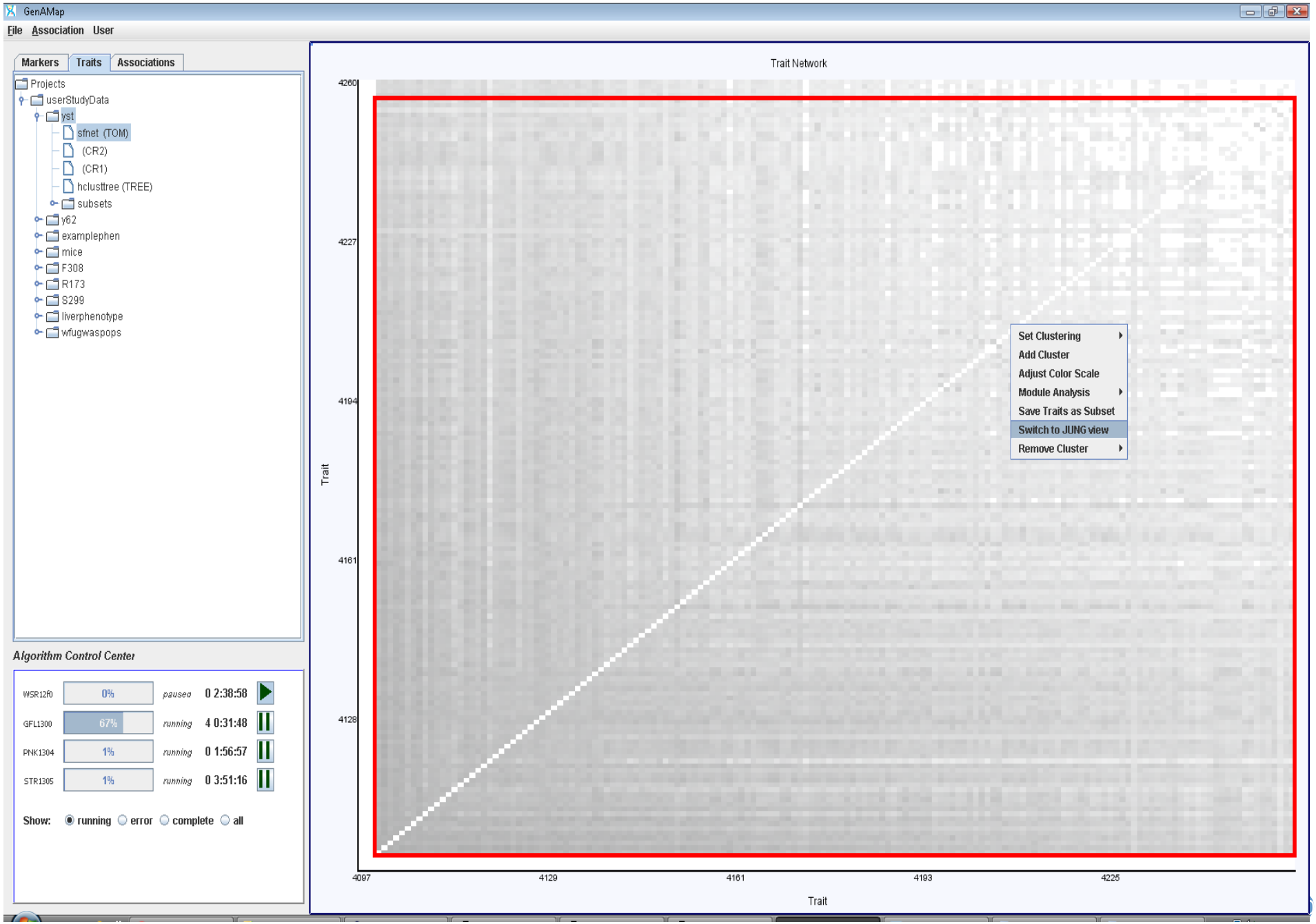


Gene-gene network exploration: ribosome biogenesis module



Gene-gene network exploration: zoom into mitochondrion module




GenAMap
File Association User
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R173
S299
liverphenotype
wfugwaspops
Algorithm Control Center
WSR12F0 0% paused 0 2:38:58
GFL1300 67% running 4 0:31:48
PNK1304 1% running 0 1:56:57
STR1305 1% running 0 3:51:16
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Trait
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4227
4194
4161
4128
4097
4129
4161
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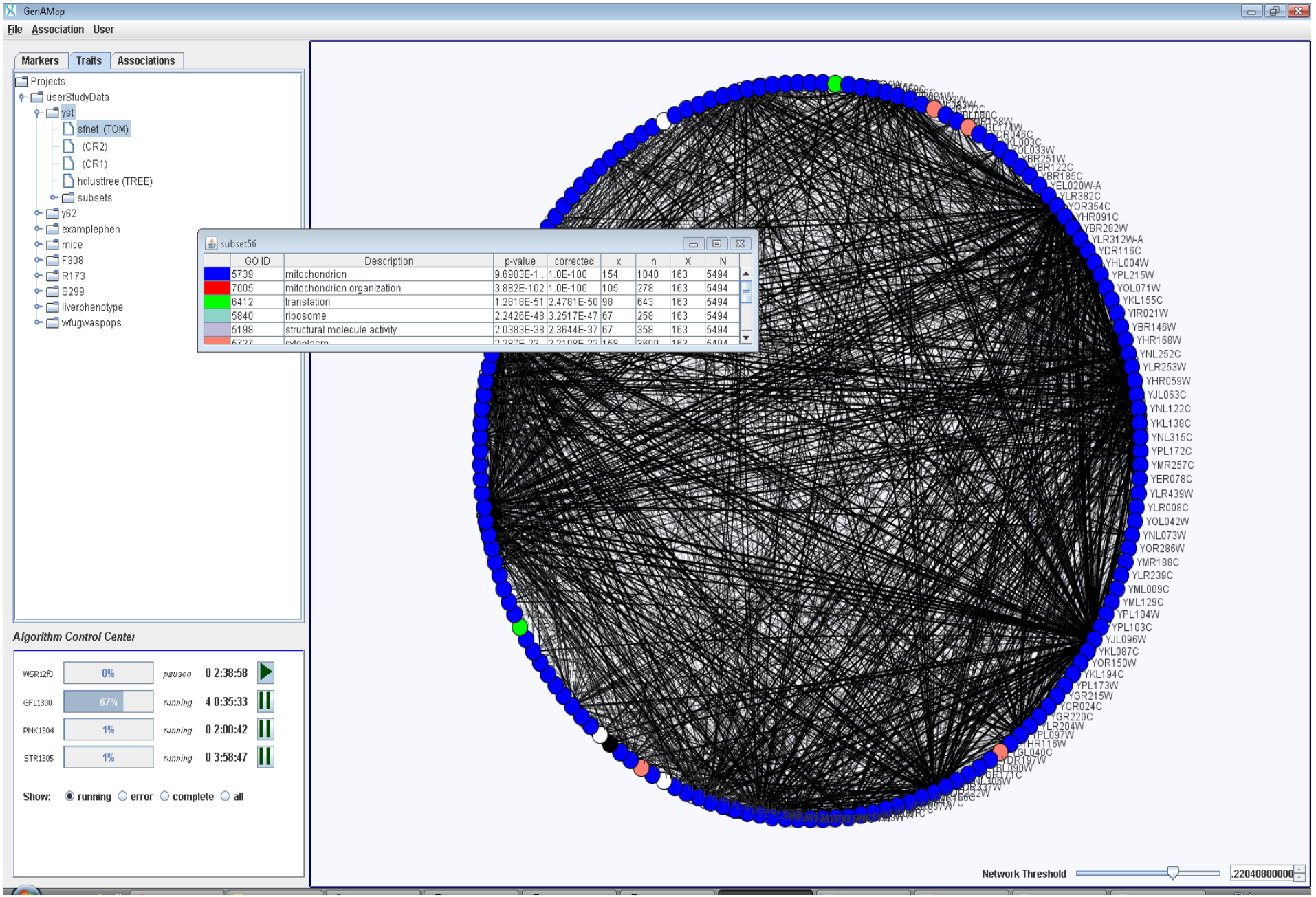
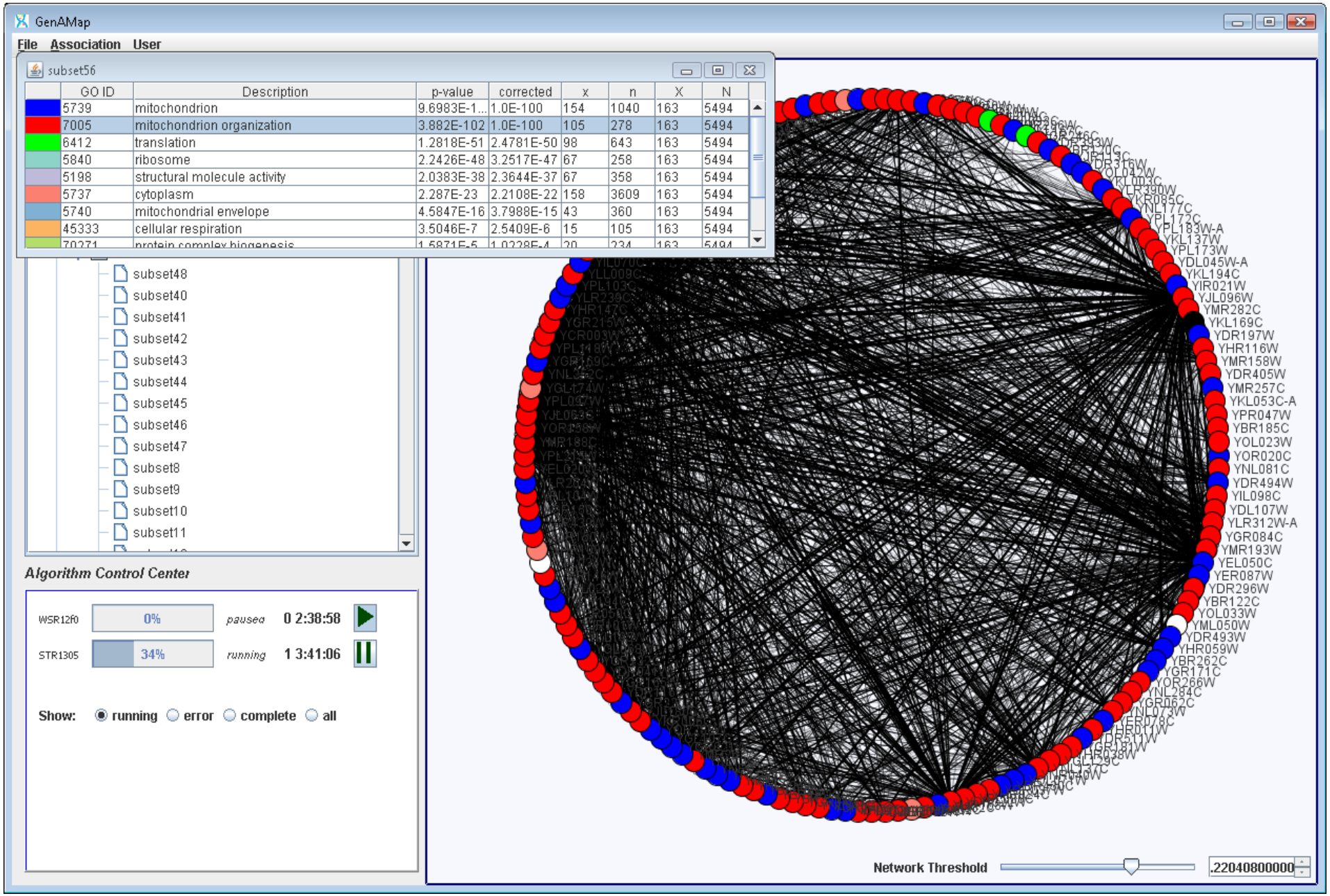
4225
Trait
Set Clustering
Add Cluster
Adjust Color Scale
Module Analysis
Save Traits as Subset
Switch to JUNG view
Remove Cluster

Gene-gene network exploration: GO analysis

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7005 mitochondrion organization 3.882E-102 1.0E-100 105 278 163 5494
6412 translation 1.2818E-51 2.4781E-50 98 643 163 5494
5840 ribosome 2.2426E-48 3.2517E-47 67 258 163 5494
5198 structural molecule activity 2.0383E-38 2.3644E-37 67 358 163 5494
5737 cytoplasm 2.287E-23 2.2108E-22 158 3609 163 5494
5740 mitochondrial envelope 4.5847E-16 3.7988E-15 43 360 163 5494
45333 cellular respiration 3.5046E-7 2.5409E-6 15 105 163 5494
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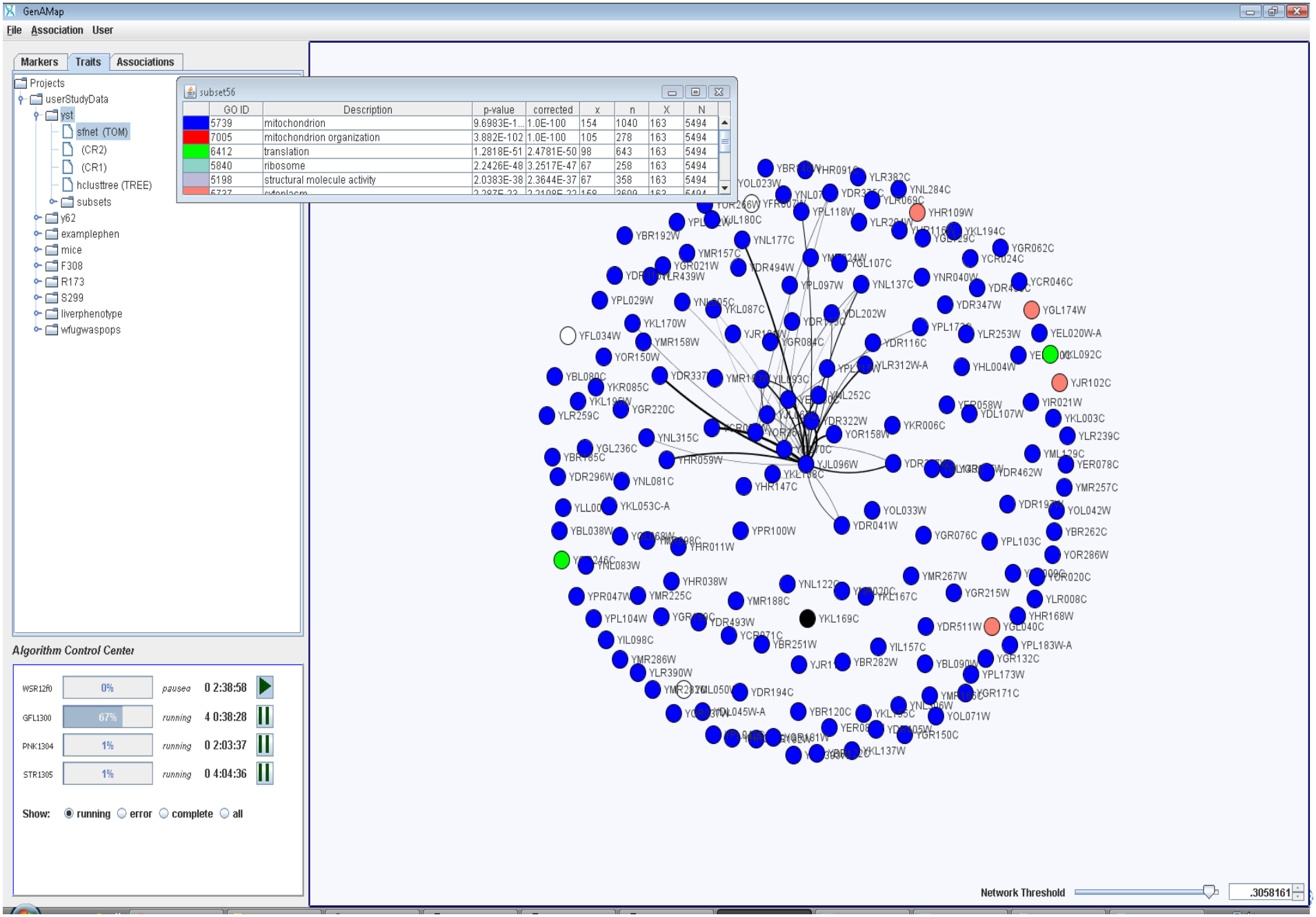
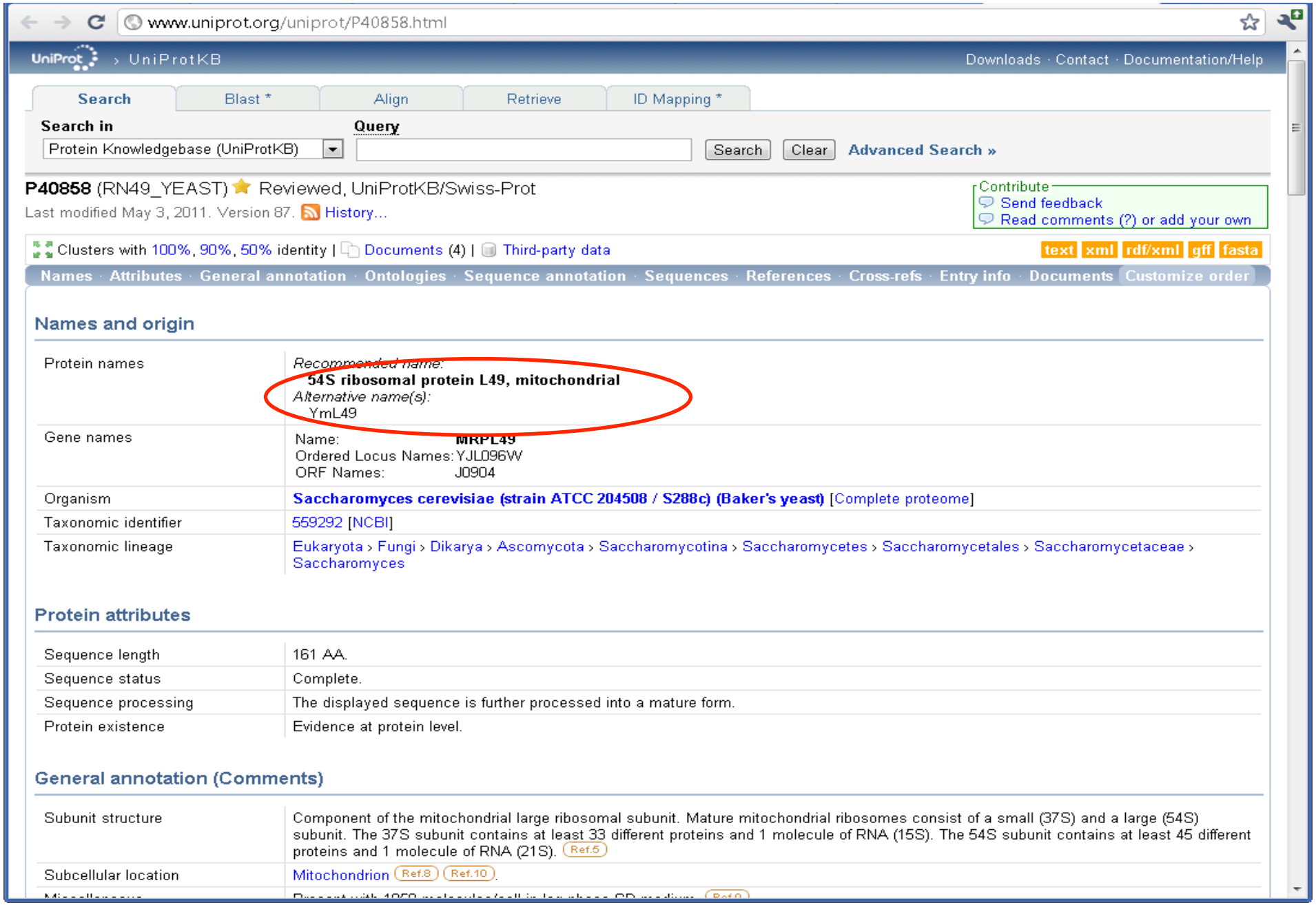
subset10
subset11
Algorithm Control Center
WSR12f0
0%
paused
0 2:38:58
STR1305
34%
running
1 3:41:06
Show:
running
error
complete
all
Network Threshold
.22040800000

Gene-gene network exploration: Identify hubs

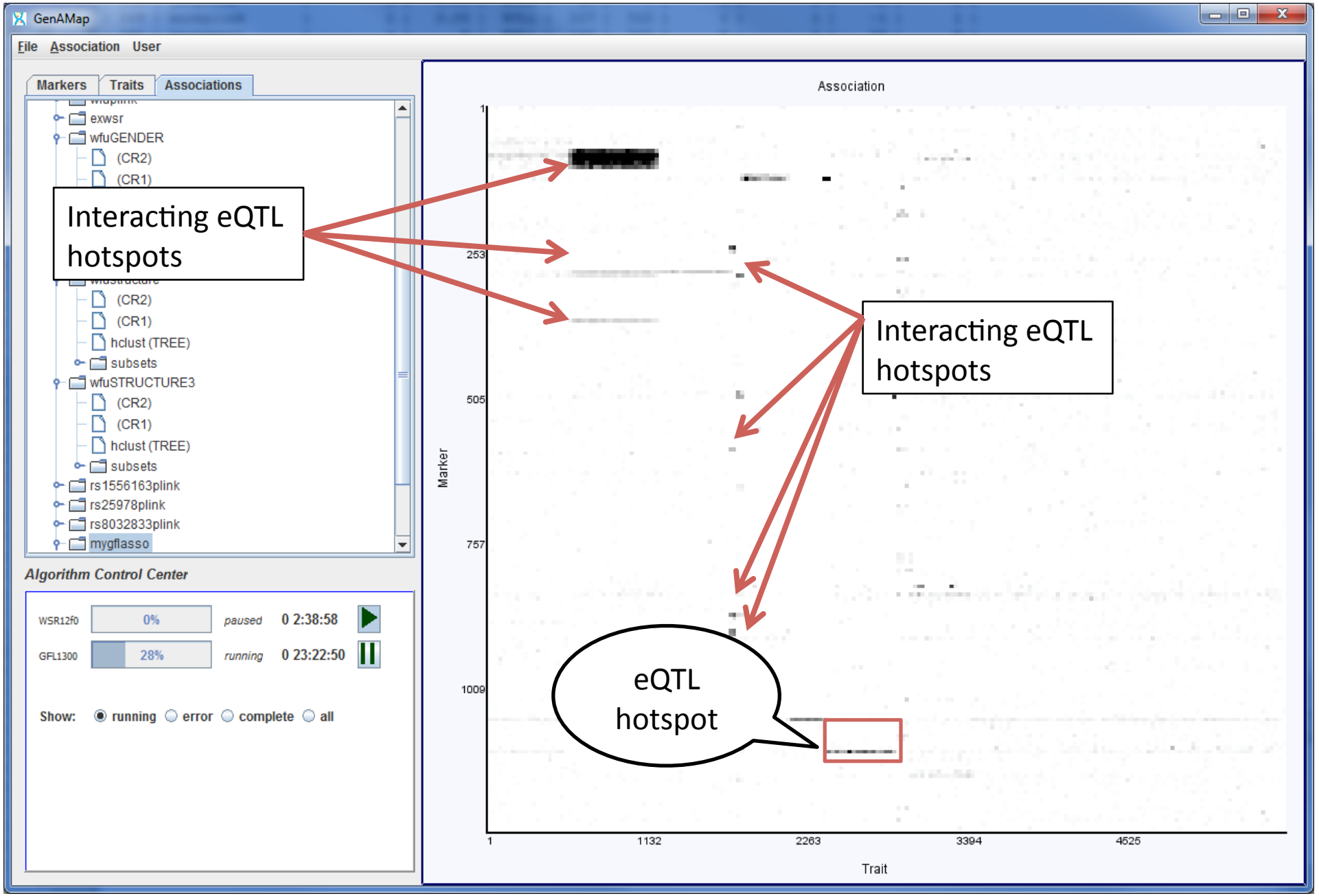


Gene-gene network exploration: UniProt information

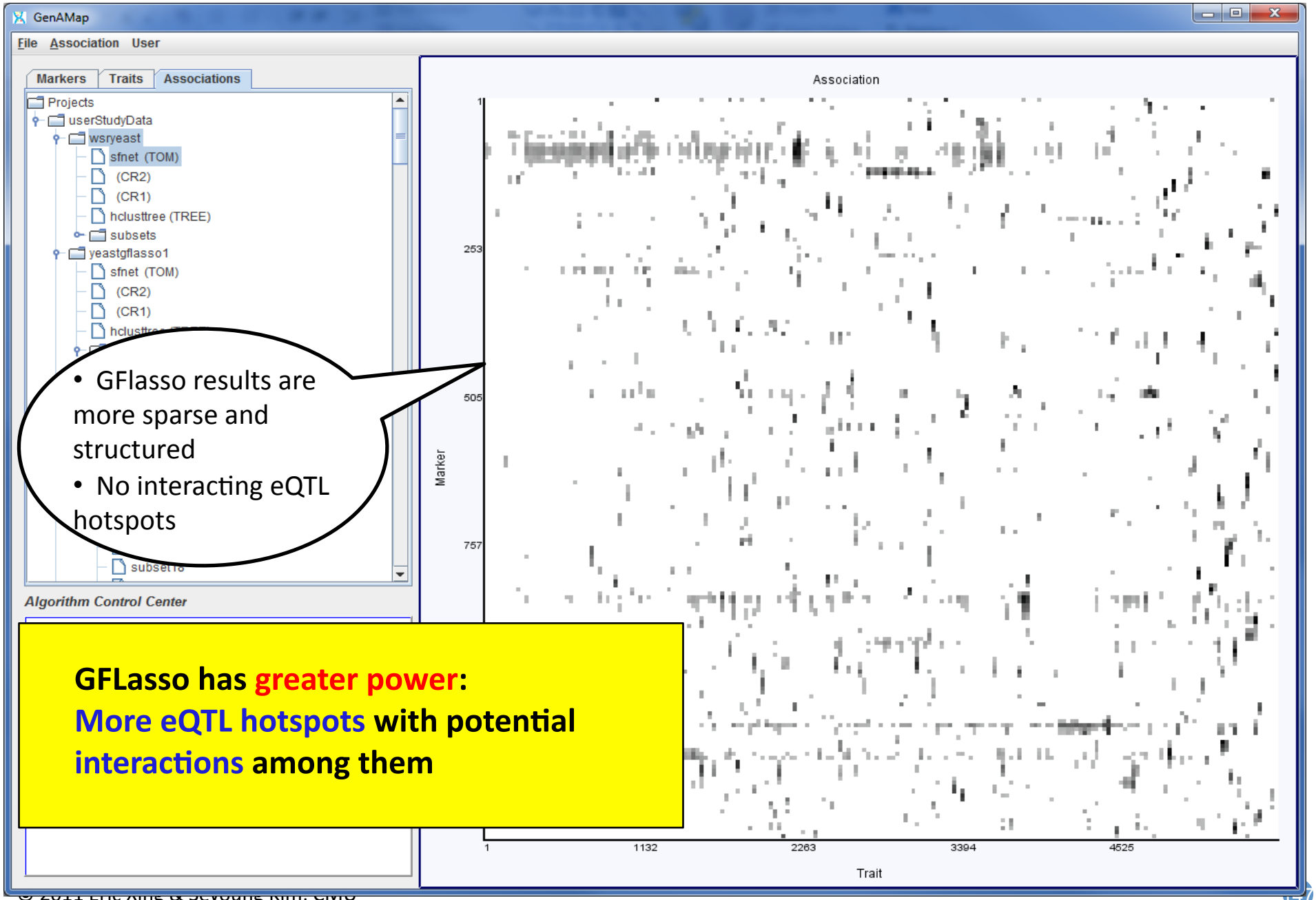


GFlasso association results

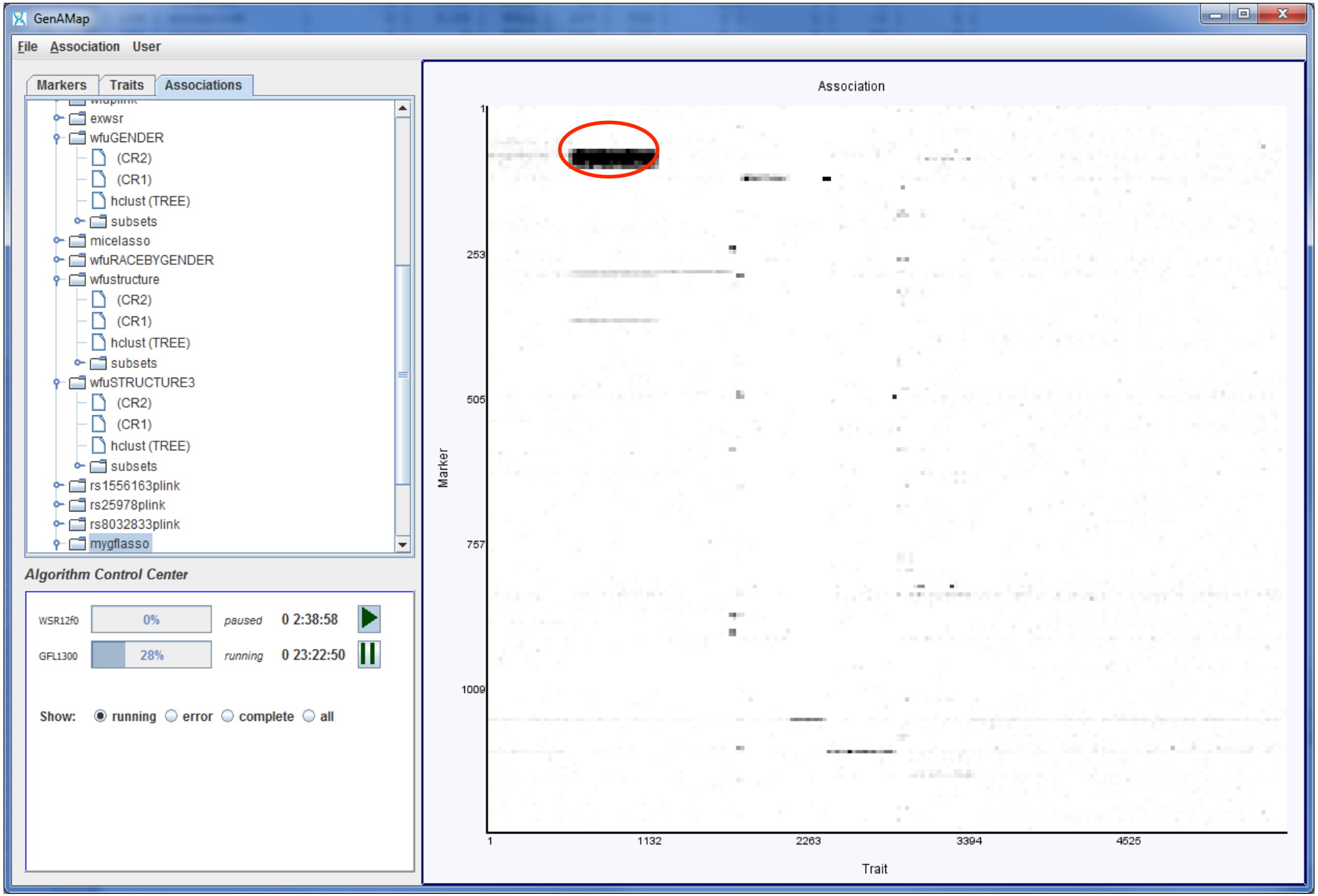
GFlasso results



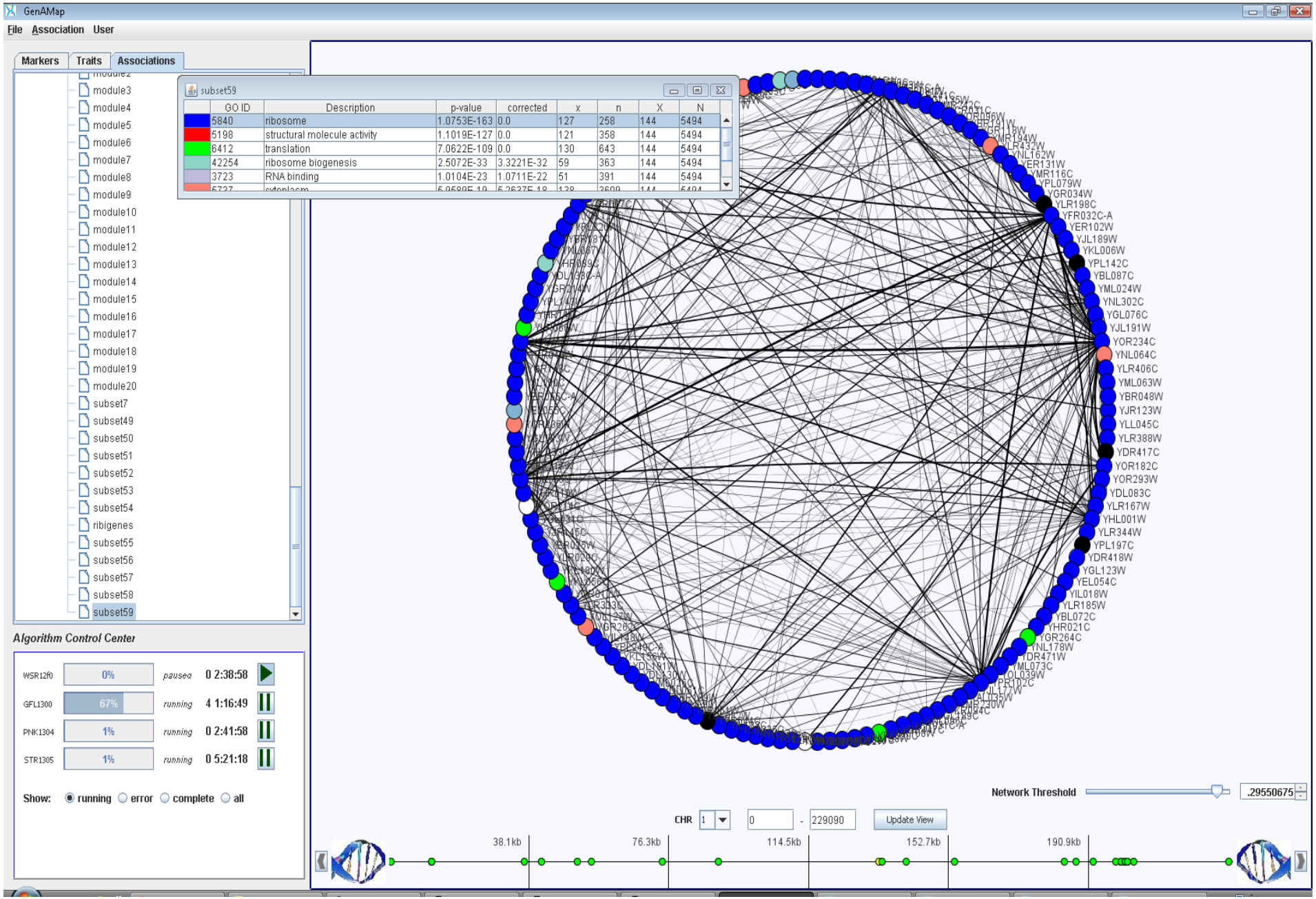
Comparing results with wilcoxon-sum-rank test (single SNP/gene analysis)



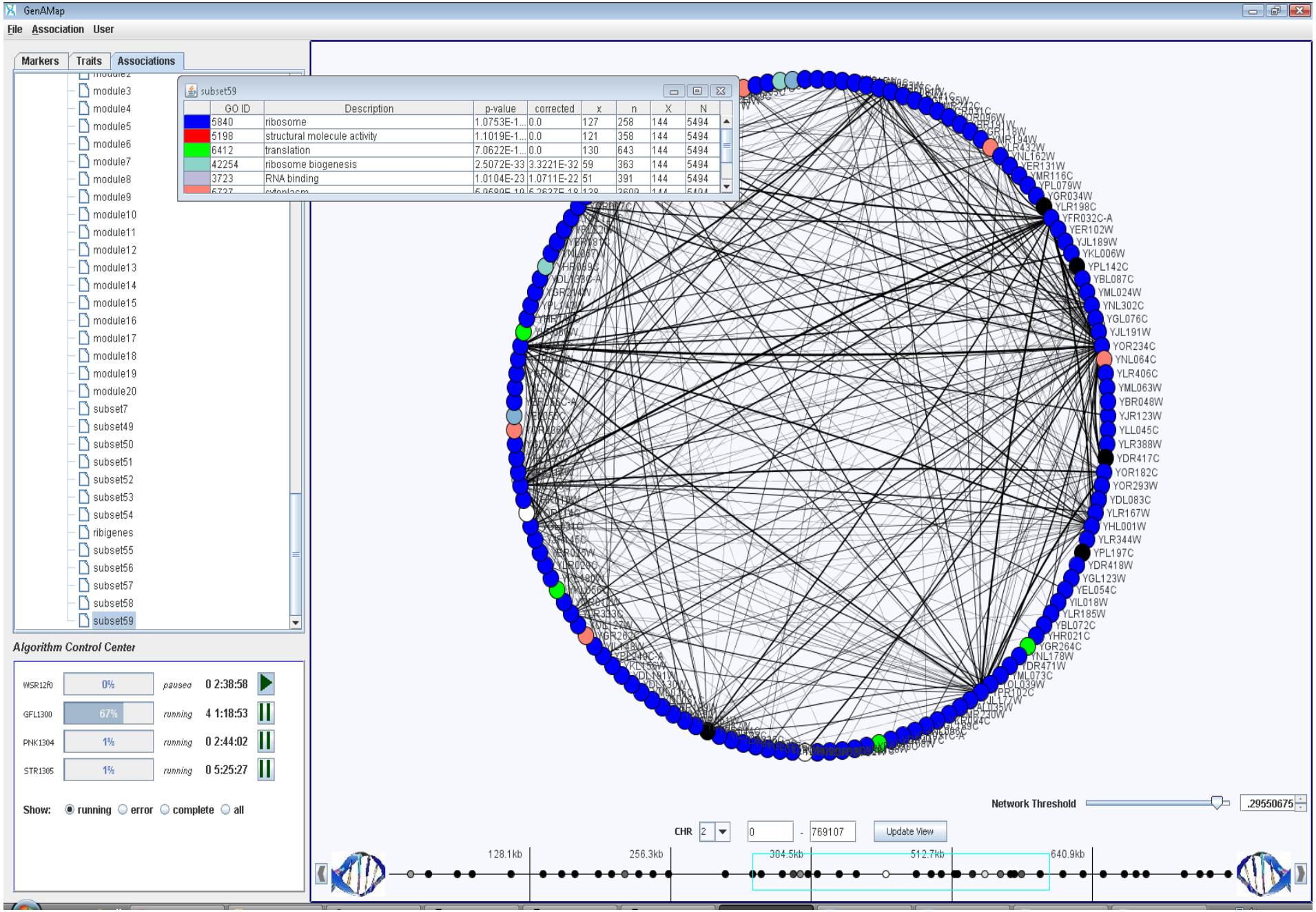
Investigate an eQTL hotspot associated with a single locus



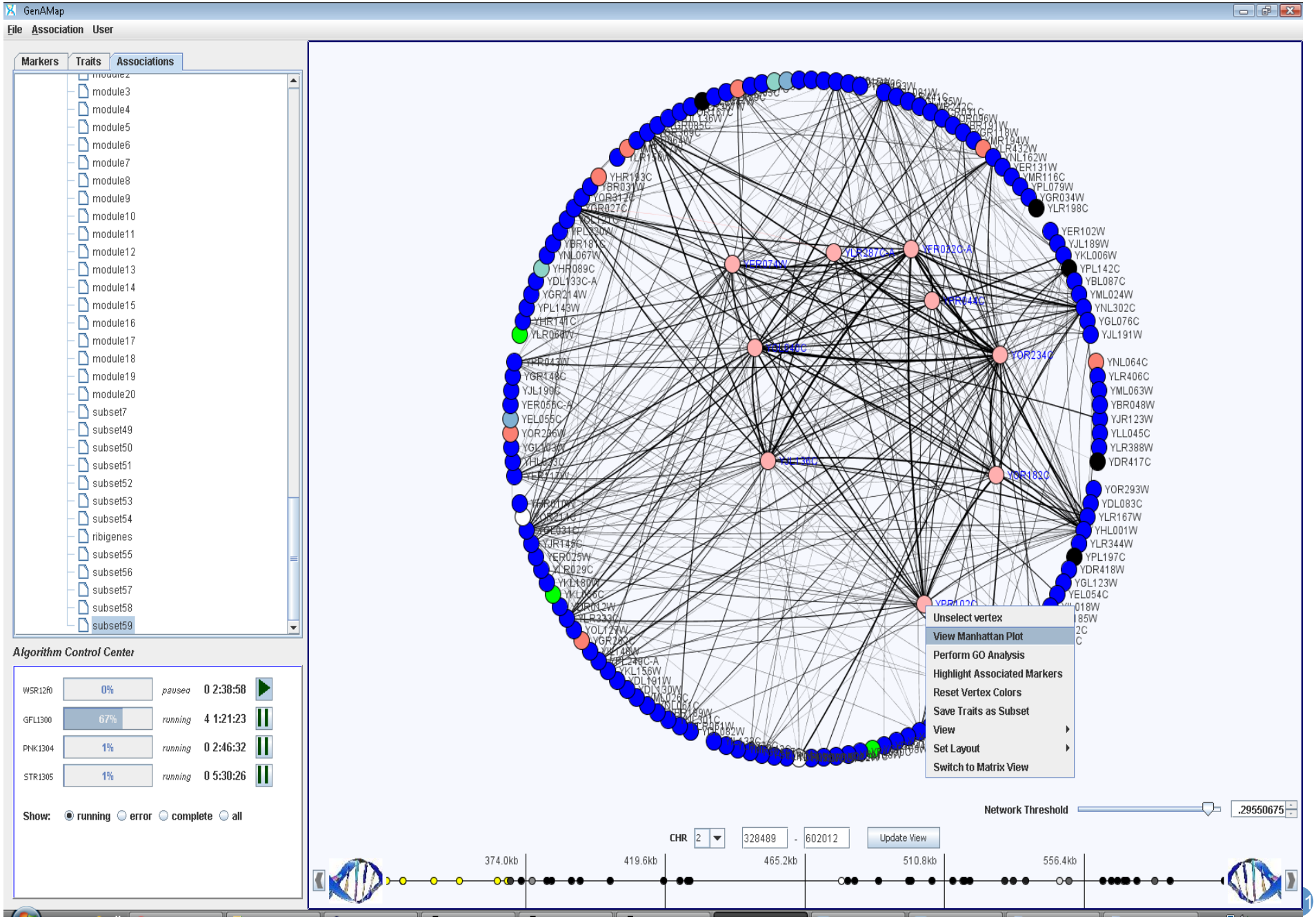
GO analysis reveals hotspot is enriched for ribosome genes



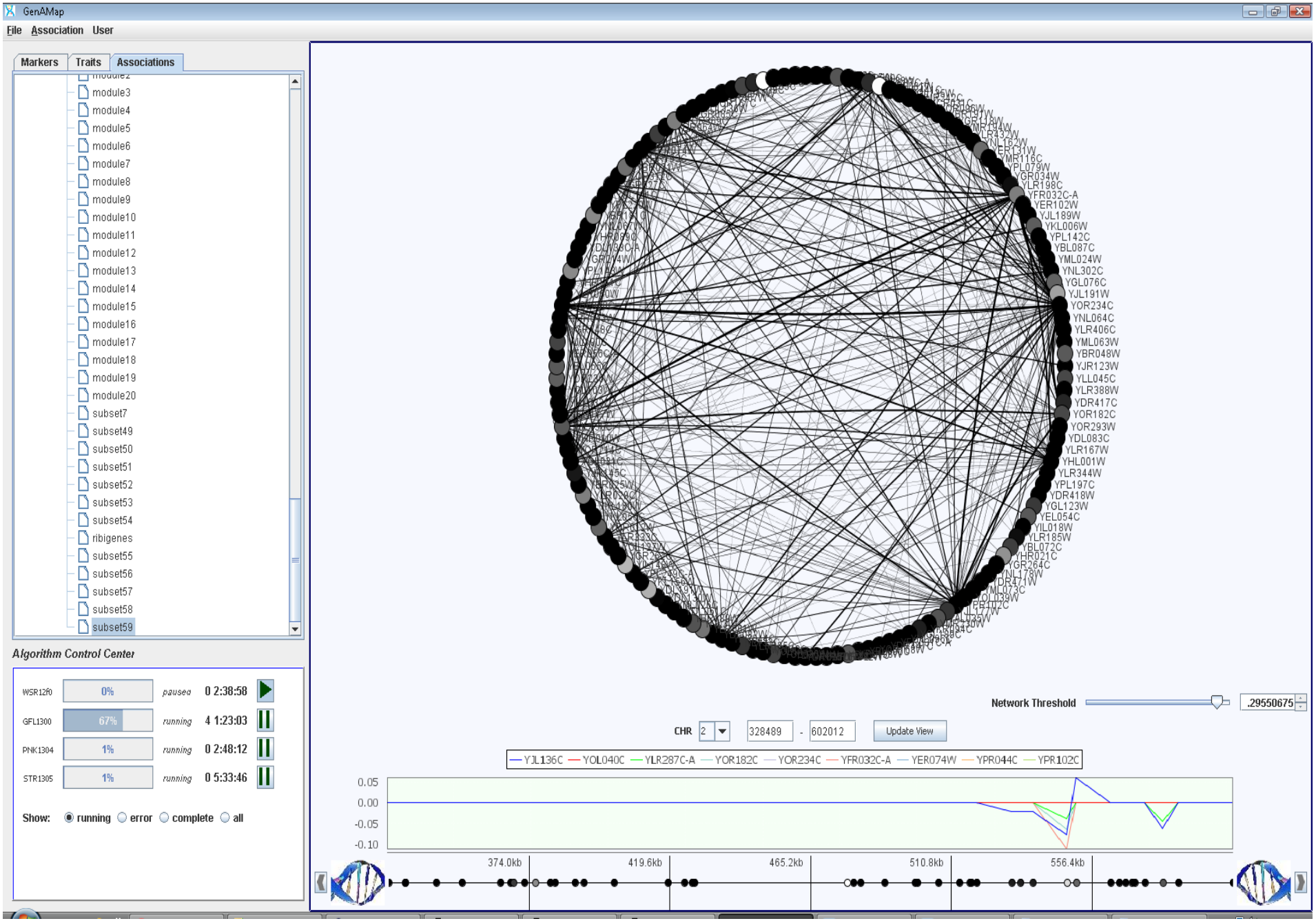
Associations on chromosome 2

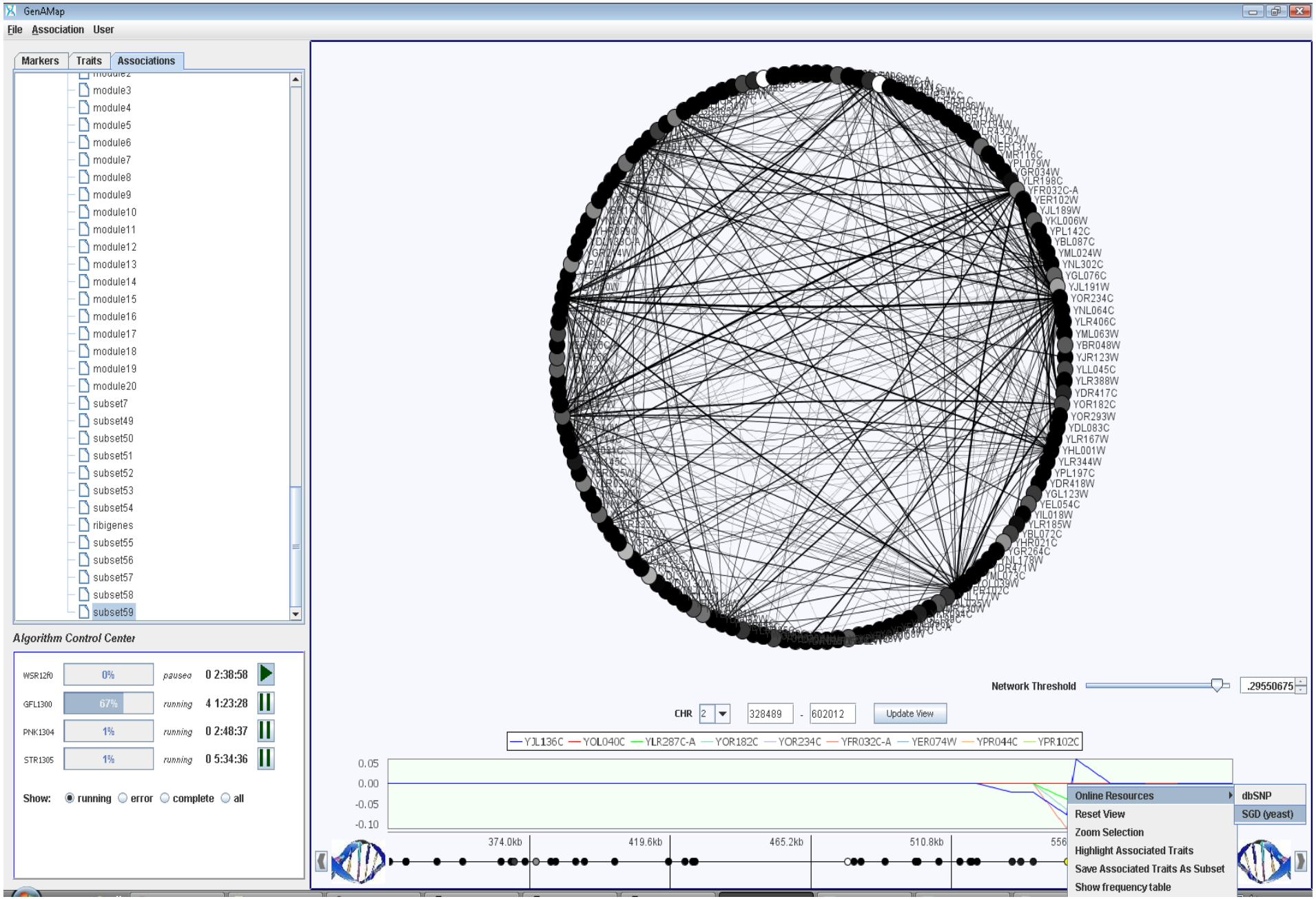


Look at association strengths to highest connected genes



Only a few genes are associated with the hotspot around this SNP (not black), but the highest connected genes are associated with this hotspot.




GenAMap
File Association User
Markers Traits Associations
module3
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GFL1300 67% running 4 1:23:28
PNK1304 1% running 0 2:48:37
STR1305 1% running 0 5:34:36
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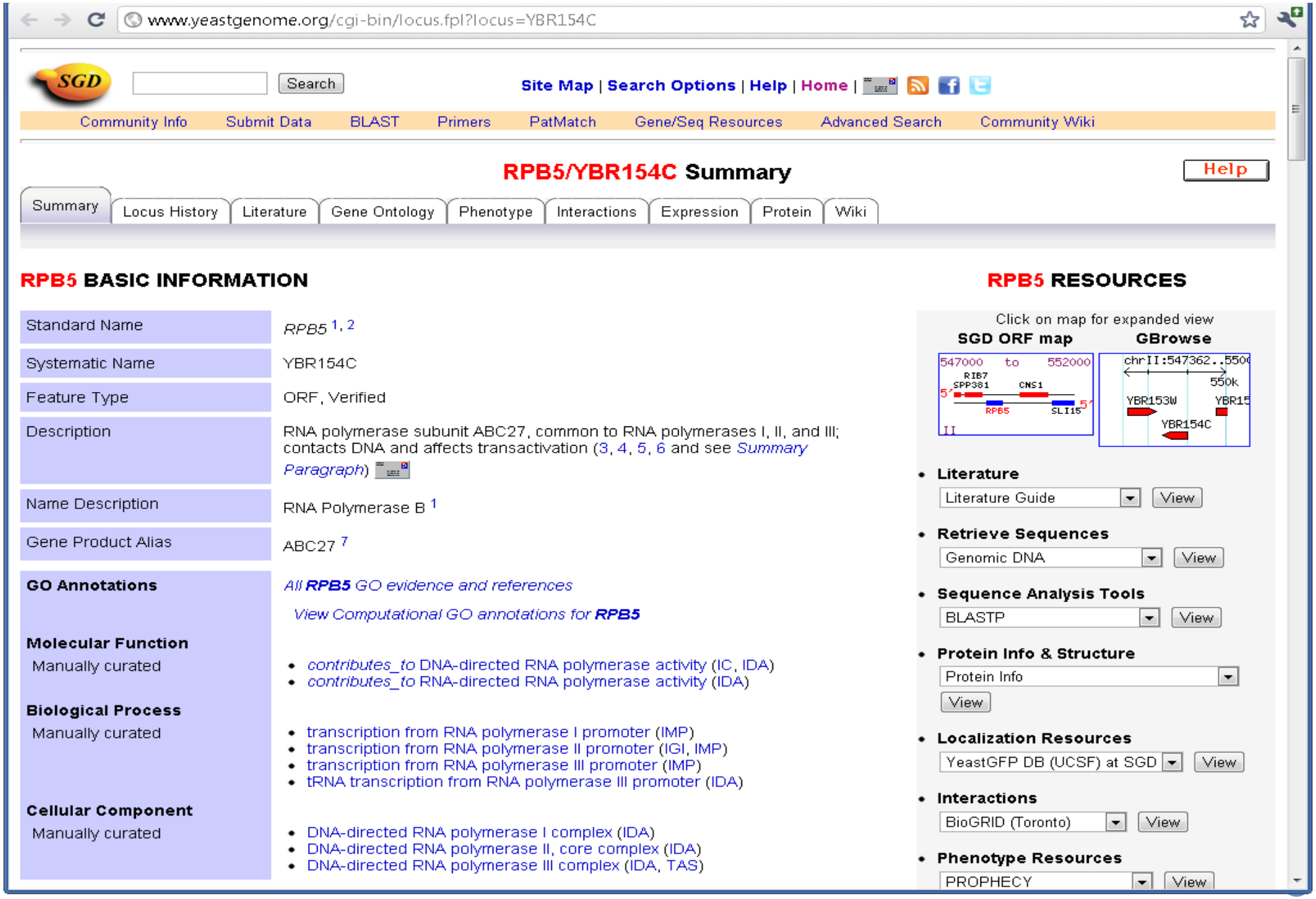
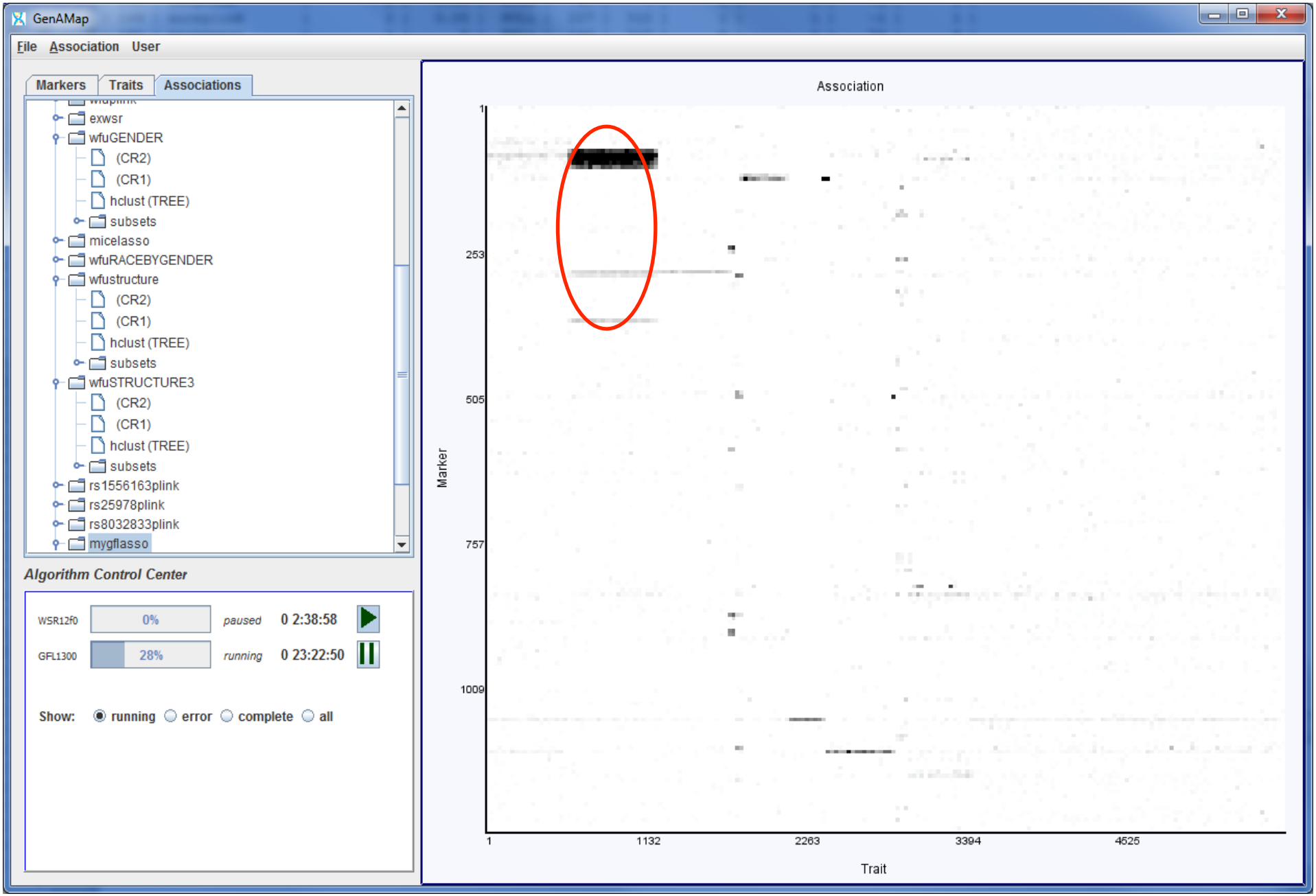
374.0kb
419.6kb
465.2kb
510.8kb
Online Resources
Reset View
Zoom Selection
Highlight Associated Traits
Save Associated Traits As Subset
Show frequency table
dbSNP
SGD (yeast)

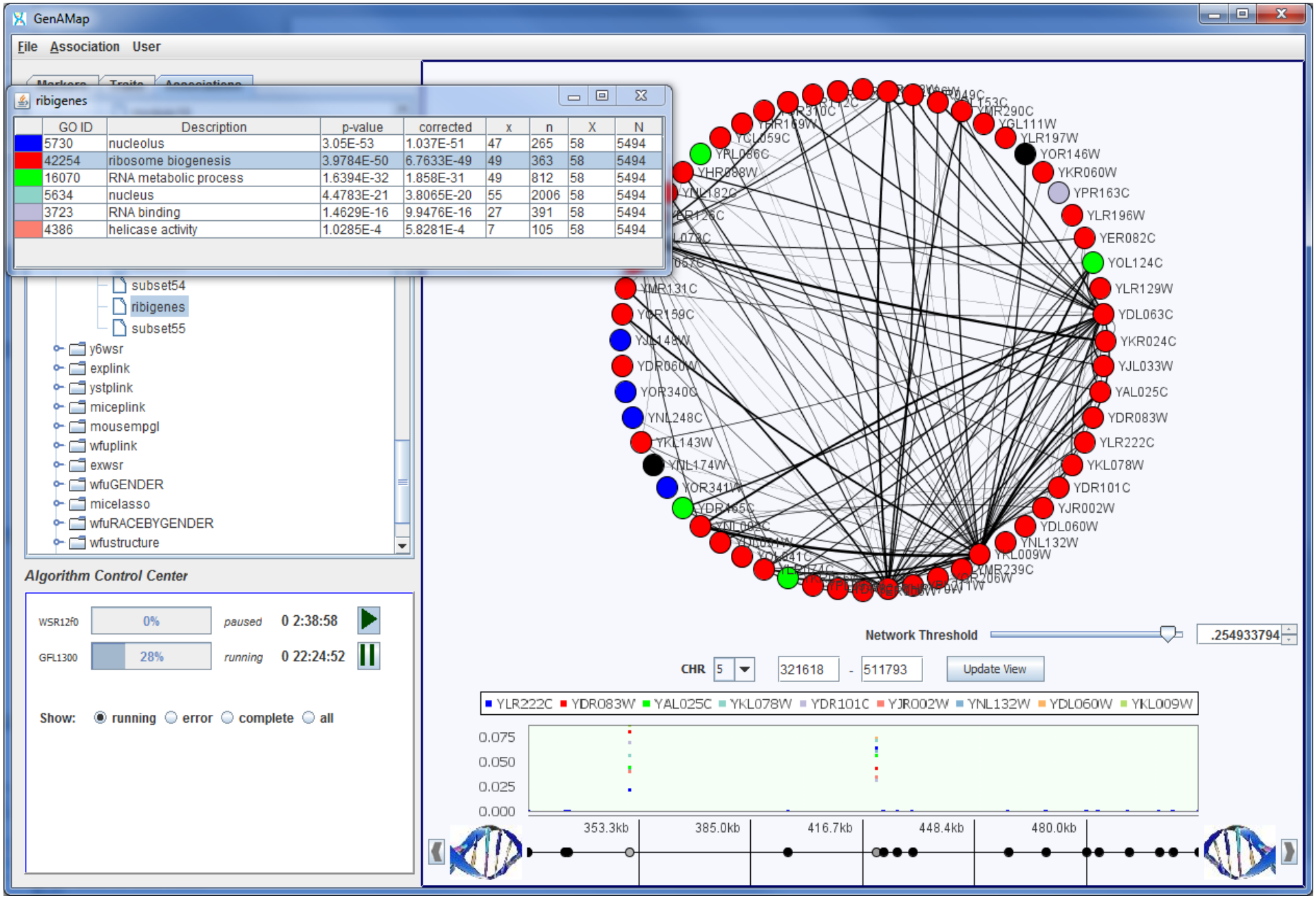
SNP in RPB5 – causal or linked?



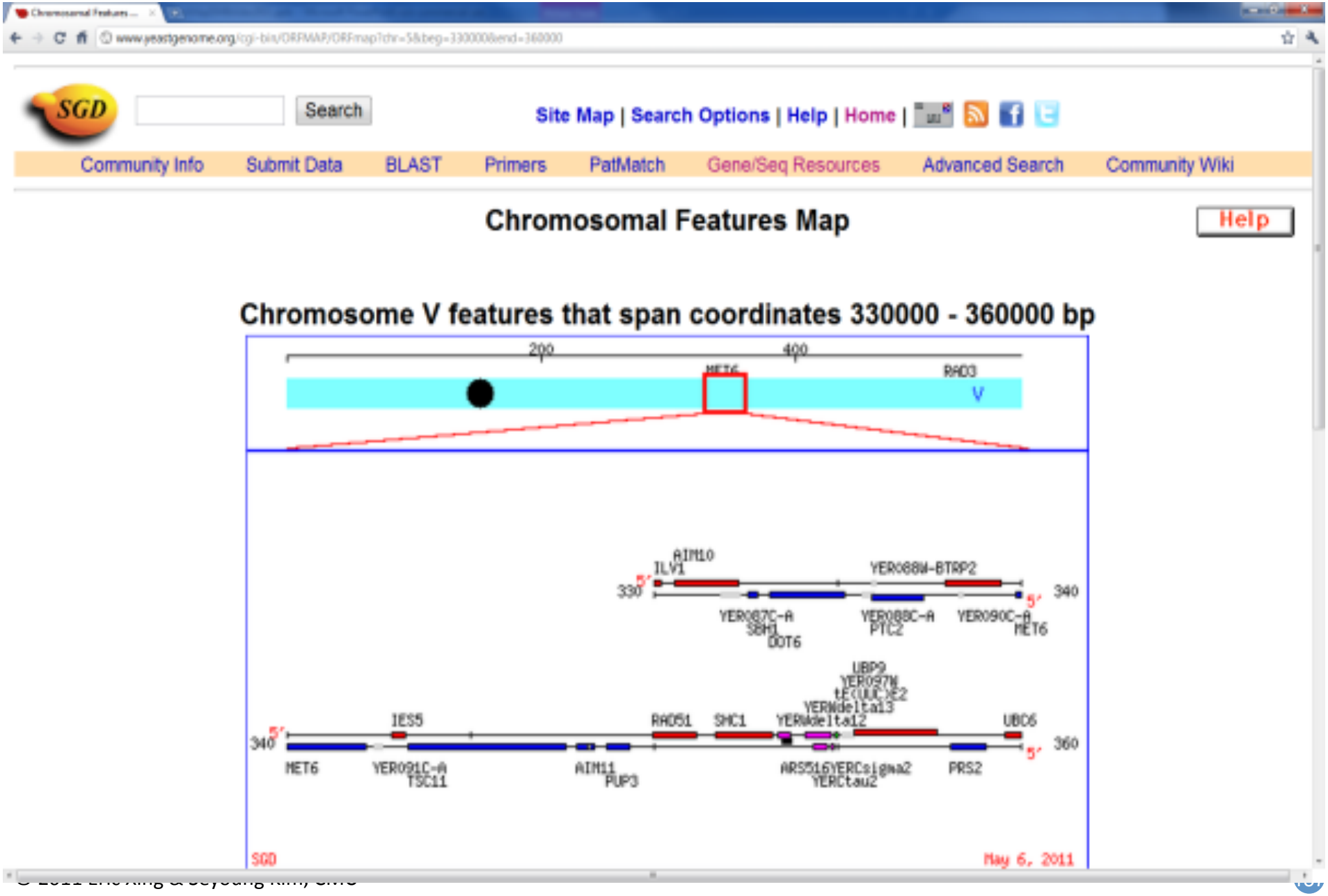
Investigate interacting eQTL hotspots

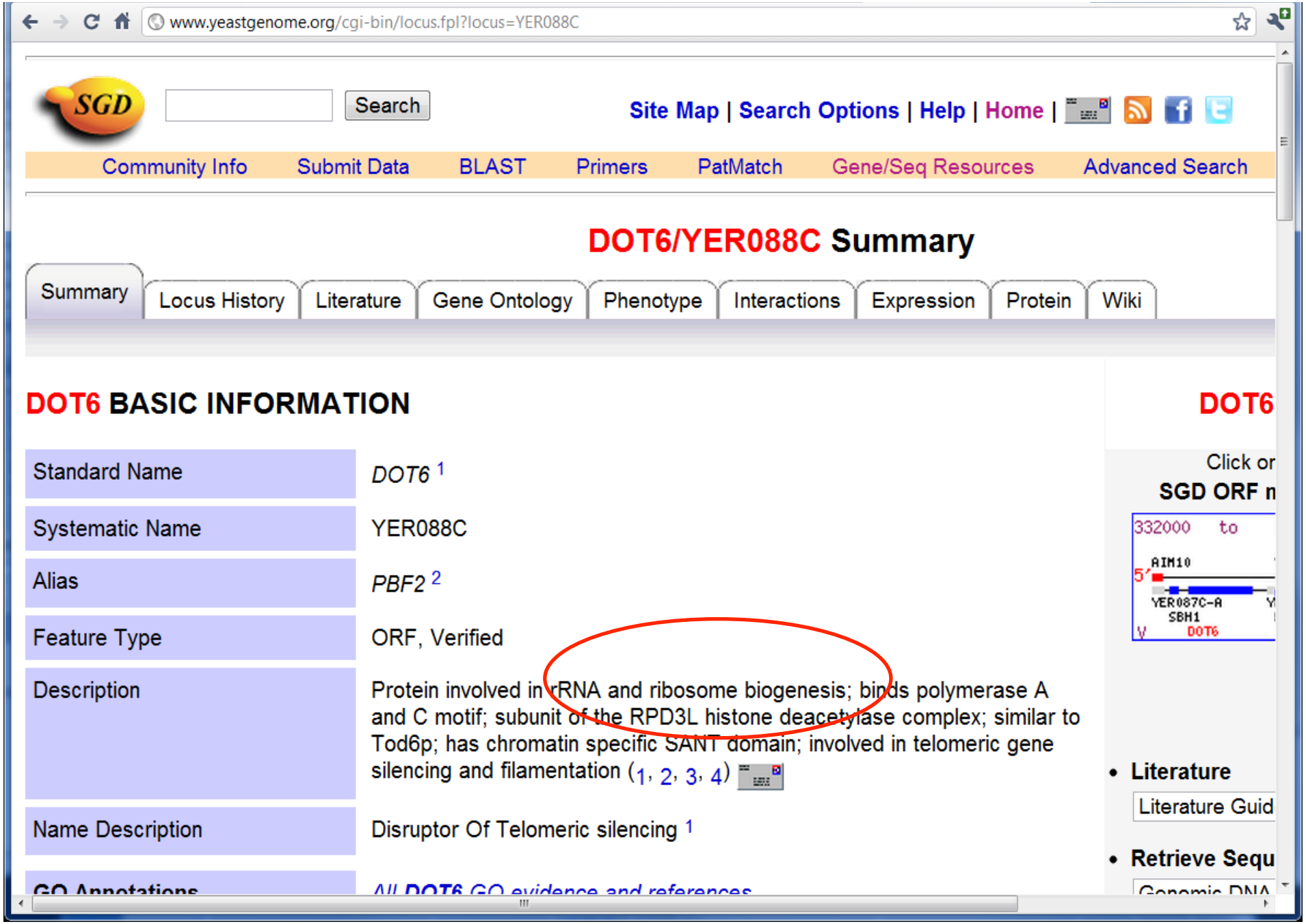


Genes are enriched for ribosome biogenesis and are associated with these SNPs on chromosome 5.

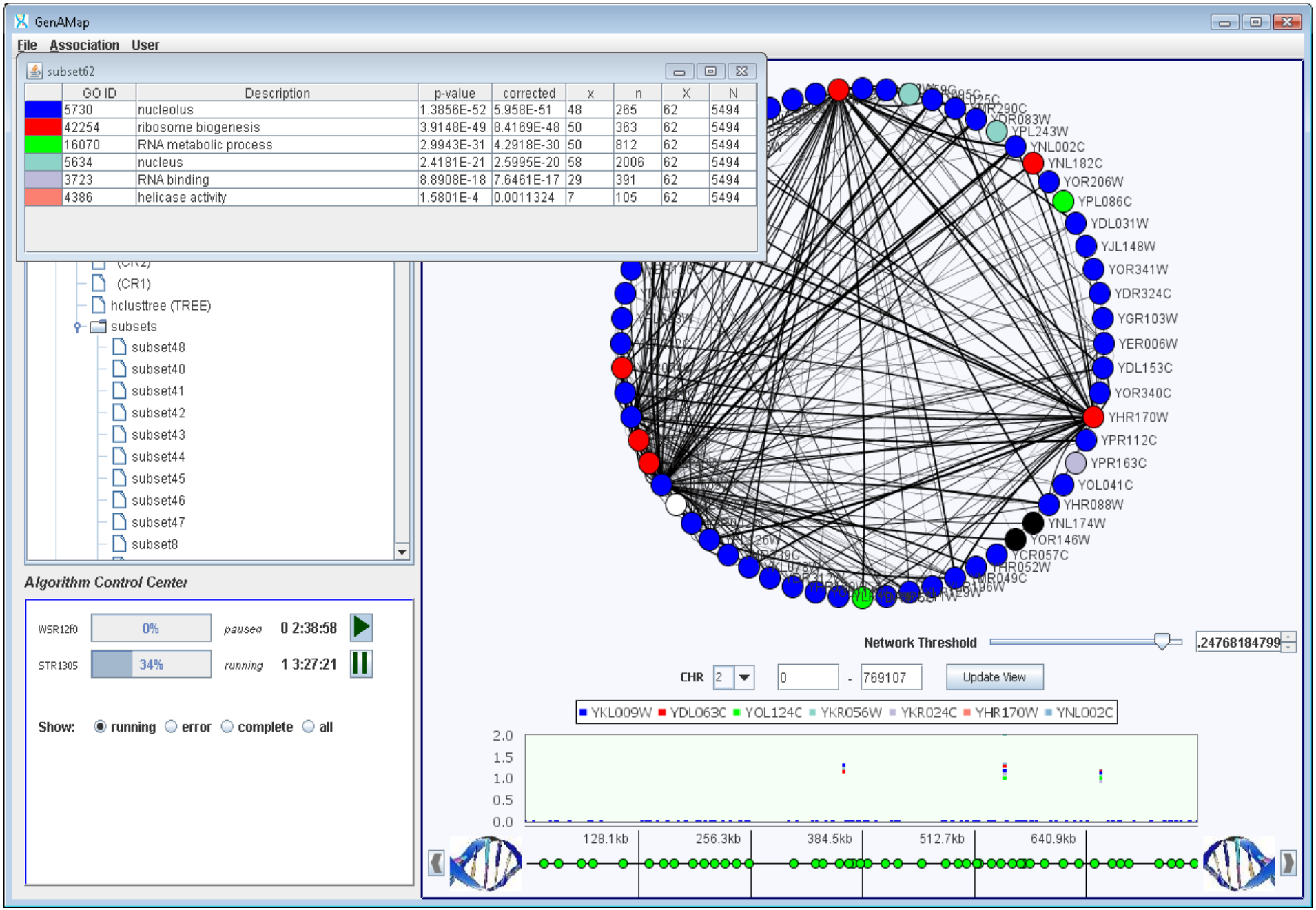


DOT6 (also known as *PBF2*) is located in *cis* with these SNPs

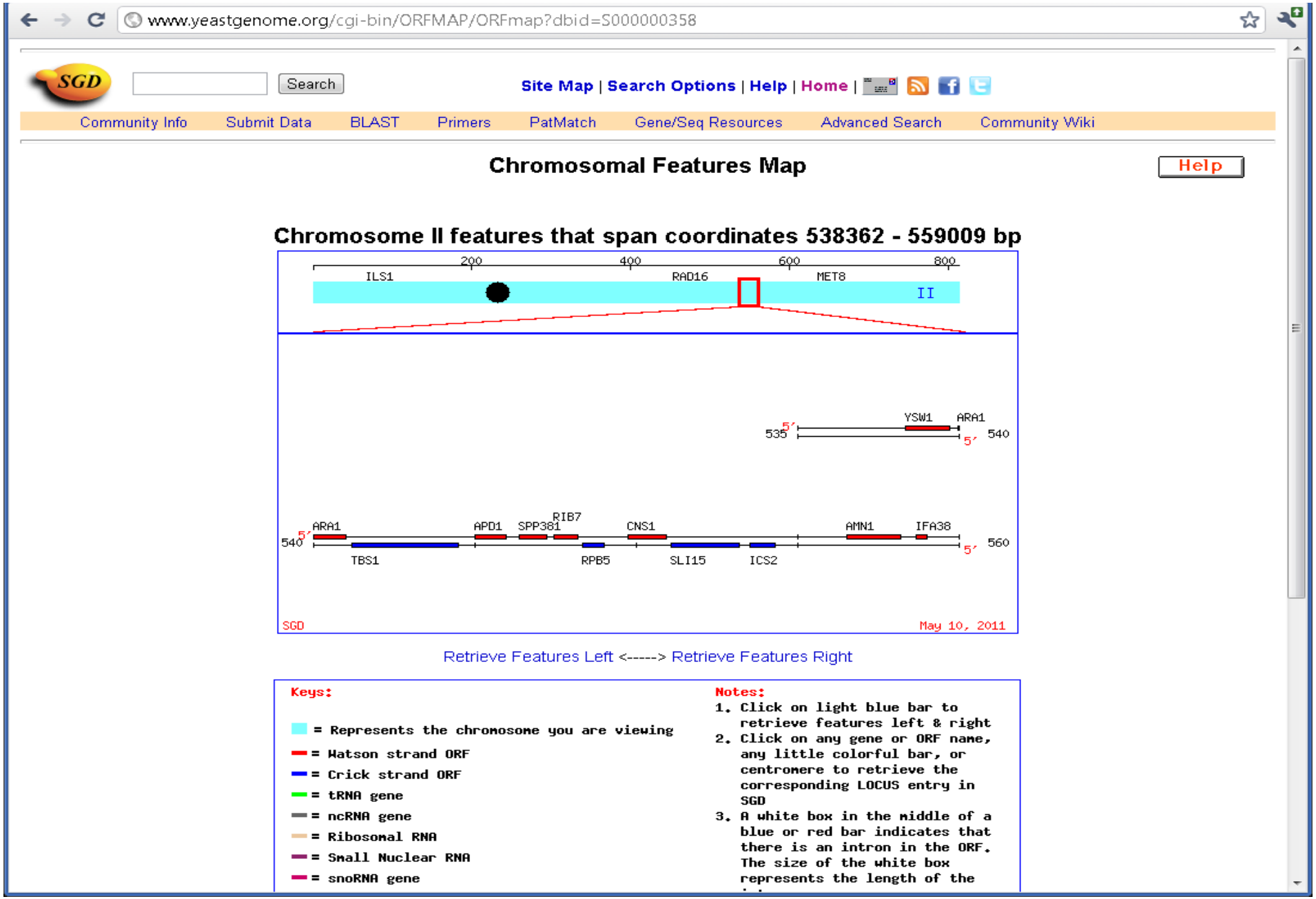



www.yeastgenome.org/cgi-bin/locus.fpl?locus=YER088C
SGD
Search
Site Map | Search Options | Help | Home |
Community Info Submit Data BLAST Primers PatMatch Gene/Seq Resources Advanced Search
DOT6/YER088C Summary
Summary Locus History Literature Gene Ontology Phenotype Interactions Expression Protein Wiki
DOT6 BASIC INFORMATION
Standard Name DOT6 1
Systematic Name YER088C
Alias PBF2 2
Feature Type ORF, Verified
Description Protein involved in rRNA and ribosome biogenesis; binds polymerase A and C motif; subunit of the RPD3L histone deacetylase complex; similar to Tod6p; has chromatin specific SANT domain; involved in telomeric gene silencing and filamentation (1, 2, 3, 4)
Name Description Disruptor Of Telomeric silencing 1
GO Annotations All DOT6 GO evidence and references
DOT6
Click or
SGD ORF n
332000 to
AIM10
5'
YER087C-A
SBH1
DOT6
Literature
Literature Guid
Retrieve Sequ
Genomic DNA

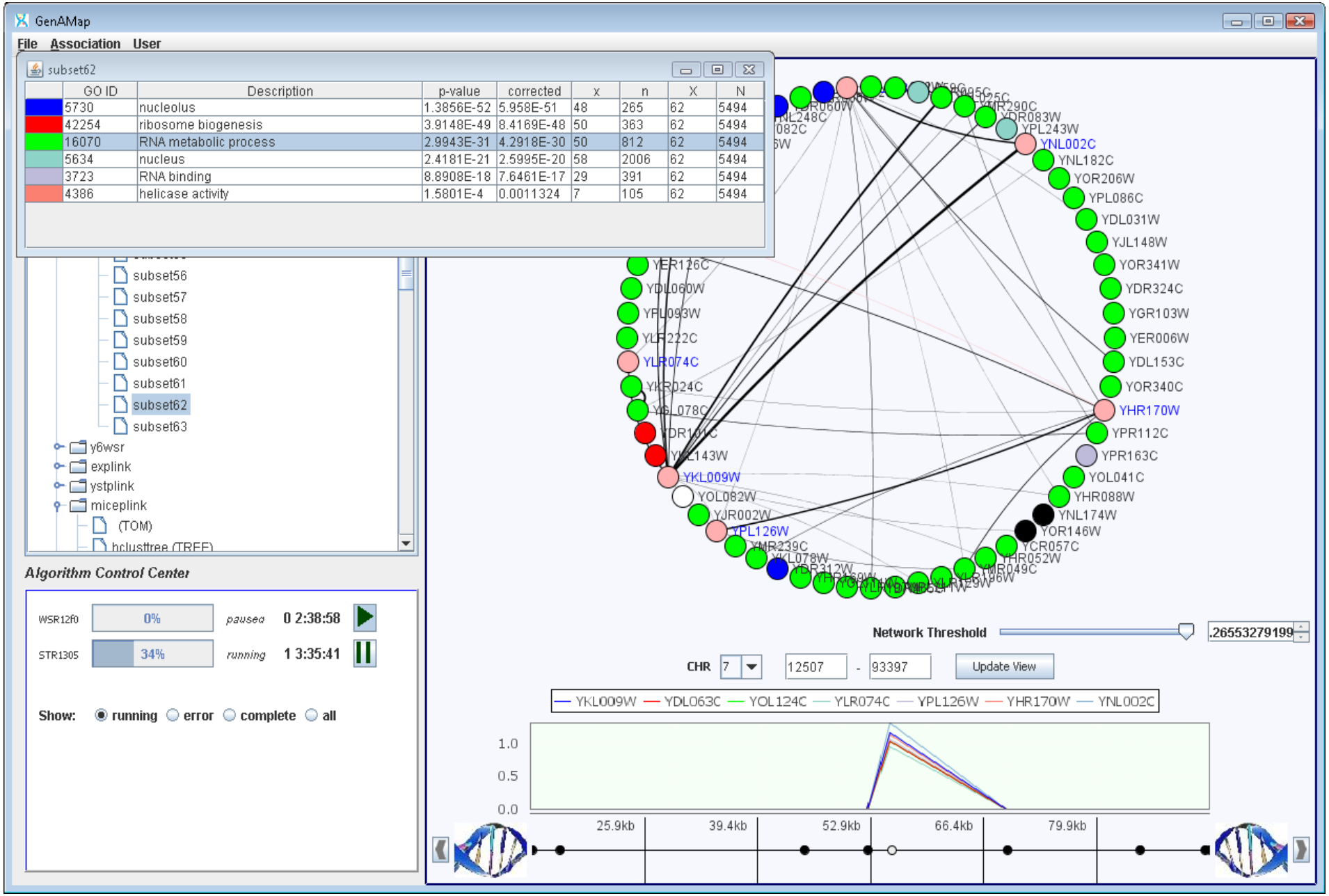
Genes are also associated with these SNPs on chromosome 2.



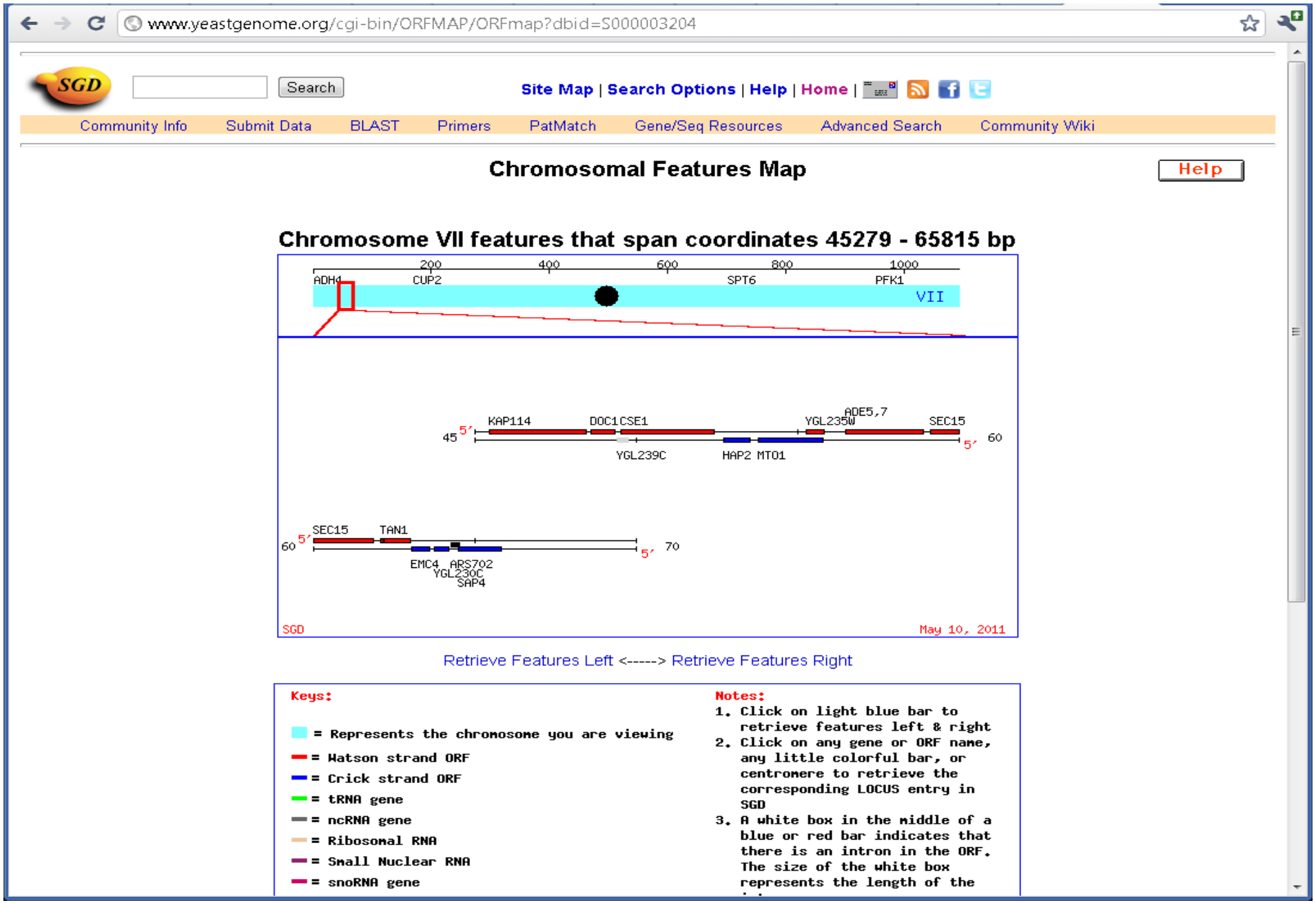
Candidate regulators on chromosome 2.



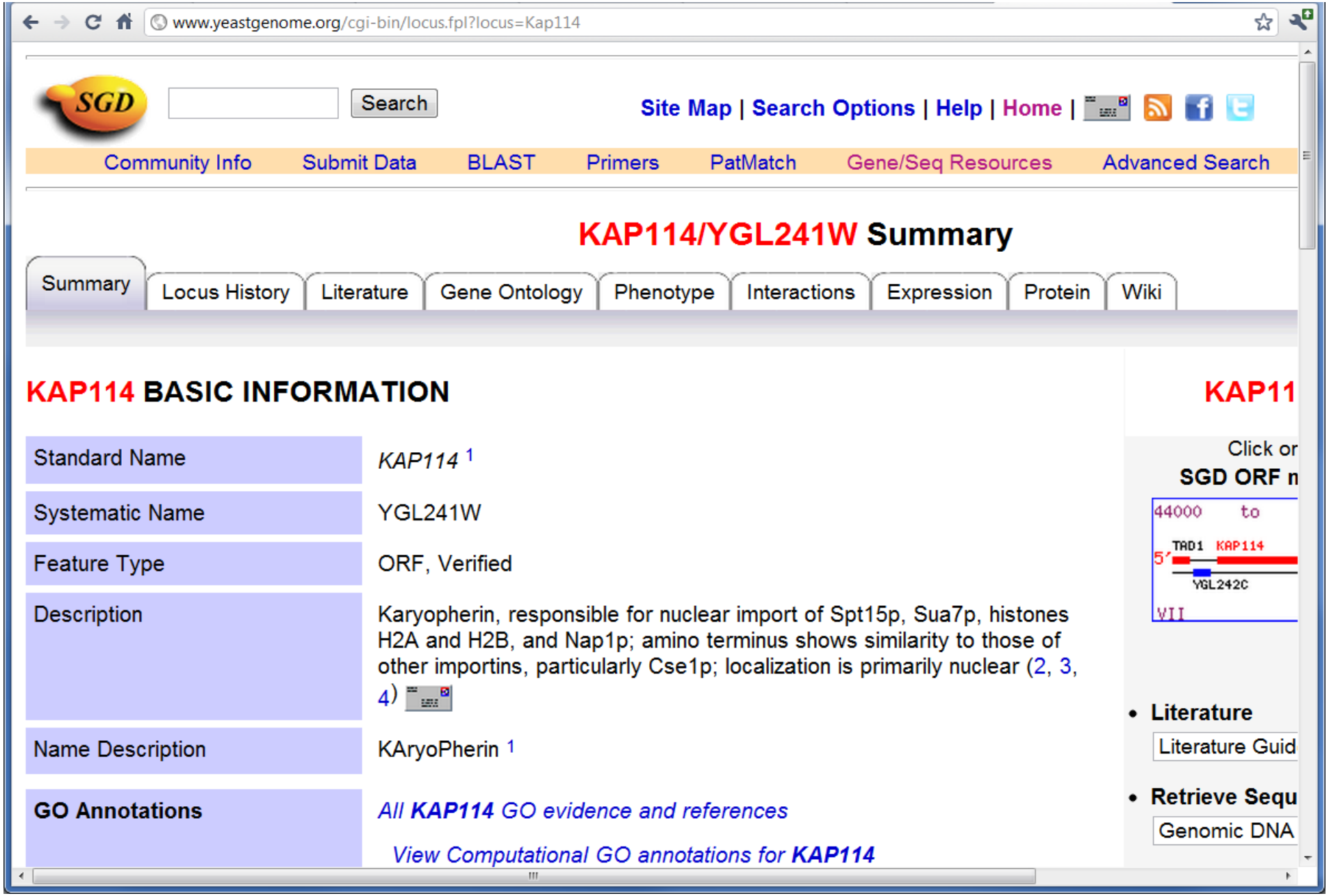
Genes are also associated with these SNPs on chromosome 7.



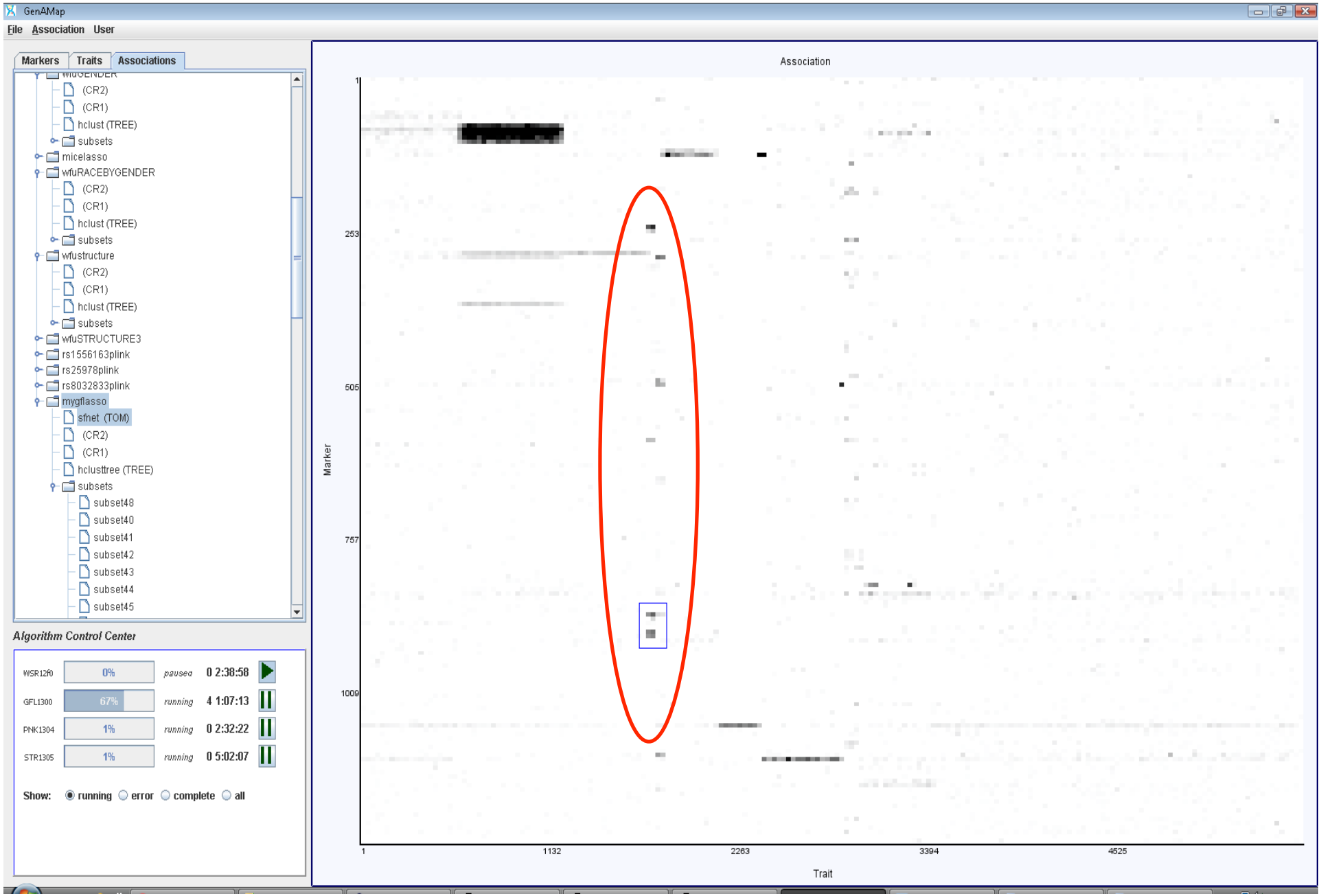
Candidate regulators on chromosome 7

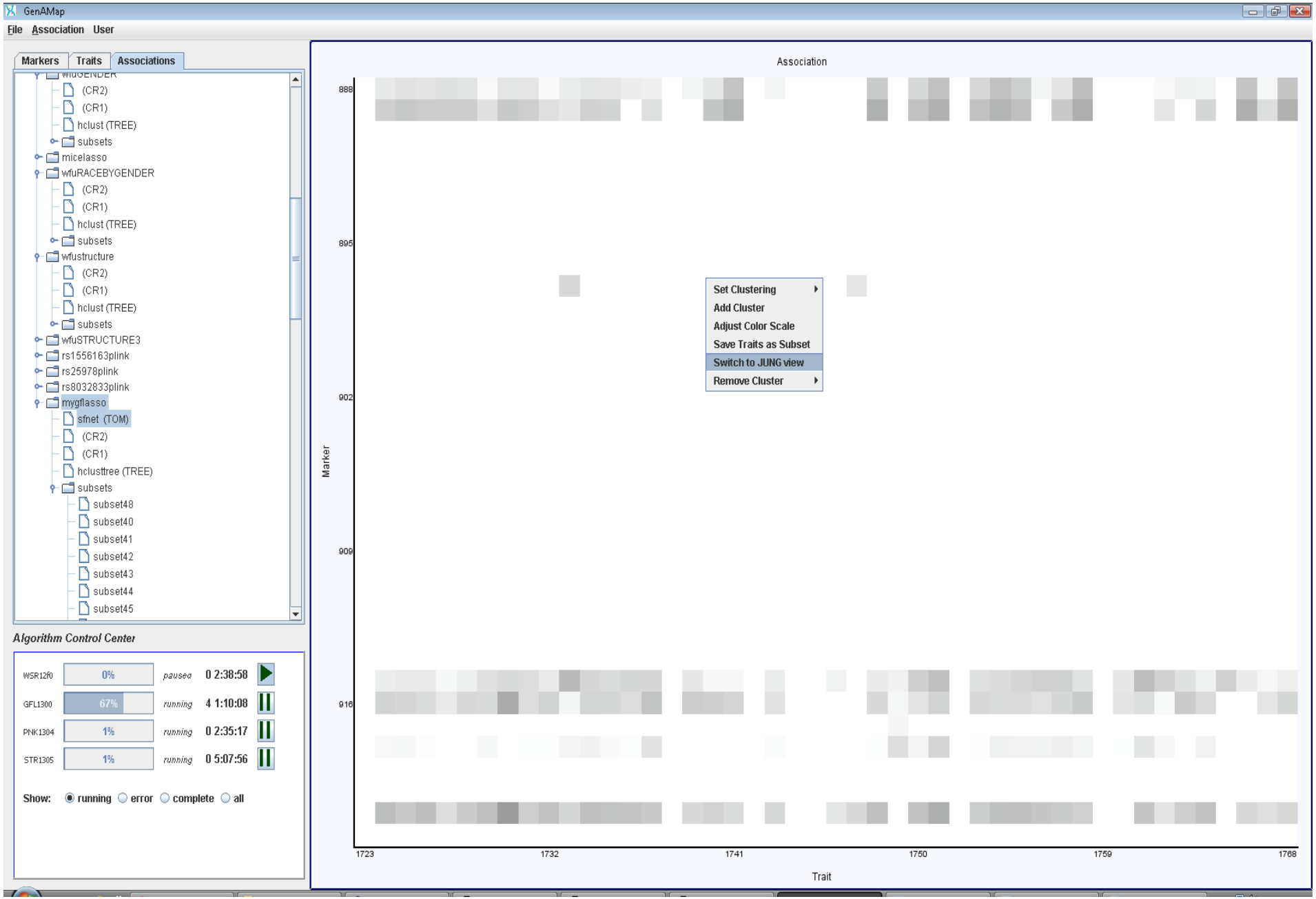


Could KAP114 also import Ribi genes?

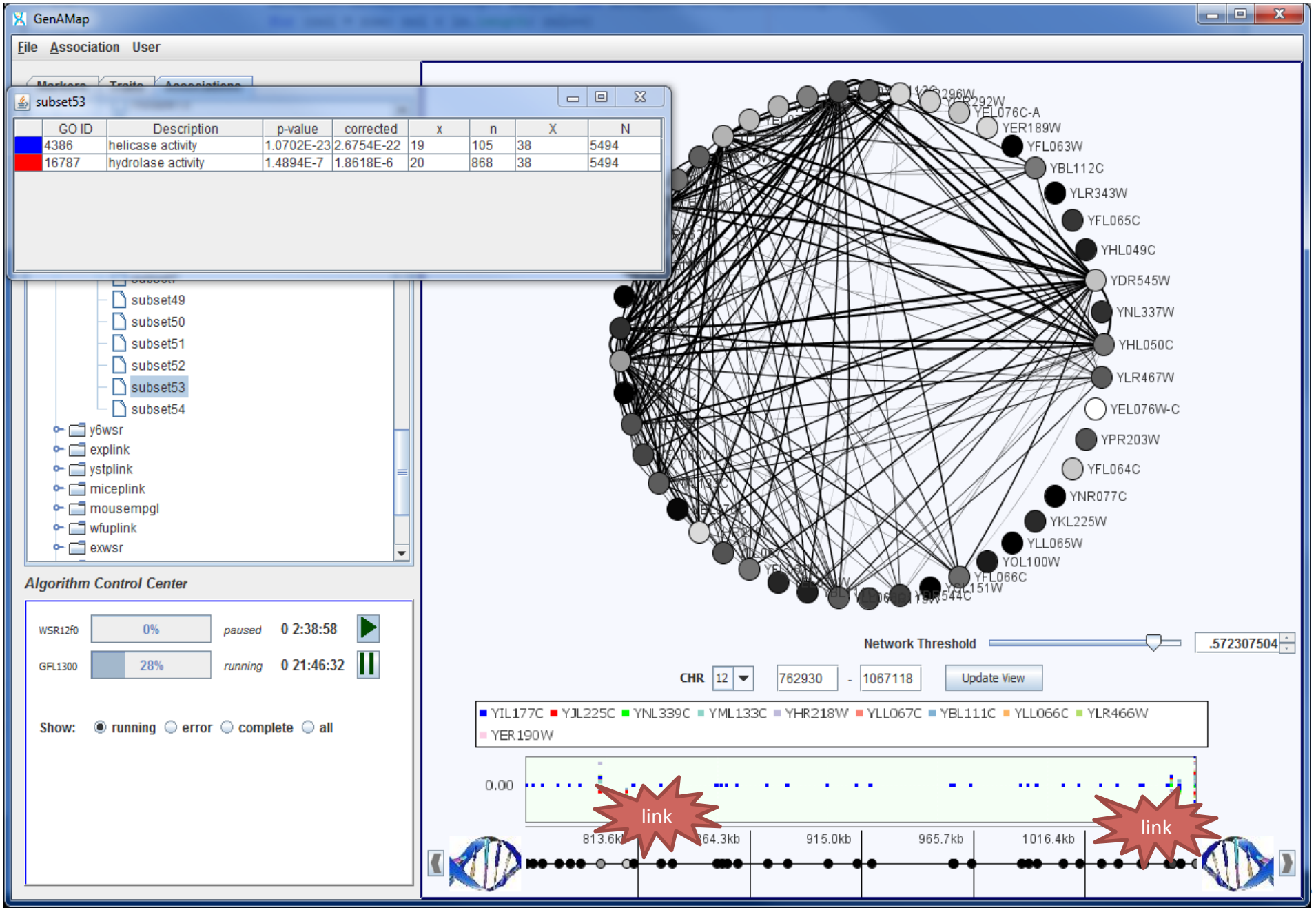


Investigate interacting eQTL hotspots

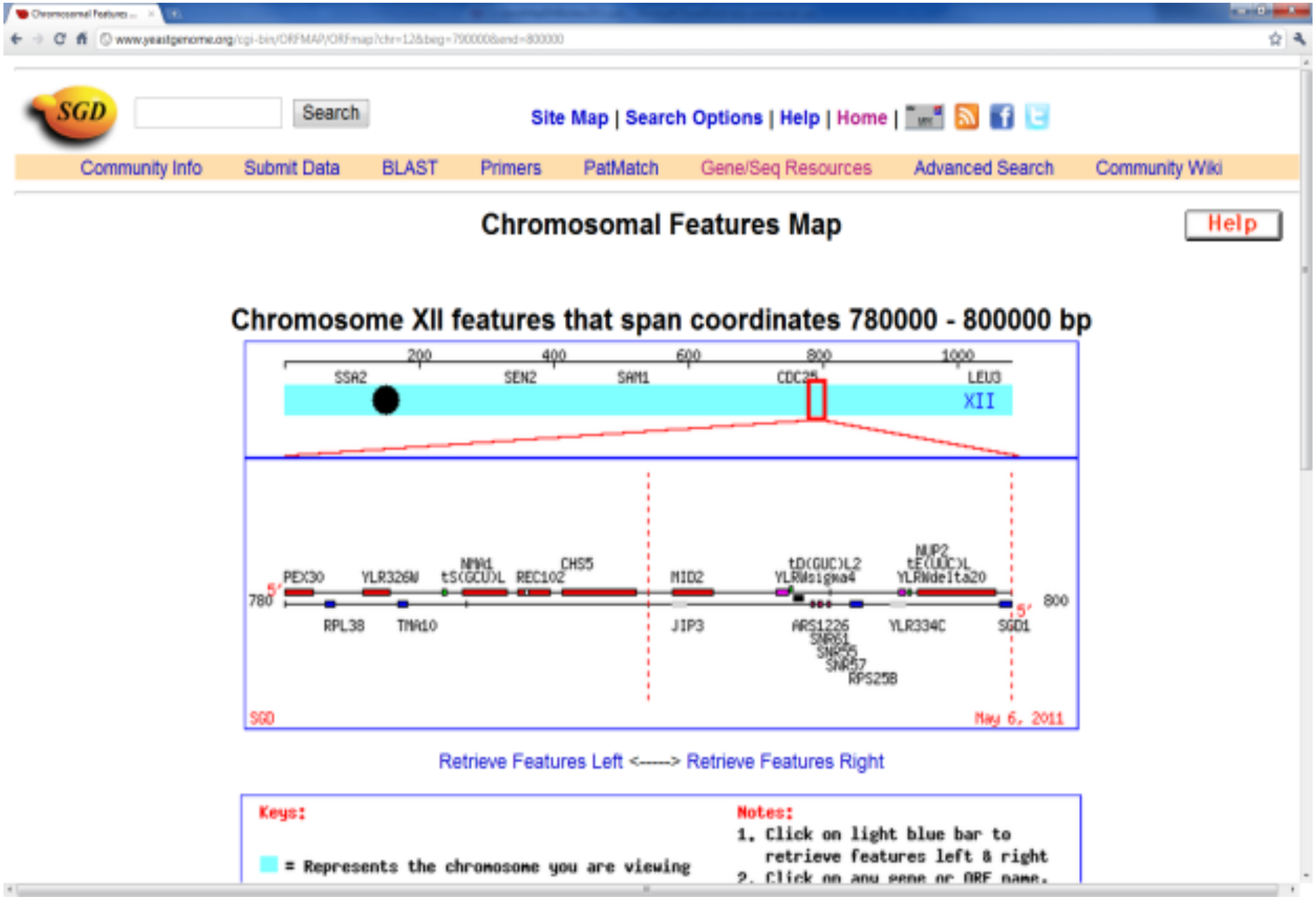


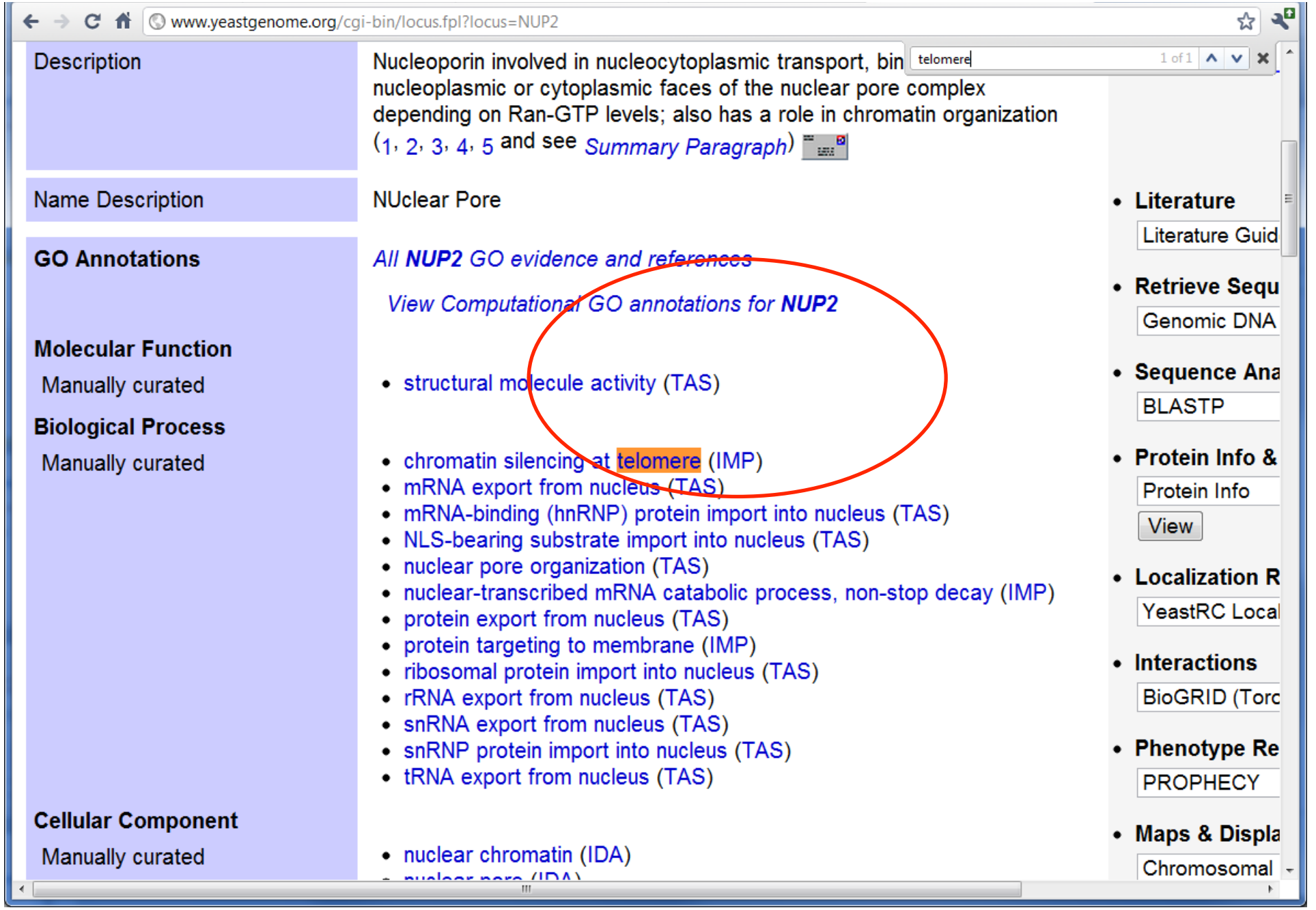

GenAMap
File Association User
Markers Traits Associations
(CR2)
(CR1)
hclust (TREE)
subsets
micelasso
wfuRACEBYGENDER
(CR2)
(CR1)
hclust (TREE)
subsets
wfustructure
(CR2)
(CR1)
hclust (TREE)
subsets
wfuSTRUCTURE3
rs1556163plink
rs25978plink
rs8032833plink
mygflasso
sfnet (TOM)
(CR2)
(CR1)
hclusttree (TREE)
subsets
subset48
subset40
subset41
subset42
subset43
subset44
subset45
Algorithm Control Center
WSR12f0 0% paused 0 2:38:58
GFL1300 67% running 4 1:10:08
PNK1304 1% running 0 2:35:17
STR1305 1% running 0 5:07:56
Show: running error complete all
Association
888
895
902
909
916
Marker
Set Clustering
Add Cluster
Adjust Color Scale
Save Traits as Subset
Switch to JUNG view
Remove Cluster
1723
1732
1741
1750
1759
1768
Trait

Two SNPs on chromosome 12 are associated with these genes.

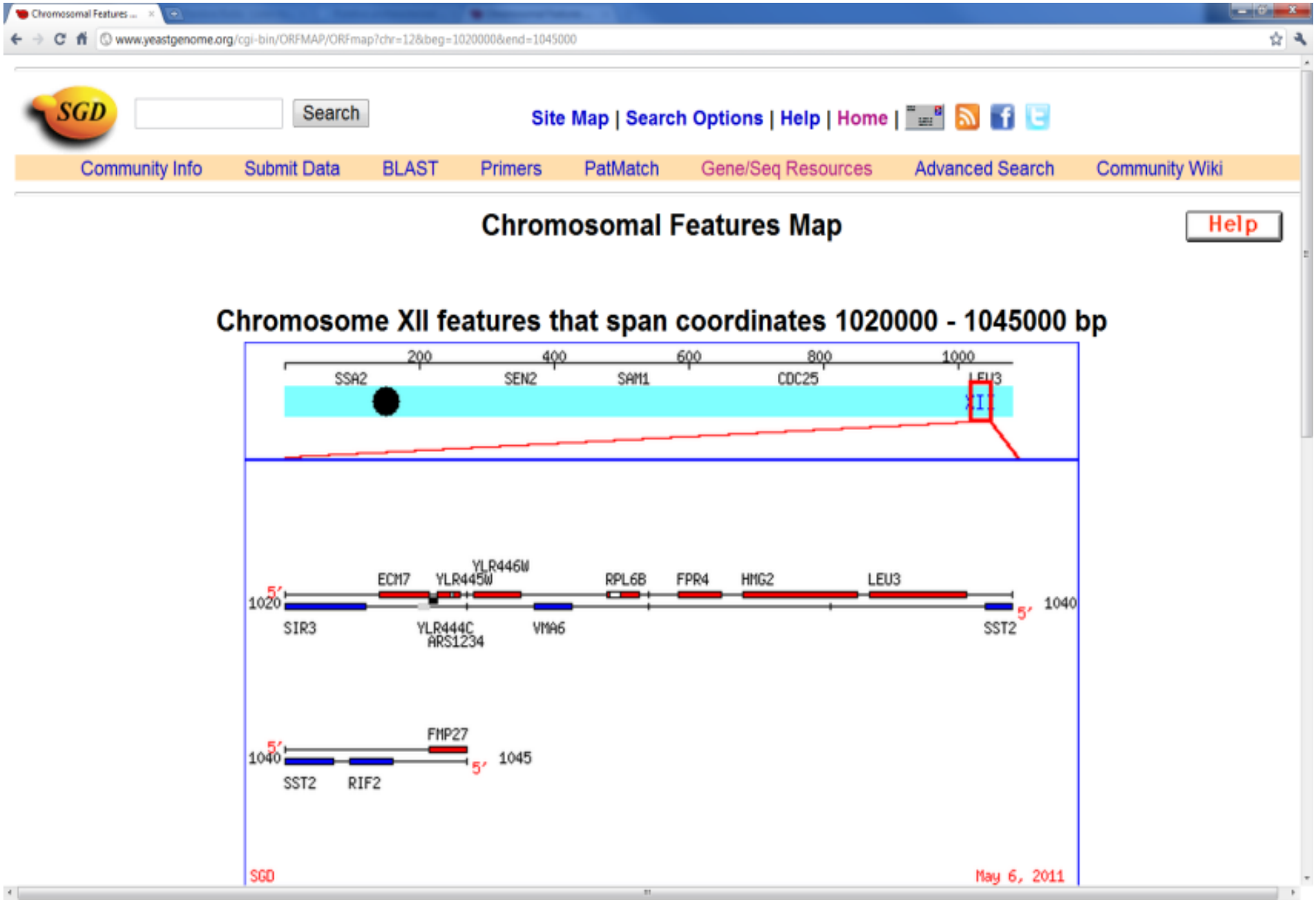


NUP2


www.yeastgenome.org/cgi-bin/ORFMAP/ORFmap?chr=12&beg=780000&end=800000
SGD
Search
Site Map | Search Options | Help | Home |
Community Info
Submit Data
BLAST
Primers
PatMatch
Gene/Seq Resources
Advanced Search
Community Wiki
Chromosomal Features Map
Help
Chromosome XII features that span coordinates 780000 - 800000 bp
200
400
600
800
1000
SSA2
SEN2
SAM1
CDC25
LEU3
XII
PEX30
YLR326W
tS(GCU)L
NMA1
REC102
CHS5
MID2
tD(GUC)L2
YLRWsigma4
NUP2
tE(UUC)L
YLRWdelta20
780
800
5'
RPL38
TMA10
JIP3
ARS1226
SNR61
SNR55
SNR57
RPS25B
YLR334C
SGD1
SGD
May 6, 2011
Retrieve Features Left <-----> Retrieve Features Right
Keys:
= Represents the chromosome you are viewing
Notes:
1. Click on light blue bar to retrieve features left & right
2. Click on any gene or ORF name.


www.yeastgenome.org/cgi-bin/locus.fpl?locus=NUP2
telomere
1 of 1
Description
Nucleoporin involved in nucleocytoplasmic transport, bin
nucleoplasmic or cytoplasmic faces of the nuclear pore complex
depending on Ran-GTP levels; also has a role in chromatin organization
(1, 2, 3, 4, 5 and see Summary Paragraph)
Name Description
NUclear Pore
GO Annotations
All NUP2 GO evidence and references
View Computational GO annotations for NUP2
Molecular Function
Manually curated
structural molecule activity (TAS)
Biological Process
Manually curated
chromatin silencing at telomere (IMP)
mRNA export from nucleus (TAS)
mRNA-binding (hnRNP) protein import into nucleus (TAS)
NLS-bearing substrate import into nucleus (TAS)
nuclear pore organization (TAS)
nuclear-transcribed mRNA catabolic process, non-stop decay (IMP)
protein export from nucleus (TAS)
protein targeting to membrane (IMP)
ribosomal protein import into nucleus (TAS)
rRNA export from nucleus (TAS)
snRNA export from nucleus (TAS)
snRNP protein import into nucleus (TAS)
tRNA export from nucleus (TAS)
Cellular Component
Manually curated
nuclear chromatin (IDA)
Literature
Literature Guid
Retrieve Sequ
Genomic DNA
Sequence Ana
BLASTP
Protein Info &
Protein Info
View
Localization R
YeastRC Local
Interactions
BioGRID (Torc
Phenotype Re
PROPHECY
Maps & Displa
Chromosomal

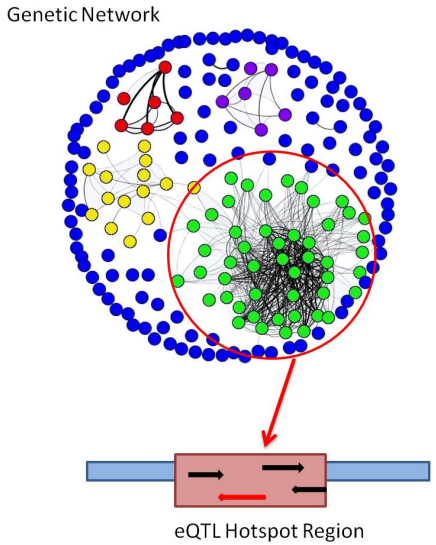
SIR3 / RIF2


Chromosomal Features ...
www.yeastgenome.org/cgi-bin/ORFMAP/ORFmap?chr=12&beg=1020000&end=1045000
SGD
Search
Site Map | Search Options | Help | Home |
Community Info
Submit Data
BLAST
Primers
PatMatch
Gene/Seq Resources
Advanced Search
Community Wiki
Chromosomal Features Map
Help
Chromosome XII features that span coordinates 1020000 - 1045000 bp
200
400
600
800
1000
SSA2
SEN2
SAM1
CDC25
LEU3
XII
YLR446W
ECM7
YLR445W
RPL6B
FPR4
HMG2
LEU3
5′
1020
1040
SIR3
YLR444C
ARS1234
VMA6
SST2
FMP27
1045
RIF2
SGD
May 6, 2011

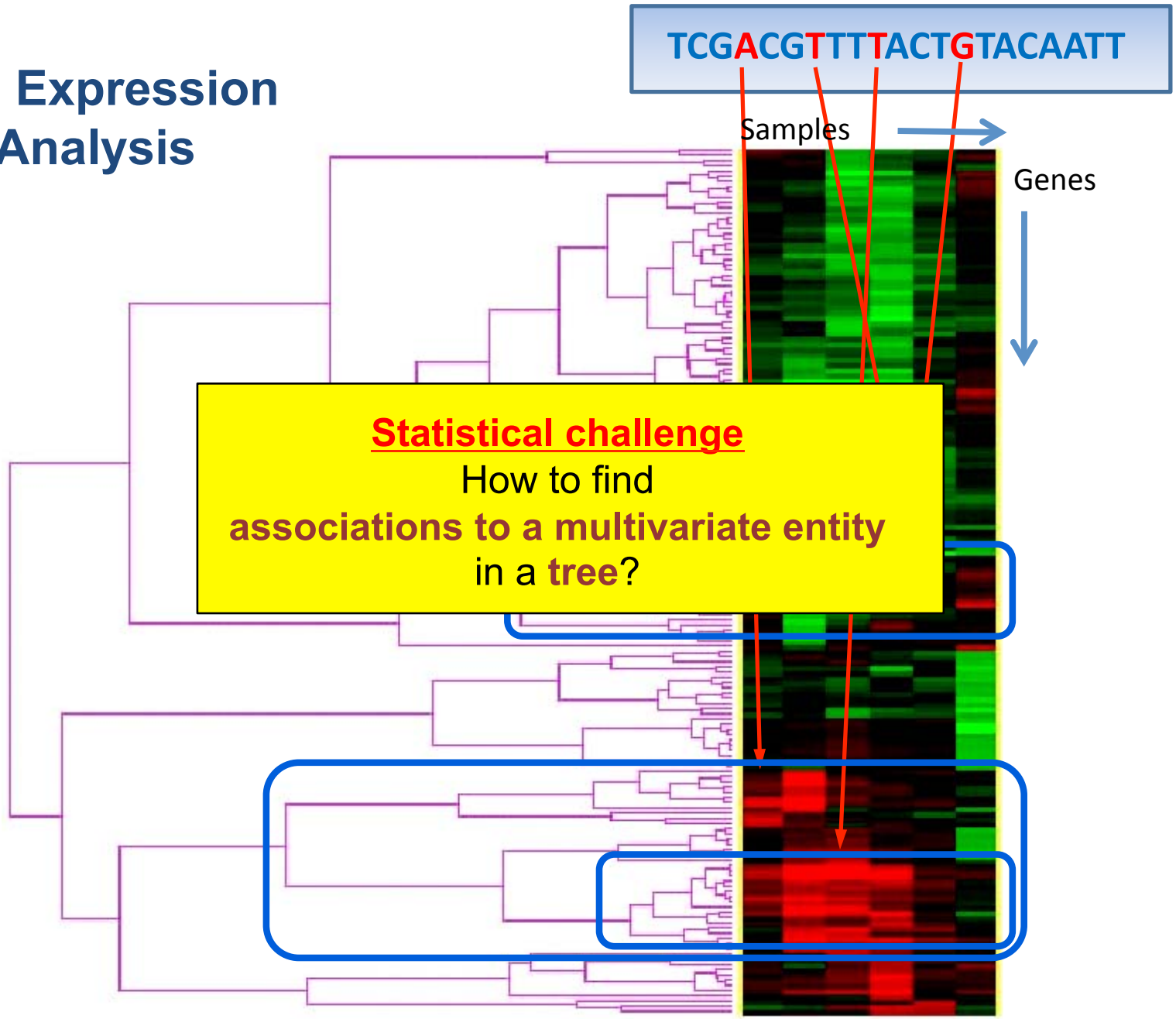

www.yeastgenome.org/cgi-bin/locus.fpl?locus=SIR3
SGD
Search
Site Map | Search Options | Help | Home |
Community Info Submit Data BLAST Primers PatMatch Gene/Seq Resources Advanced Search
SIR3/YLR442C Summary
Summary Locus History Literature Gene Ontology Phenotype Interactions Expression Protein Wiki
SIR3 BASIC INFORMATION
Standard Name SIR3 1
Systematic Name YLR442C
Alias CMT1 2 , MAR2 3 , 4 , STE8 5
Feature Type ORF, Verified
Description Silencing protein that interacts with Sir2p and Sir4p, and histone H3 and H4 tails; to establish a transcriptionally silent chromatin state; required for spreading of silenced chromatin; recruited to chromatin through interaction with Rap1p (1, 6, 7 and see Summary Paragraph)
Name Description Silent Information Regulator 1
SIR3
Click or
SGD ORF n
1018000 to 1
5′
RPS1A
SIR3
XII
Literature
Literature Guid
Retrieve Sequ
Genomic DNA
Sequence Ana

Summary

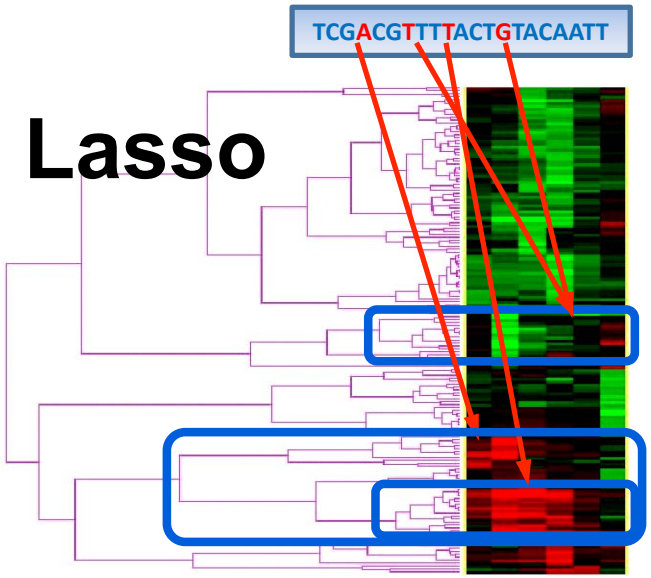
- Exploiting transcriptome structure in association analysis
  - Pleiotropy
    - Pathway-based statistical tests
    - Leveraging gene expression network
- Structured association – a new paradigm
  - Association to a **graph**-structured transcriptome
    - Graph-guided fused lasso (Kim & Xing, PLoS Genetics, 2009)
- More structures (next)
  - Leveraging gene expression hierarchical cluster
  - Association to a **tree**-structured transcriptome
    - Tree-guided group lasso (Kim & Xing, ICML 2010)



Gene Expression Trait Analysis



Tree-Guided Group Lasso

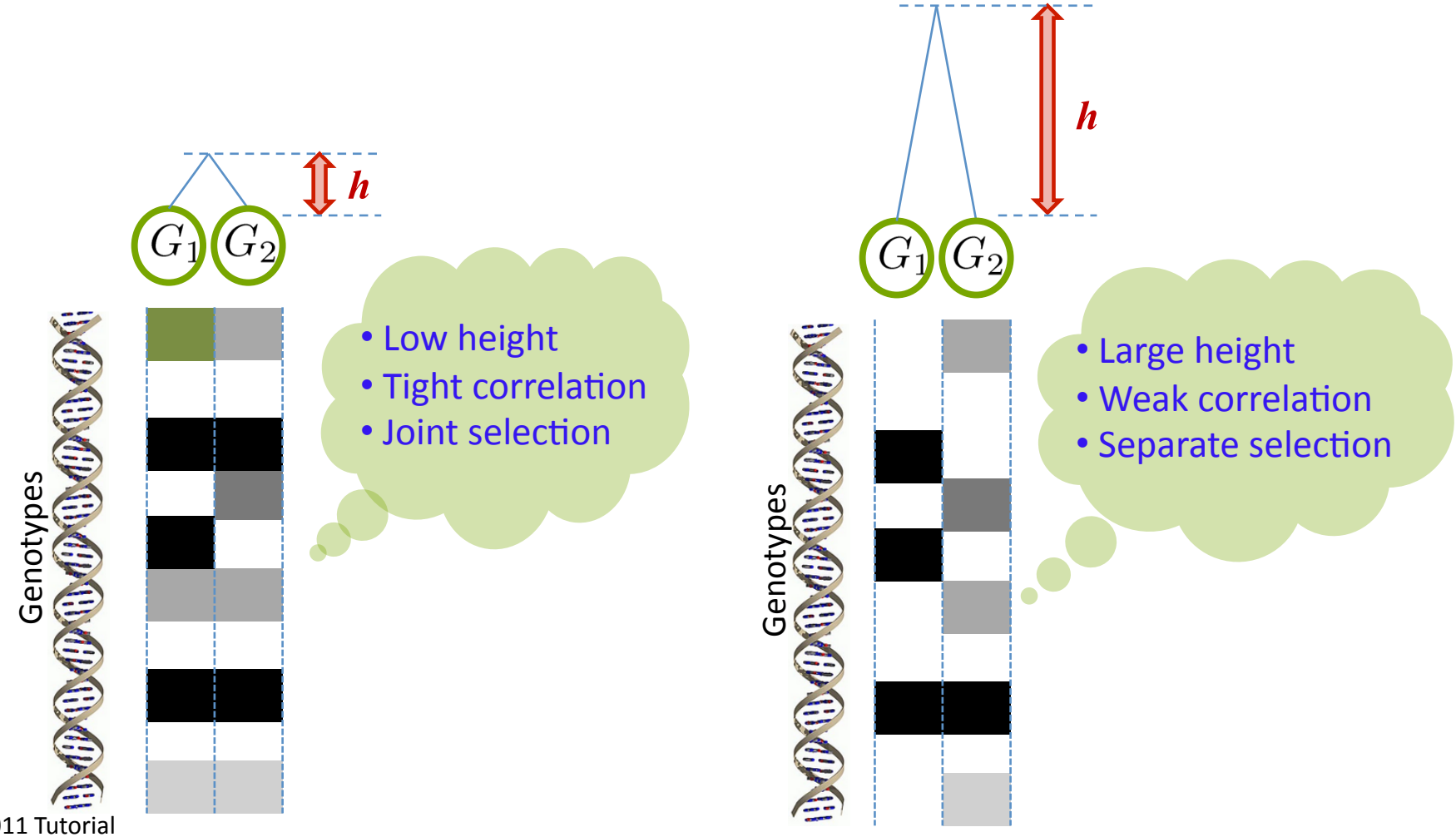


- Why tree?
  - Tree represents a clustering structure
  - Scalability to a very large number of phenotypes
    - Graph : $O(|V|^2)$ edges
    - Tree : $O(|V|)$ edges
  - Expression quantitative trait mapping (eQTL)
    - Agglomerative hierarchical clustering is a popular tool

Kim & Xing, ICML 2010

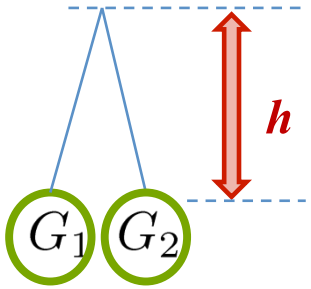
Tree-Guided Group Lasso

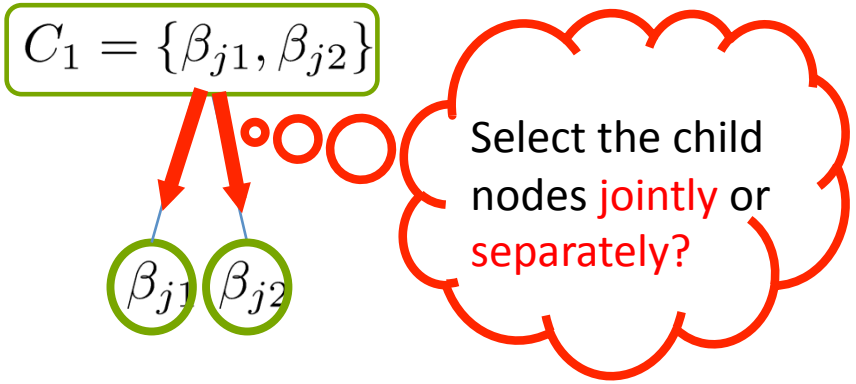
- In a simple case of two genes

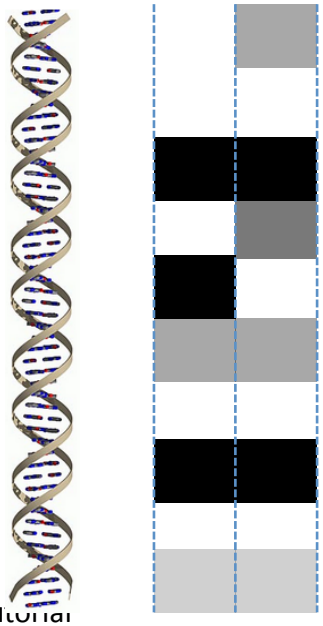


Tree-Guided Group Lasso

- In a simple case of two genes







Tree-guided group lasso

$$\text{argmin}\ (y - X\beta)' \cdot (y - X\beta)$$
$$+\lambda \sum_j \left[h\left(|\beta_{j1}| + |\beta_{j2}|\right) + (1-h)\left(\sqrt{\beta_{j1}^2 + \beta_{j2}^2}\right) \right]$$

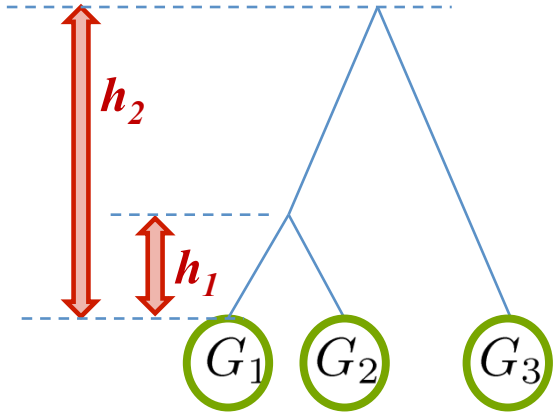
L_1 penalty
- Lasso penalty
- **Separate** selection

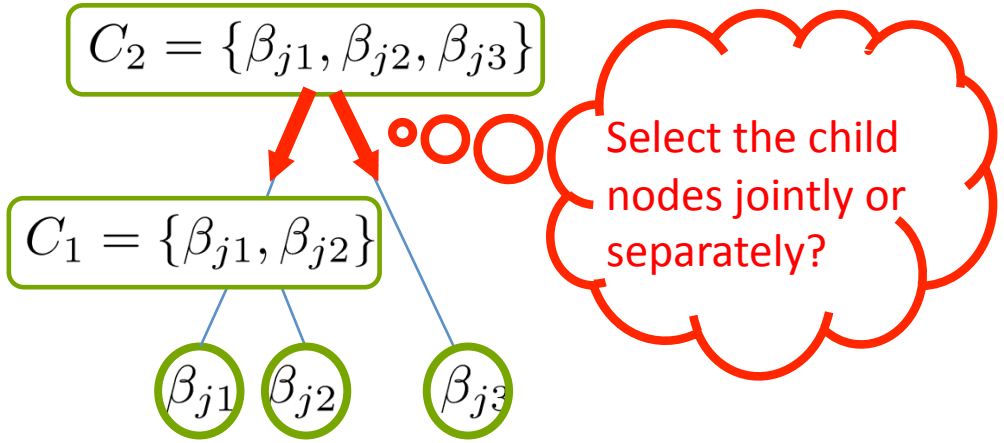
L_2 penalty
- Group lasso
- **Joint** selection

Similar to elastic net (Zou & Hastie, J. R. Statist. Soc. 2005)

Tree-Guided Group Lasso

- For a general tree





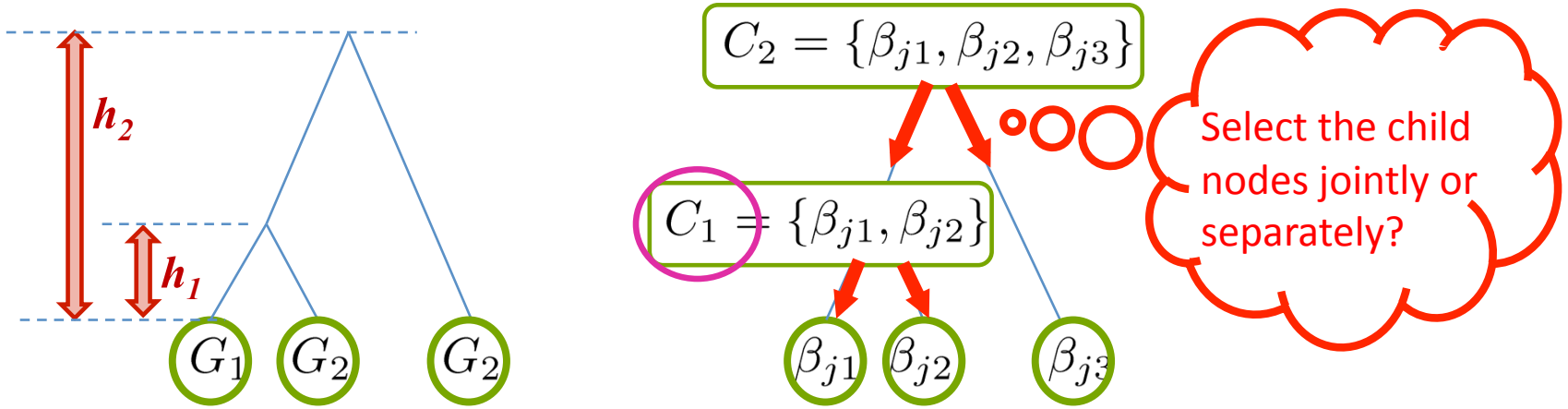
Tree-guided group lasso

$$\text{argmin} \ (y - X\beta)' \cdot (y - X\beta)$$
$$+\lambda \sum_j \left[(1 - h_2) \left(\sqrt{\beta_{j1}^2 + \beta_{j2}^2 + \beta_{j3}^2} \right) + h_2 \left(|C_1| + |\beta_{j3}| \right) \right]$$

Joint selection **Separate selection**

Tree-Guided Group Lasso

- For a general tree



Tree-guided group lasso

$$\text{argmin } (y - X\beta)' \cdot (y - X\beta)$$

$$+\lambda \sum_j \left[(1-h_2)\left(\sqrt{\beta_{j1}^2 + \beta_{j2}^2 + \beta_{j3}^2}\right) + h_2\left(|C_1| + |\beta_{j3}|\right) \right]$$

$$(1-h_1)\left(\sqrt{\beta_{j1}^2 + \beta_{j2}^2}\right) + h_1\left(|\beta_{j1}| + |\beta_{j2}|\right)$$

Joint selection **Separate selection**

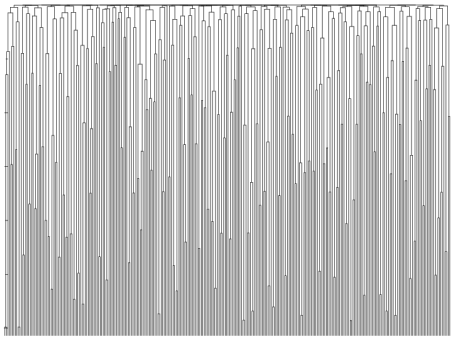
Estimating Parameters

- Second-order cone program

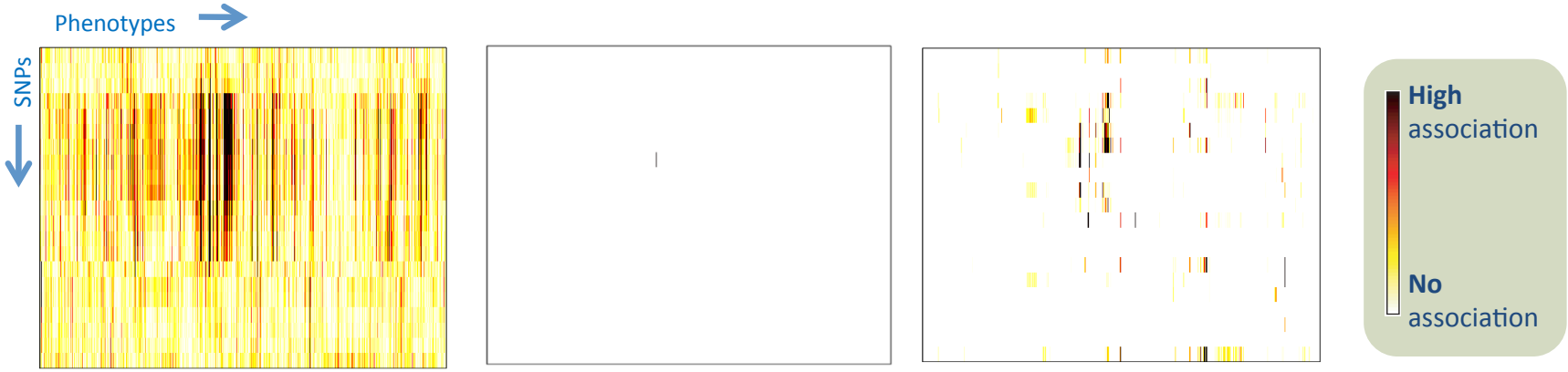
$$\hat{\mathbf{B}}^T = \text{argmin} \sum_k (\mathbf{y}_k - \mathbf{X}\beta_k)^T \cdot (\mathbf{y}_k - \mathbf{X}\beta_k) + \lambda \sum_j \sum_{v \in V} w_v \|\beta^j_{G_v}\|_2$$

  - Many publicly available software packages for solving convex optimization problems can be used

Yeast eQTL Analysis



Hierarchical clustering tree



Single-Marker Single-Trait Test

Lasso

Tree-guided group lasso

Summary

- Exploiting transcriptome structure in association analysis

  - Pleiotropy
    - Pathway-based statistical tests

    - Leveraging gene expression network
      - Association to a **graph**-structured transcriptome using graph-guided fused lasso

    - Leveraging gene expression hierarchical cluster
      - Association to a **tree**-structured transcriptome using tree-guided group lasso

Summary: why care about structure?

- Theoretically, it increase the power [Mladen and Xing, 2010]

$$\mathbb{P}[\mathcal{M}_* \subseteq \mathcal{M}^{(m^*_{\max})}] \geq 1 - C_1 \exp\left(-C_2 \frac{n^{1-6\delta_s-6\delta_{\min}}}{\max\{\log(p), \log(T)\}}\right)$$

Summary: why care about structure?

- Incorporating more information leads to enhanced discovery and lower false discovery (results from simulation test)
  - If our underlying model is correct!

Method	Power (multi-trait)	FDR
GFlasso	0.889	0.009
plink	0.803	0.014
Sum-rank	0.748	0.008
Screen & Clean	0.780	0.153
Lasso	0.991	0.886
Forward Selection	0.931	0.867

Improving Scalability of Structured Genome-Transcriptome-Phenome Association Methods

- Common challenges in optimization
  - Tree-guided group lasso, GFlasso, temporally-smoothed lasso
    - Non-smooth penalty
    - Non-separability
      - Coordinate descent algorithm (Friedman et al., Annals of Applied Statistics 2007) cannot be applied.

- Proximal-gradient method (Xi et al., submitted)
  - Step 1: Introduce a smooth approximation to the non-smooth penalty
  - Step 2: Apply accelerated gradient method

Proximal Gradient Descent

Original Problem:

$$\arg\min_{\boldsymbol{\beta}\in\mathbb{R}^J} f(\boldsymbol{\beta}) \equiv \frac{1}{2}\|\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\|_2^2 + \Omega(\boldsymbol{\beta})$$

$$\Omega(\boldsymbol{\beta}) = \max_{\boldsymbol{\alpha}\in\mathcal{Q}} \boldsymbol{\alpha}^T C\boldsymbol{\beta}$$

Approximation Problem:

$$\arg\min_{\boldsymbol{\beta}\in\mathbb{R}^J} \widetilde{f}(\boldsymbol{\beta}) \equiv \frac{1}{2}\|\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\|_2^2 + f_\mu(\boldsymbol{\beta})$$

$$f_\mu(\boldsymbol{\beta}) = \max_{\boldsymbol{\alpha}\in\mathcal{Q}} \boldsymbol{\alpha}^T C\boldsymbol{\beta} - \mu d(\boldsymbol{\alpha})$$

Gradient of the Approximation:

$$\nabla\widetilde{f}(\boldsymbol{\beta}) = \mathbf{X}^T(\mathbf{X}\boldsymbol{\beta}-\mathbf{y}) + C^T\boldsymbol{\alpha}^*$$

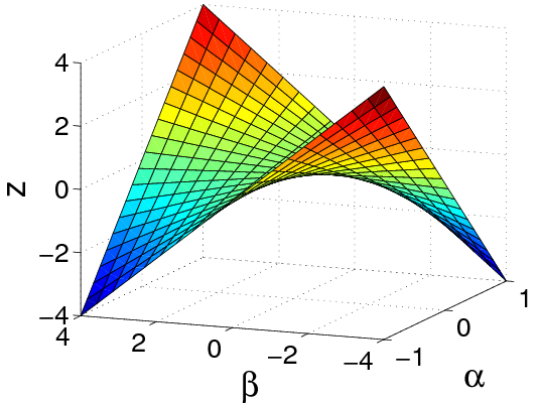
$$\boldsymbol{\alpha}^* = \arg\max_{\boldsymbol{\alpha}\in\mathcal{Q}} \boldsymbol{\alpha}^T C\boldsymbol{\beta} - \mu d(\boldsymbol{\alpha})$$

$\nabla\widetilde{f}(\boldsymbol{\beta})$ is Lipschitz continuous with the Lipschitz constant L

$$L = \lambda_{\max}(\mathbf{X}^T\mathbf{X}) + L_\mu$$

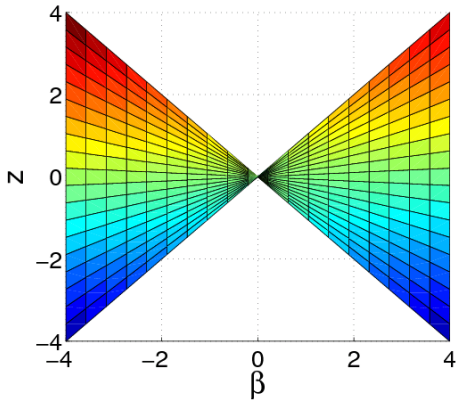
Geometric Interpretation

- Smooth approximation

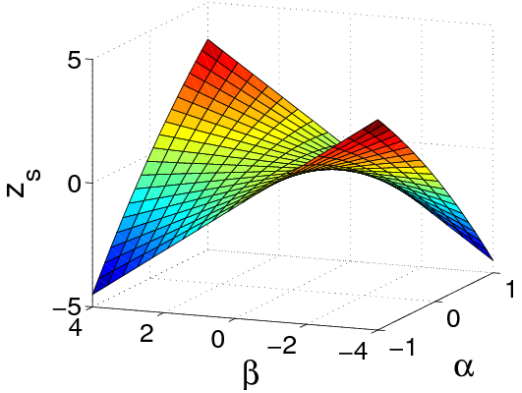


$z(\alpha, \beta) = \alpha\beta$

Projection onto $z - \beta$ Plane



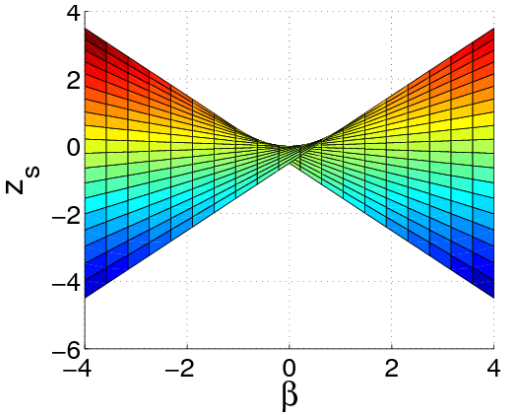
Uppermost Line Nonsmooth



$z_s(\alpha, \beta) = \alpha\beta - \frac{1}{2}\alpha^2$

Projection onto $z_s - \beta$ Plane

$f_0(\beta) = \max_{\alpha \in [-1,1]} z(\alpha, \beta) = |\beta|$



Uppermost Line Smooth

$f_1(\beta) = \max_{\alpha \in [-1,1]} z_s(\alpha, \beta)$

Convergence Rate

Theorem: If we require $f(\boldsymbol{\beta}^t) - f(\boldsymbol{\beta}^*) \leq \epsilon$ and set $\mu = \frac{\epsilon}{2D}$, the number of iterations is upper bounded by:

$$t \leq \sqrt{\frac{4\|\boldsymbol{\beta}^*\|_2^2}{\epsilon}\left(\lambda_{\max}(\mathbf{X}^T\mathbf{X}) + \frac{2D\|\Gamma\|^2}{\epsilon}\right)} = O(\frac{1}{\epsilon})$$

Remarks: state of the art IPM method for for SOCP converges at a rate $O(\frac{1}{\epsilon^2})$

Multi-Task Time Complexity

- Pre-compute:

$$\mathbf{X}^T\mathbf{X},\ \mathbf{X}^T\mathbf{Y}: \quad O(J^2N + JKN)$$

- Per-iteration Complexity (computing gradient)

Tree:

IPM for SOCP	$O\left(J^2(K+\lvert\mathcal{G}\rvert)^2(KN + J(\sum_{g\in\mathcal{G}}\lvert g\rvert))\right)$
Proximal-Gradient	$O(J^2K + J\sum_{g\in\mathcal{G}}\lvert g\rvert)$

Graph:

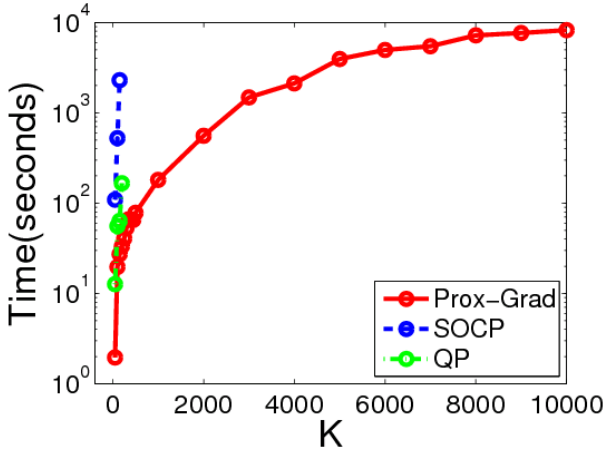
IPM for SOCP	$O\left(J^2(K+\lvert E\rvert)^2(KN + JK + J\lvert E\rvert)\right)$
Proximal-Gradient	$O(J^2K + J\lvert E\rvert)$

Proximal-Gradient: Independent of Sample Size

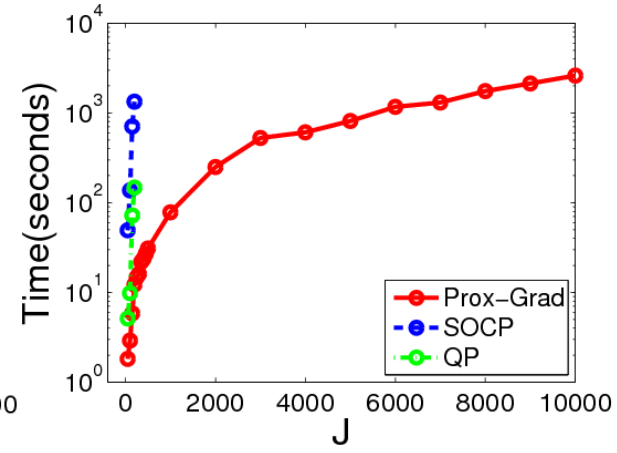
Linear in #.of Traits

Experiments

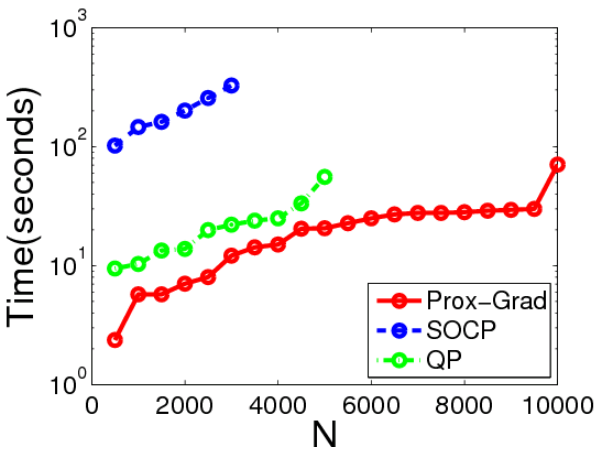
- Multi-task Graph Structured Sparse Learning (GFlasso)



$N = 500, J = 100$



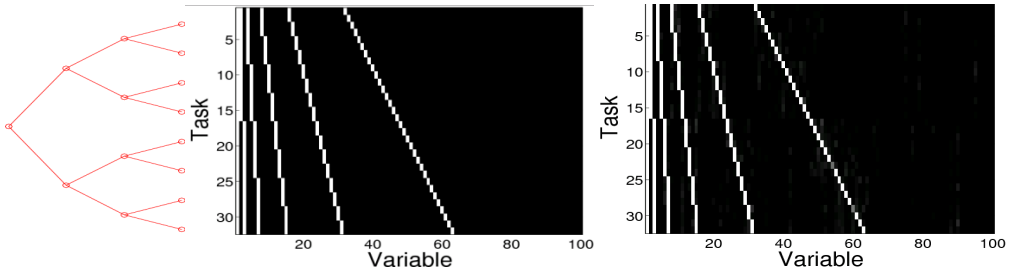
$N = 1000, K = 50$



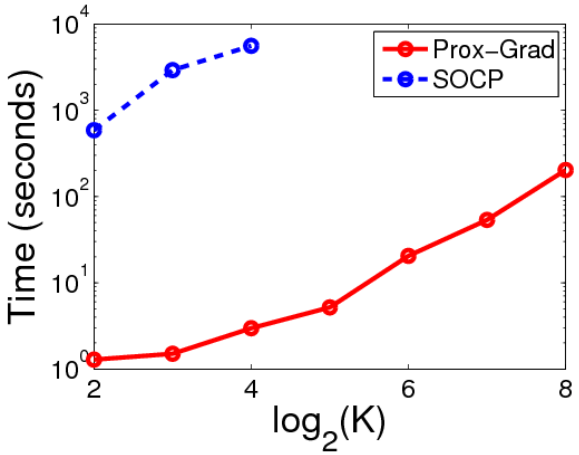
$J = 100, K = 50$

$\mu = 10^{-4}, \rho = 0.5$

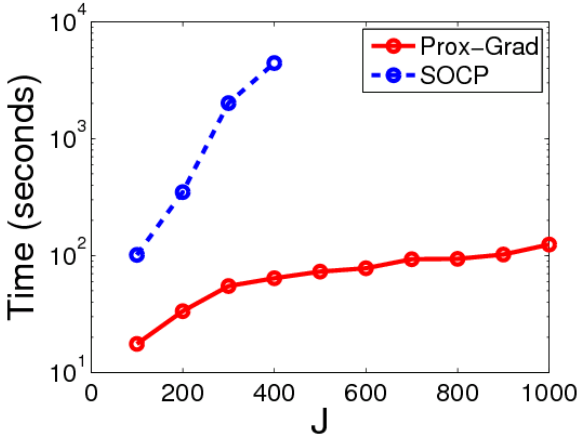
Experiments



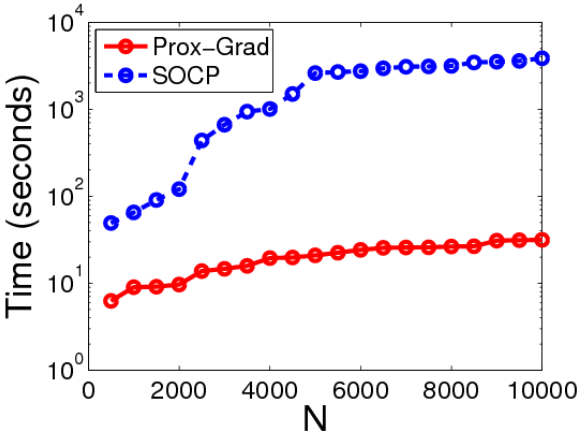
- Multi-task Tree-Structured Sparse Learning (TreeLasso)



$N = 1000, J = 600$



$N = 1000, K = 32$



$J = 100, K = 32$

$\epsilon = 0.1$

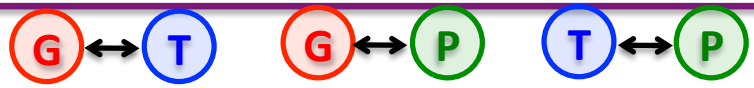
Overview

- Genome structure in association analysis
  - Linkage disequilibrium
  - Population structure
  - Epistasis

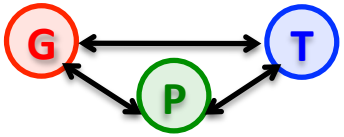
- Transcriptome structure in association analysis
  - Pleiotropy
    - Pathway-based statistical tests
    - Leveraging gene expression network
    - Leveraging gene expression tree

- Phenome structure in association analysis
  - Pleiotropy
  - Dynamic trait

- Two-way structured association



- Three-way structured association



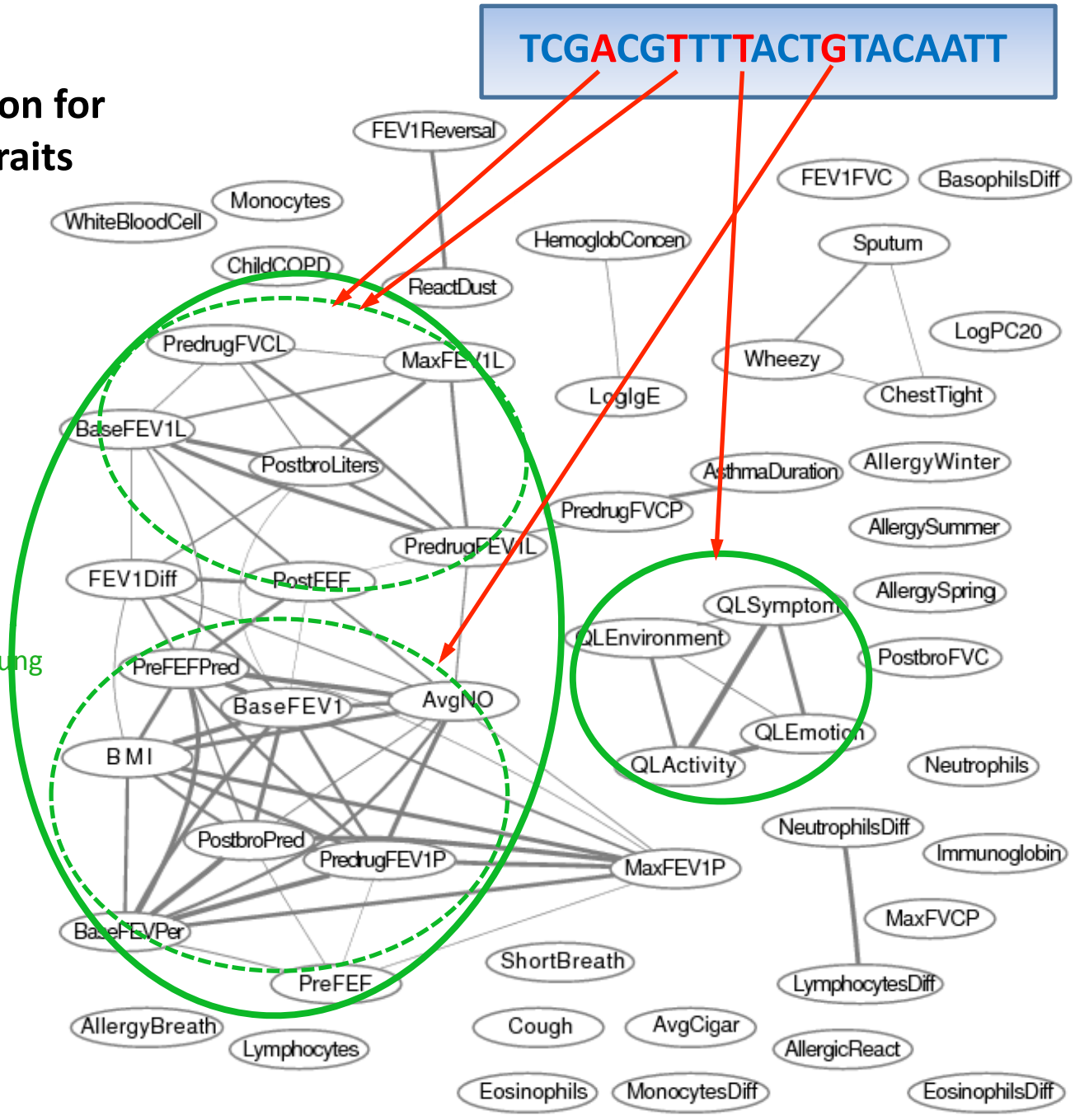
- Visualization software

Association to Phenome

- Pleiotropy: a genetic locus influencing multiple different phenotypes

- Methods for transcriptome association can be applied
  - Graph-guided fused lasso (Kim & Xing, PLoS Genetics 2009)
  - Tree-guided fused lasso (Kim & Xing, ICML 2010)

Genetic Association for Asthma Clinical Traits



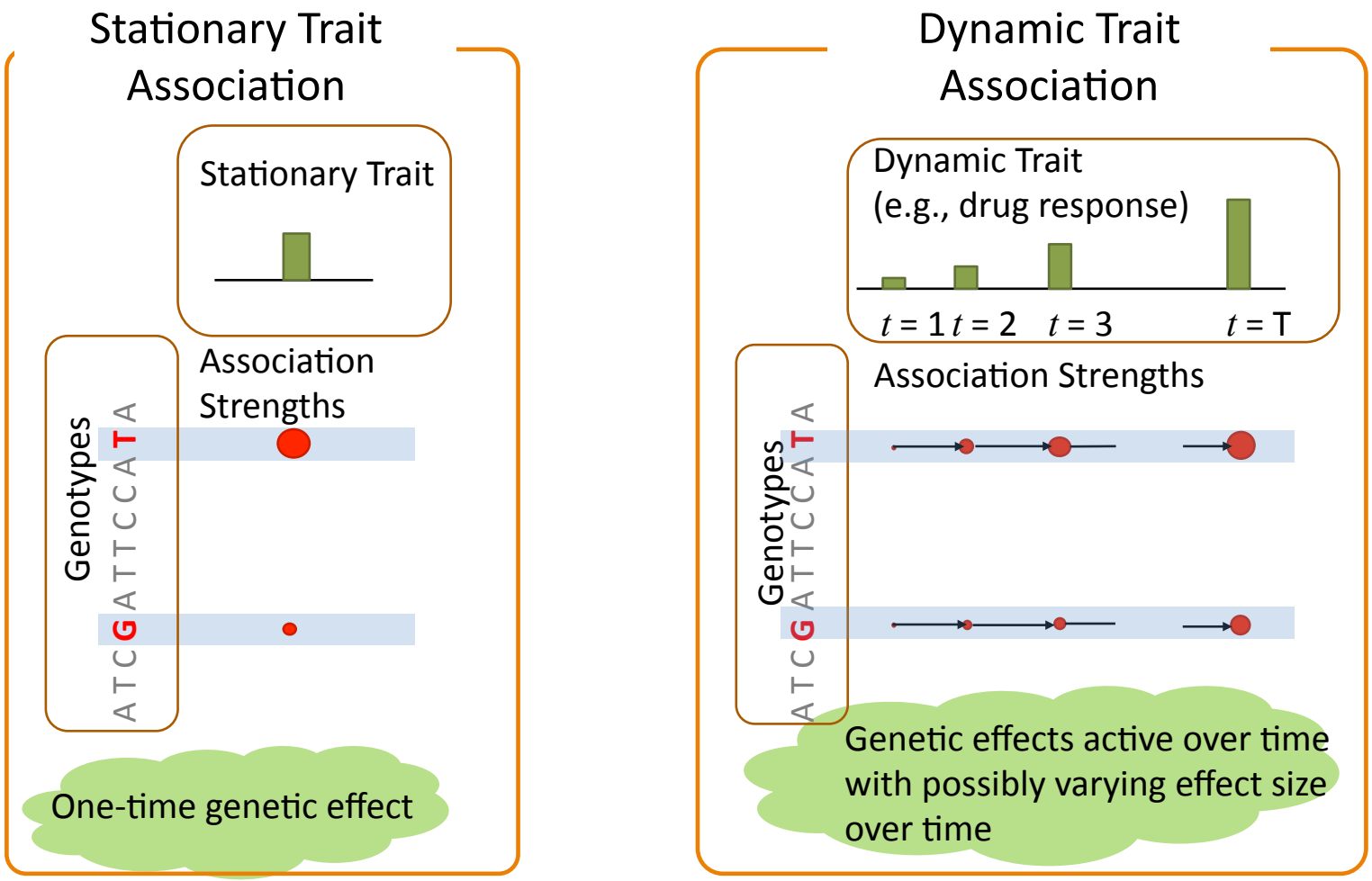
Subnetworks for lung physiology

Dynamic-Trait Association Mapping

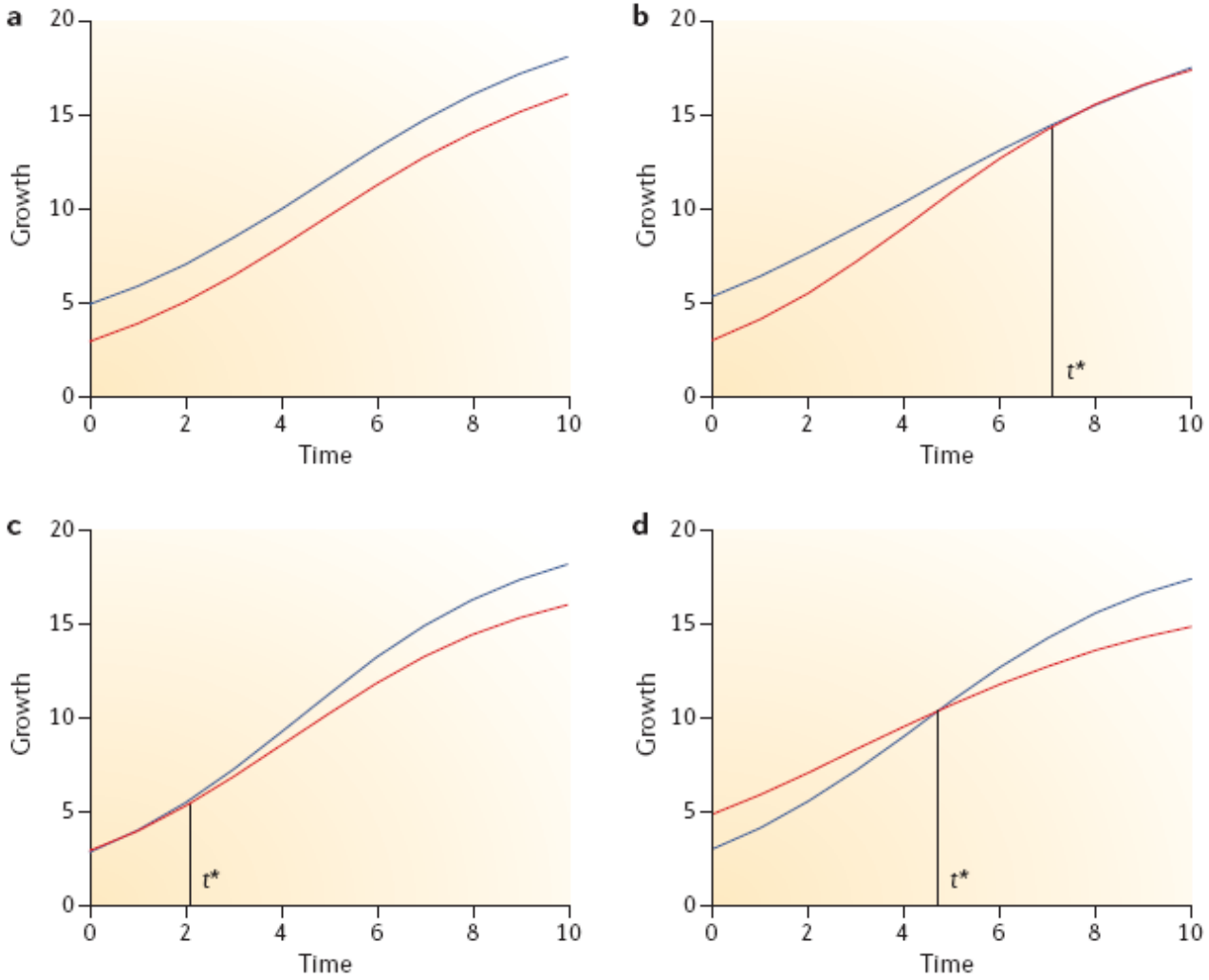
- Dynamic trait with a temporal trend
  - Growth of tumor over time
  - Height, weight over time
  - Gene expressions over time in cell cycle or embryonic development

- Are there underlying genetic variants that influence the overall trend over time?

Dynamic Trait (d-trait) Association



Genetic Control of Growth Trajectories



Wu & Lin, Nature Review Genetics 2006

Temporally-Smoothed Lasso

- Step 1: Autoregressive Model
  - Captures the shape of the temporal trend in the d-trait data
  - Estimates the model parameters based on the d-trait data only

- Step 2: Temporally-Smoothed Lasso
  - Penalized regression framework
  - Incorporates the estimated d-trait shape parameters from Step 1
  - Detects time-varying genetic effects on the d-trait

Kim et al., submitted

Step 1: Autoregressive Model

Autoregressive Model :

$$\mathbf{y}_{k,t+1} = \alpha_{k,t}\mathbf{y}_{k,t} + \alpha^0_{k,t}\mathbf{1} + \epsilon$$

Estimating Model Parameters:

$$\hat{\alpha}_{k,t} = \text{argmin } (\mathbf{y}_{k,t+1} - \alpha_{k,t}\mathbf{y}_{k,t} - \alpha^0_{k,t})^T \cdot (\mathbf{y}_{k,t+1} - \alpha_{k,t}\mathbf{y}_{k,t} - \alpha^0_{k,t})$$

Estimates of the Model Parameters:

$$\hat{\alpha}_{k,t} = \frac{\mathbf{y}^T_{k,t} \cdot \mathbf{y}_{k,t+1}}{\mathbf{y}^T_{k,t} \cdot \mathbf{y}_{k,t}}$$

Step 2: Temporally-Smoothed Lasso

Autoregressive parameters from Step 1

$$\hat{\mathrm{B}}^{\mathrm{dyn}} = \operatorname{argmin} \sum_k \sum_t (\mathrm{y}_{k,t} - \mathrm{X}\beta_{k,t})^T \cdot (\mathrm{y}_{k,t} - \mathrm{X}\beta_{k,t}) + \lambda \cdot \sum_k \sum_t \sum_j \beta^j_{k,t} + \gamma \cdot \sum_j \sum_k \sum_{t=1}^{T-1} |\beta^j_{k,t+1} - \hat{\alpha}_{k,t}\beta^j_{k,t}|$$

Lasso Penalty

Temporally-smoothed Lasso Penalty

Estimating Association Strengths

$$\hat{\mathrm{B}}^{\mathrm{dyn}} = \operatorname{argmin} \sum_k \sum_t (\mathbf{y}_{k,t} - \mathbf{X}\boldsymbol{\beta}_{k,t})^T \cdot (\mathbf{y}_{k,t} - \mathbf{X}\boldsymbol{\beta}_{k,t})$$
$$\text{such that } S(\mathrm{B}) \leq s_1, T(\mathrm{B}) \leq s_2$$

- Quadratic programming
- Convex optimization: many publicly available software packages can be used.
- **Proximal gradient algorithm** can be applied

Proximal Gradient Descent

Original Problem:

$$\arg\min_{\boldsymbol{\beta}\in\mathbb{R}^J} f(\boldsymbol{\beta}) \equiv \frac{1}{2}\|\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\|_2^2 + \Omega(\boldsymbol{\beta})$$

$$\Omega(\boldsymbol{\beta}) = \max_{\boldsymbol{\alpha}\in\mathcal{Q}} \boldsymbol{\alpha}^T C\boldsymbol{\beta}$$

Approximation Problem:

$$\arg\min_{\boldsymbol{\beta}\in\mathbb{R}^J} \widetilde{f}(\boldsymbol{\beta}) \equiv \frac{1}{2}\|\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\|_2^2 + f_\mu(\boldsymbol{\beta})$$

$$f_\mu(\boldsymbol{\beta}) = \max_{\boldsymbol{\alpha}\in\mathcal{Q}} \boldsymbol{\alpha}^T C\boldsymbol{\beta} - \mu d(\boldsymbol{\alpha})$$

Gradient of the Approximation:

$$\nabla\widetilde{f}(\boldsymbol{\beta}) = \mathbf{X}^T(\mathbf{X}\boldsymbol{\beta}-\mathbf{y}) + C^T\boldsymbol{\alpha}^*$$

$$\boldsymbol{\alpha}^* = \arg\max_{\boldsymbol{\alpha}\in\mathcal{Q}} \boldsymbol{\alpha}^T C\boldsymbol{\beta} - \mu d(\boldsymbol{\alpha})$$

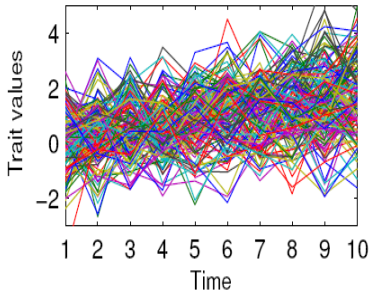
$\nabla\widetilde{f}(\boldsymbol{\beta})$ is Lipschitz continuous with the Lipschitz constant L

$$L = \lambda_{\max}(\mathbf{X}^T\mathbf{X}) + L_\mu$$

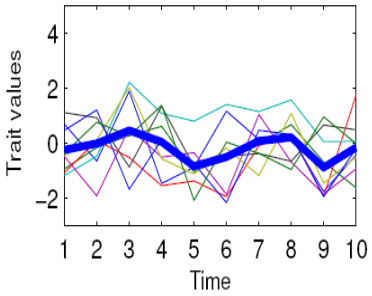
Simulation Study

- Genotype:
  - HapMap-simulated data (The international HapMap Consortium, Nature 2005)
  - 50 SNPs
- D-trait:
  - Linear dynamic
  - Cyclic dynamic
  - 10 time points
- 150 individuals

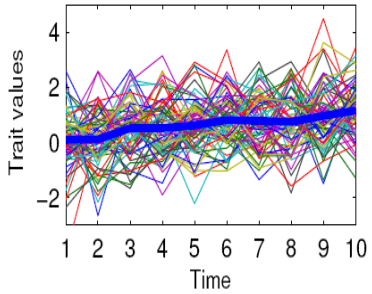
Simulation Study – Linear Dynamic



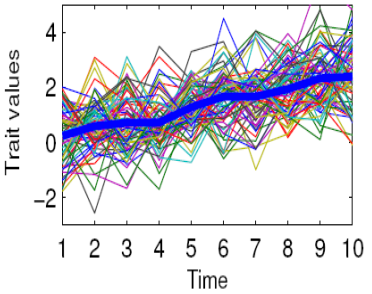
Trait data for
all individuals



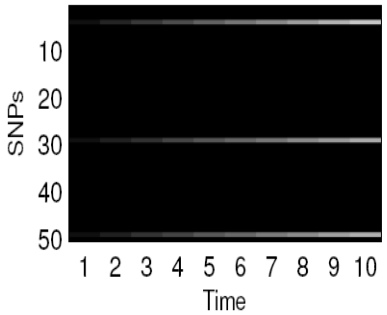
Trait data for
individuals with
no association SNPs



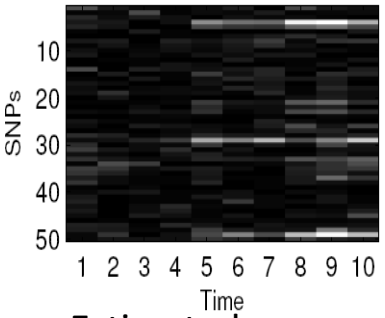
Trait data for
individuals with
1-2 association SNPs



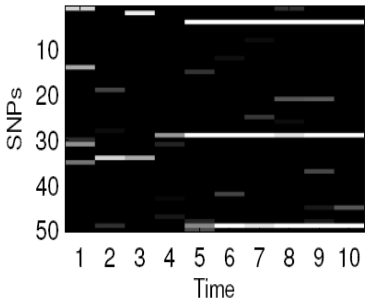
Trait data for
individuals with
>3 association SNPs



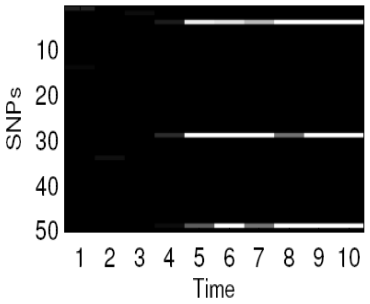
True association
strength



Estimated
association strength
(single SNP analysis)

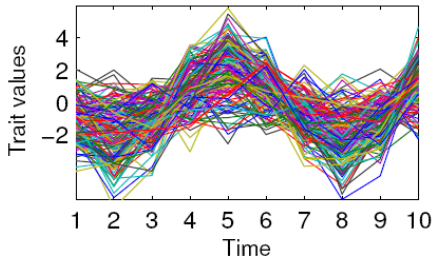


Estimated
association strength
(lasso)

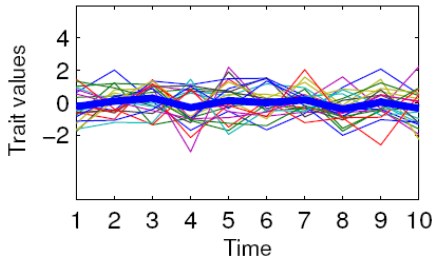


Estimated
association strength
(temporally-smoothed
lasso)

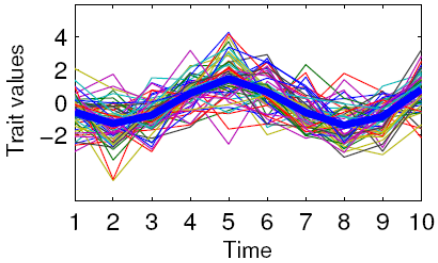
Simulation Study – Cyclic Dynamic



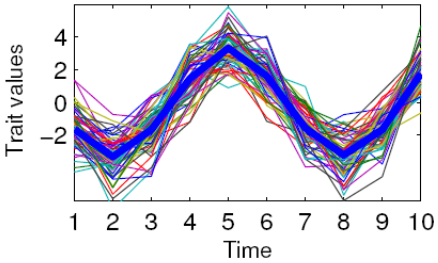
Trait data for all individuals



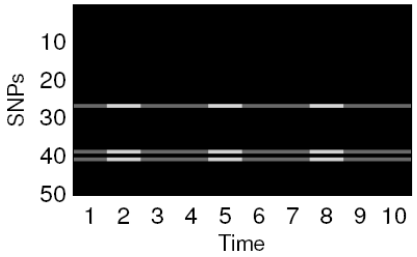
Trait data for individuals with no association SNPs



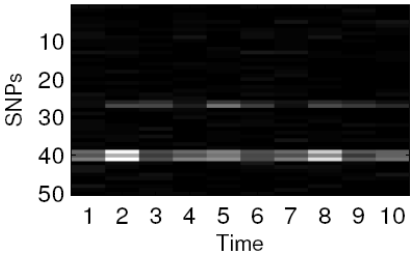
Trait data for individuals with 1-2 association SNPs



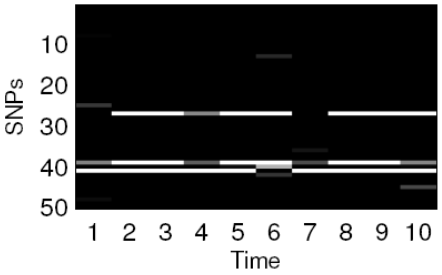
Trait data for individuals with >3 association SNPs



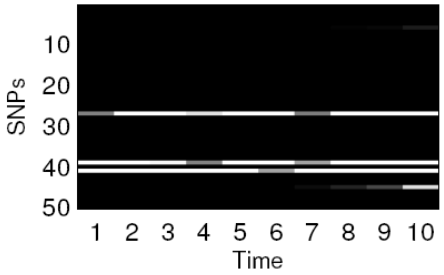
True association strength



Estimated association strength (single SNP analysis)



Estimated association strength (lasso)



Estimated association strength (temporally-smoothed lasso)

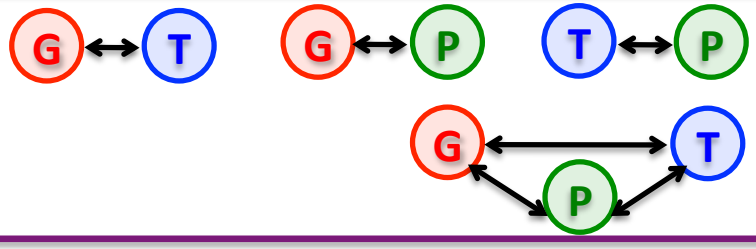
Overview

- Genome structure in association analysis
  - Linkage disequilibrium
  - Population structure
  - Epistasis

- Transcriptome structure in association analysis
  - Pleiotropy
    - Pathway-based statistical tests
    - Leveraging gene expression network
    - Leveraging gene expression tree

- Phenome structure in association analysis
  - Pleiotropy
  - Dynamic trait

- Two-way structured association
- Three-way structured association



- Visualization software

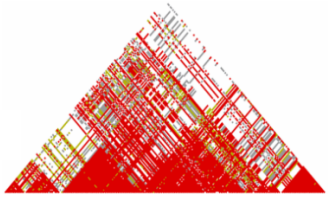
Genome Structure

Structured Association

Phenome Structure

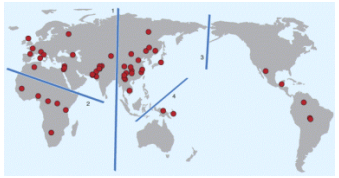
Genome Structure

Linkage Disequilibrium



Stochastic block regression
(Kim & Xing, UAI, 2008)

Population Structure



Multi-population group lasso
(Puniyani, Kim, Xing, ISMB, 2010)

Epistasis

Group lasso with networks
(Lee, Kim, Xing, Submitted)

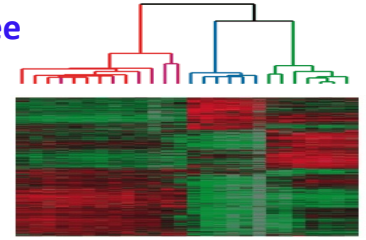
Structured Association

Phenome Structure

Graph

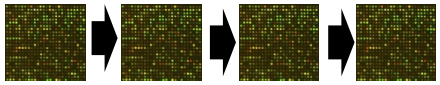
Graph-guided fused lasso
(Kim & Xing, PLoS Genetics, 2009)

Tree



Tree-guided fused lasso
(Kim & Xing, ICML 2010)

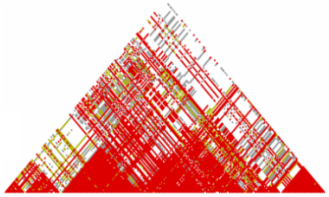
Dynamic Trait



Temporally smoothed lasso
(Kim, Howrylak, Xing, Submitted)

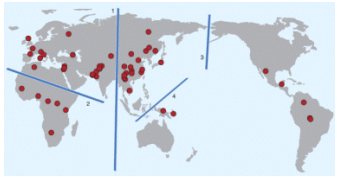
Genome Structure

Linkage Disequilibrium



Stochastic block regression
(Kim & Xing, UAI, 2008)

Population Structure



Multi-population group lasso
(Puniyani, Kim, Xing, ISMB, 2010)

Epistasis

ACGTTTTACTGTACAATT

Group lasso with networks
(Lee, Kim, Xing, Submitted)

Structured Association

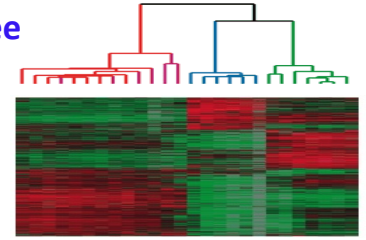
- Sparse regularized regression
- Convex Optimization

Phenome Structure

Graph

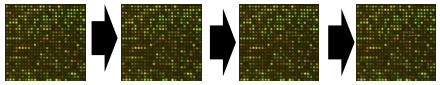
Graph-guided fused lasso
(Kim & Xing, PLoS Genetics, 2009)

Tree



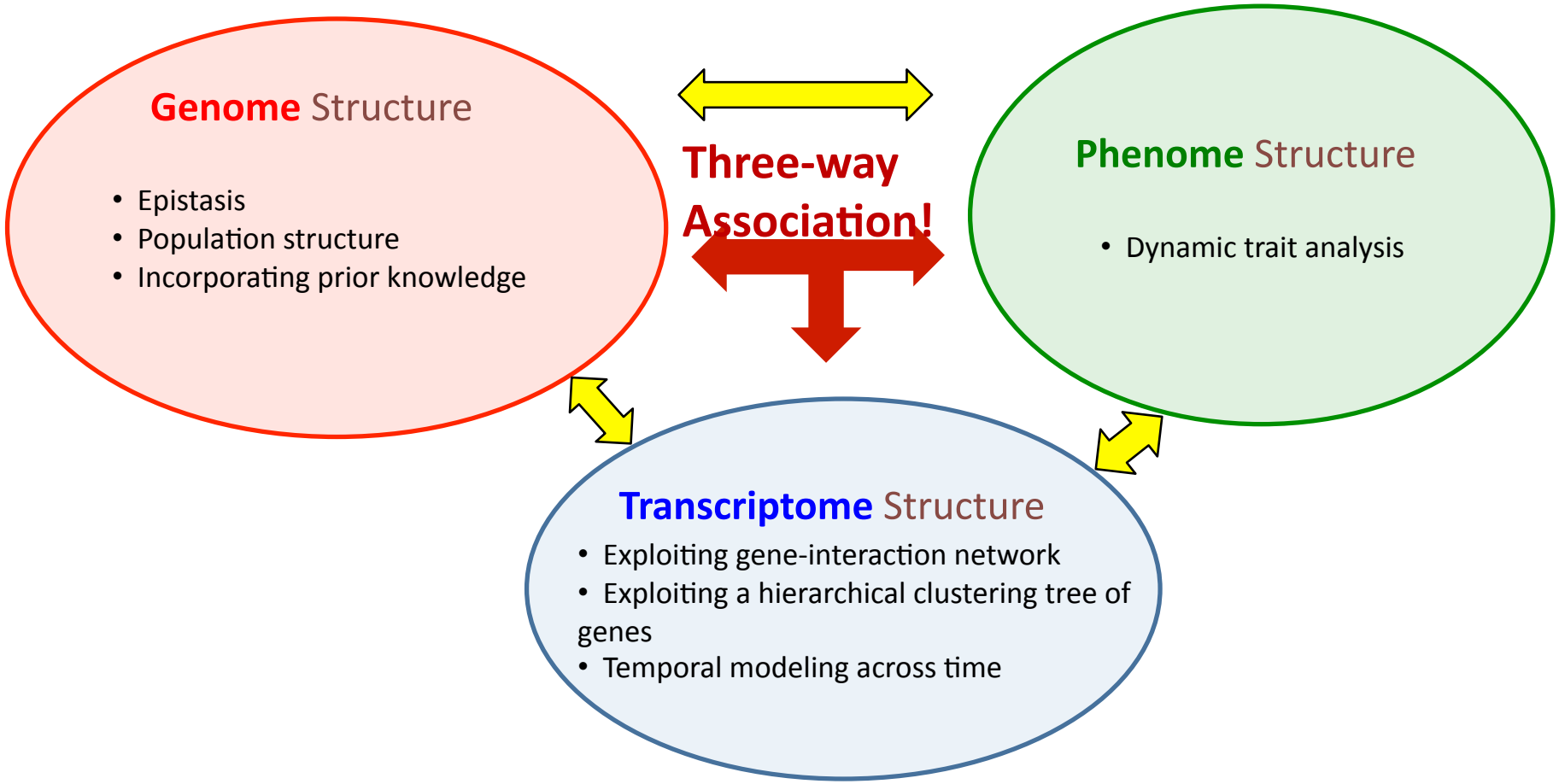
Tree-guided fused lasso
(Kim & Xing, ICML 2010)

Dynamic Trait



Temporally smoothed lasso
(Kim, Howrylak, Xing, Submitted)

Structured Genome-Transcriptome-Phenome Association Analysis



Summary: why care about structure?

- Theoretically, it increase the power [Mladen and Xing, 2010]

$$\mathbb{P}[\mathcal{M}_* \subseteq \mathcal{M}^{(m^*_{\max})}] \geq 1 - C_1 \exp\left(-C_2 \frac{n^{1-6\delta_s-6\delta_{\min}}}{\max\{\log(p), \log(T)\}}\right)$$

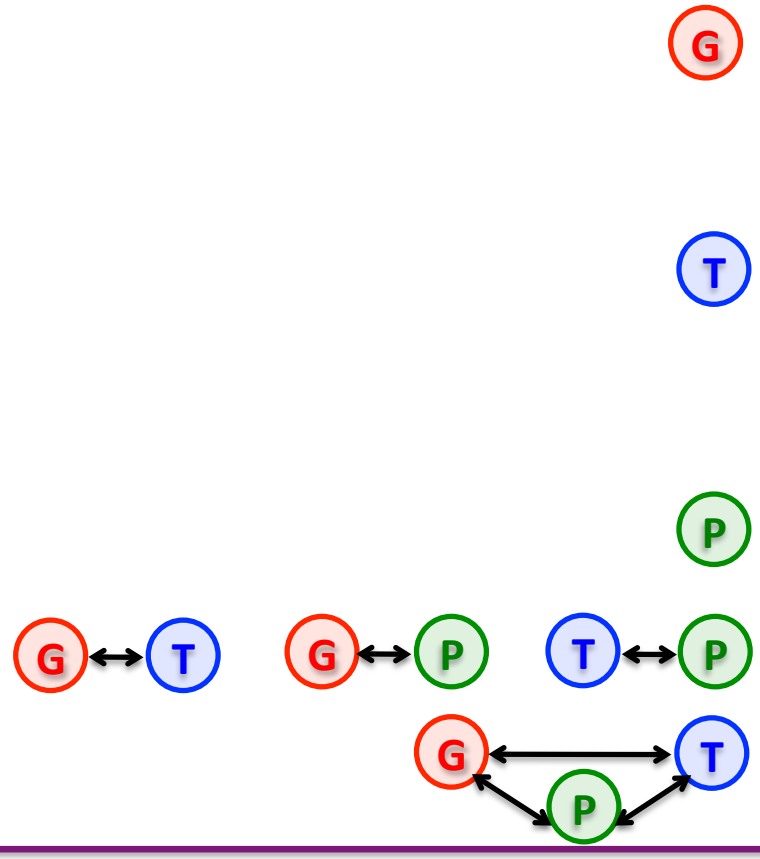
Summary: why care about structure?

- Incorporating more information leads to enhanced discovery and lower false discovery (results from simulation test)
  - If our underlying model is correct!

Method	Power (multi-trait)	FDR
GFlasso	0.889	0.009
plink	0.803	0.014
Sum-rank	0.748	0.008
Screen & Clean	0.780	0.153
Lasso	0.991	0.886
Forward Selection	0.931	0.867

Overview

- Genome structure in association analysis
  - Linkage disequilibrium
  - Population structure
  - Epistasis
- Transcriptome structure in association analysis
  - Pleiotropy
    - Pathway-based statistical tests
    - Leveraging gene expression network
    - Leveraging gene expression tree
- Phenome structure in association analysis
  - Pleiotropy
  - Dynamic trait
- Two-way structured association
- Three-way structured association
- Visualization software

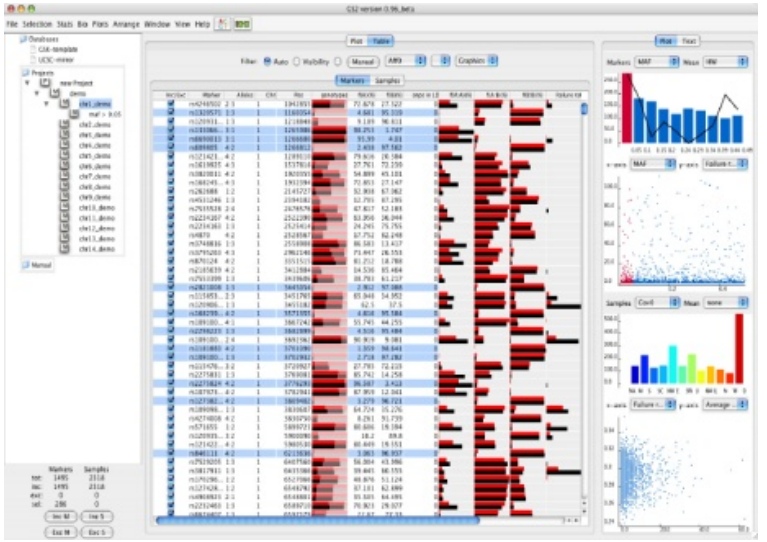


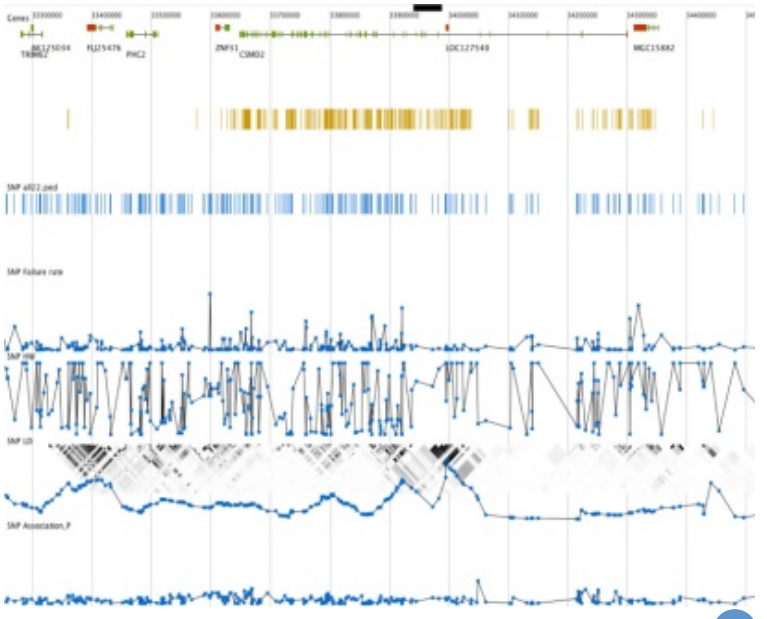
Visualization Softwares for Association Mapping

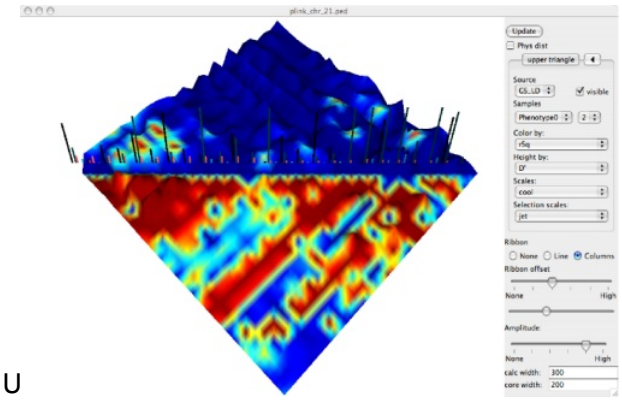
- GoldSurfer2 http://www.well.ox.ac.uk/gs2
- GoldenHelix http://www.goldenhelix.com/
- GWAS GUI http://www.sph.umich.edu/csg/weich/browser/
- MAVEN http://cbc.case.edu/maven/home.do
- Association Viewer http://www.improvedoutcomes.com/docs/WebSiteDocs/Plots/Classification_and_Prediction/SLAM_Assocation_Viewer.htm
- eQTLexplorer http://web.bioinformatics.ic.ac.uk/eqtlexplorer/
- eQTL Viewer http://statgen.ncsu.edu/eQTLViewer/svgHome.html

GoldSurfer2

- Developed by Glaxo SmithKline and Oxford University
- Features
  - Explore genome LD structure
  - Standard statistical tests for association
- Disadvantages
  - Runs locally

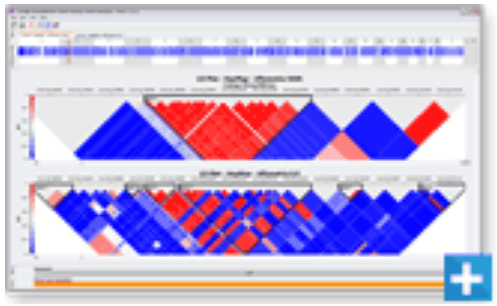


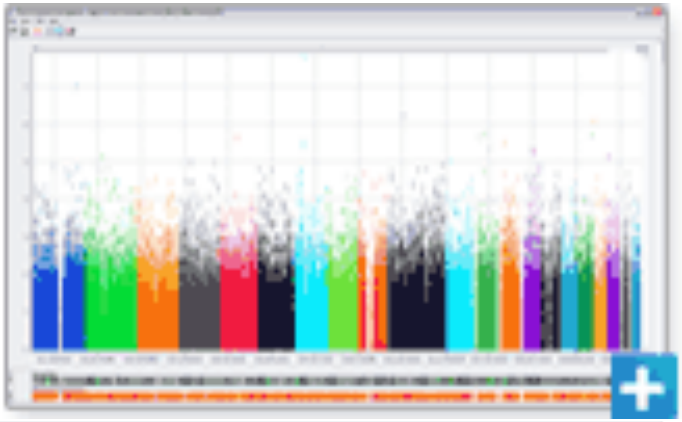


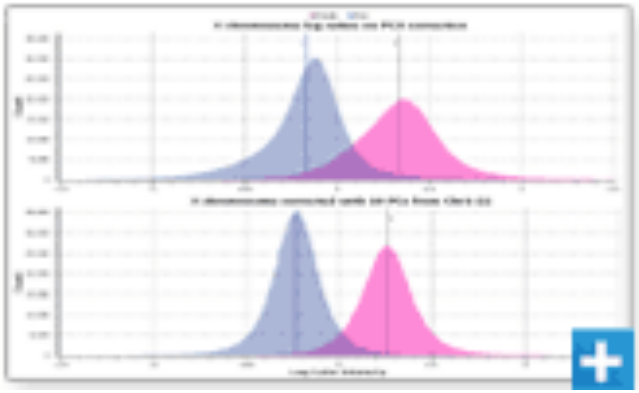


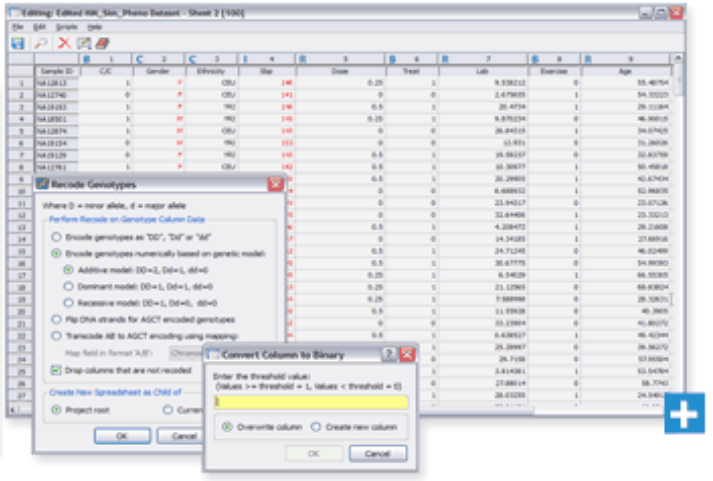
Golden Helix

- Features
  - Standard conventional association tests
  - Links to external data sources
  - Fast computation and storage
  - Data management
  - Quality assurance
- Disadvantages
  - Case/control methodology









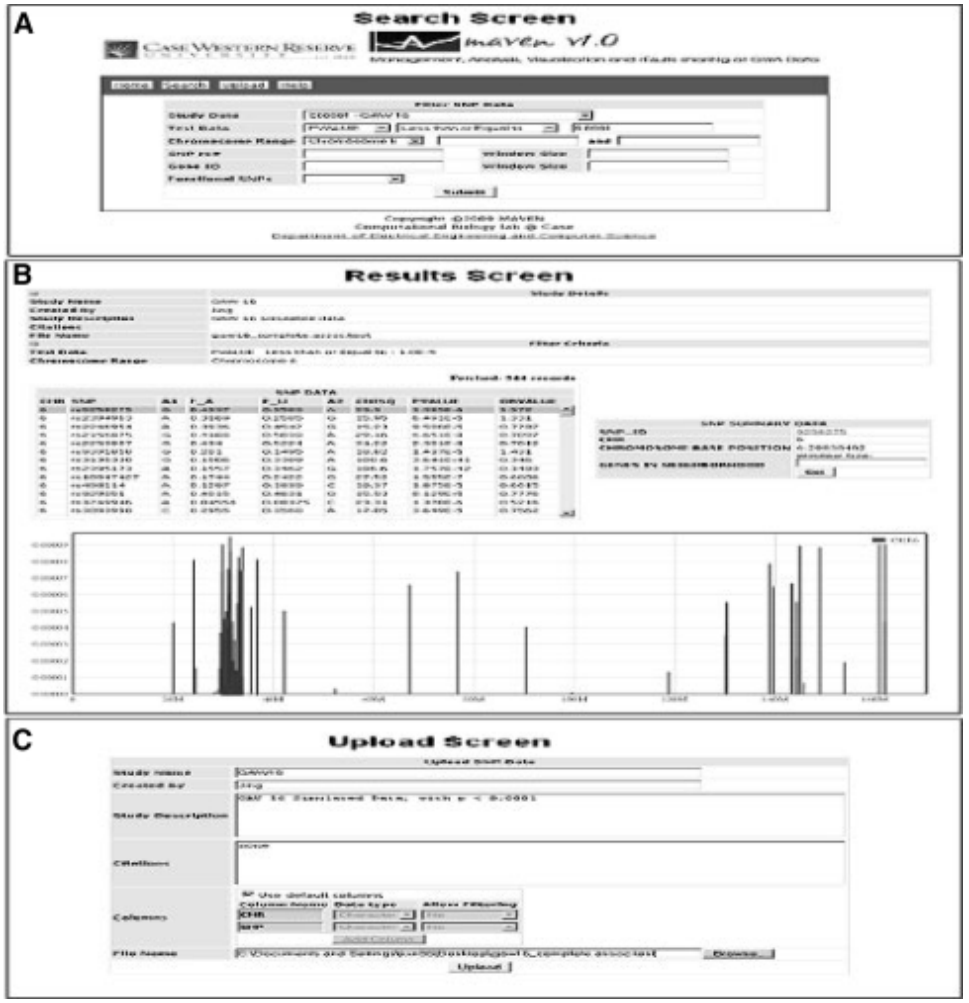
GWAS GUI

- Developed by Center for Statistical Genetics, U of Michigan

- Features
  - Manages huge datasets – including large gene expression datasets
  - Results in a graph or tabular form
  - Searching based on trait or locus
- Disadvantages
  - Must import your own association results
  - Cannot view structure in the gene expression
  - Limited visualizations

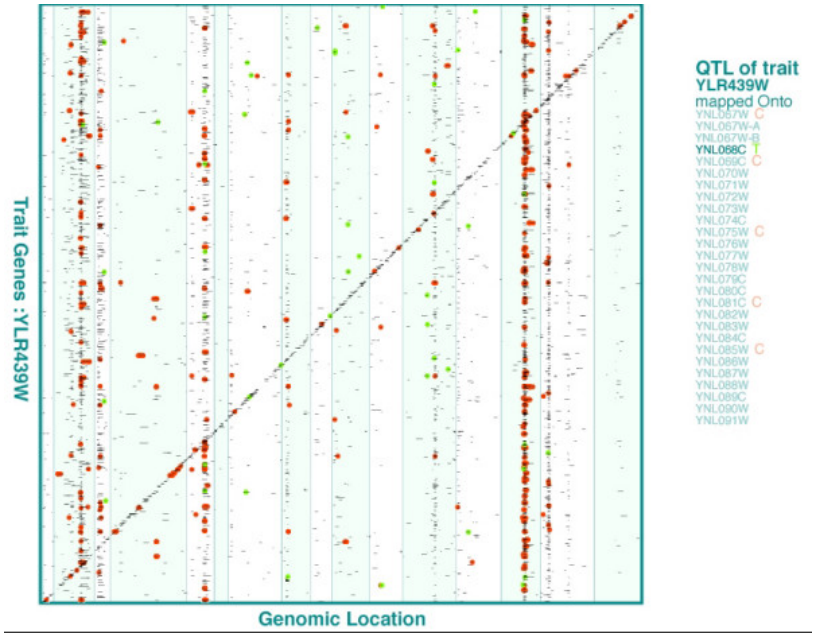
MAVEN and AssociationViewer

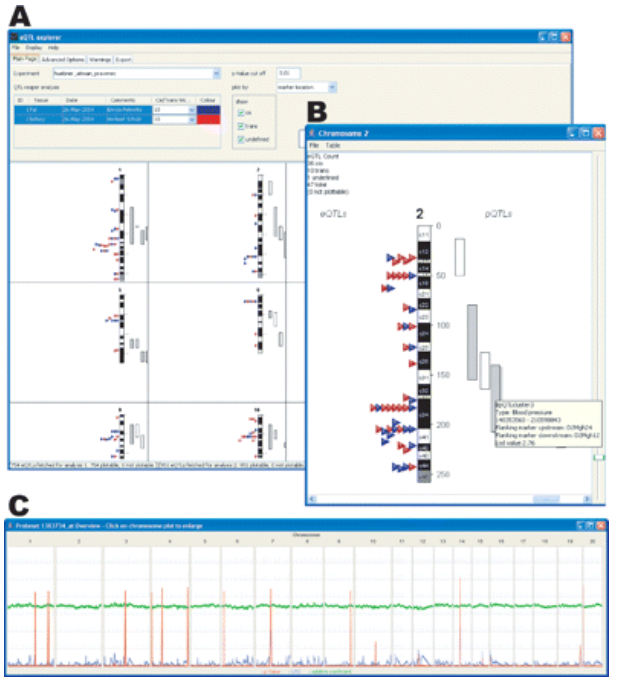
- Similar to GWAS GUI, but only for case/ control studies
- Maven links to external databases
- AssociationViewer has advanced memory management capability.



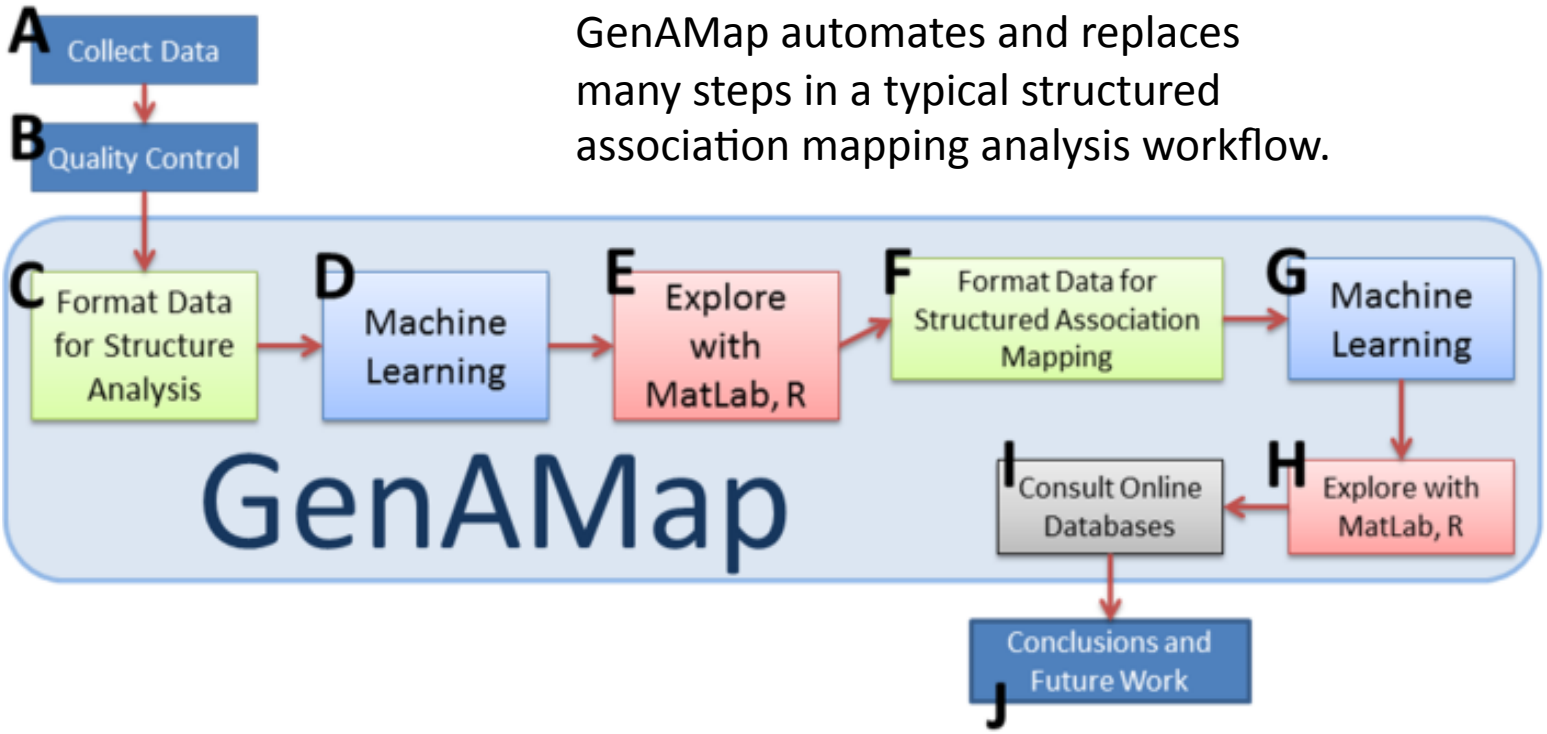
eQTL Explorer and eQTL Viewer

- Features – can explore eQTL results, link out to external information





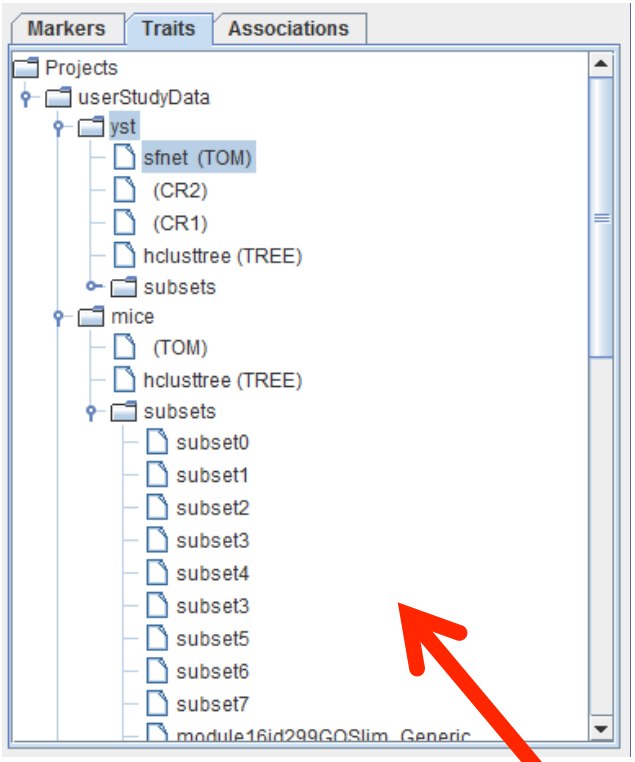
GenAMap: Structured Association Mapping Workflow

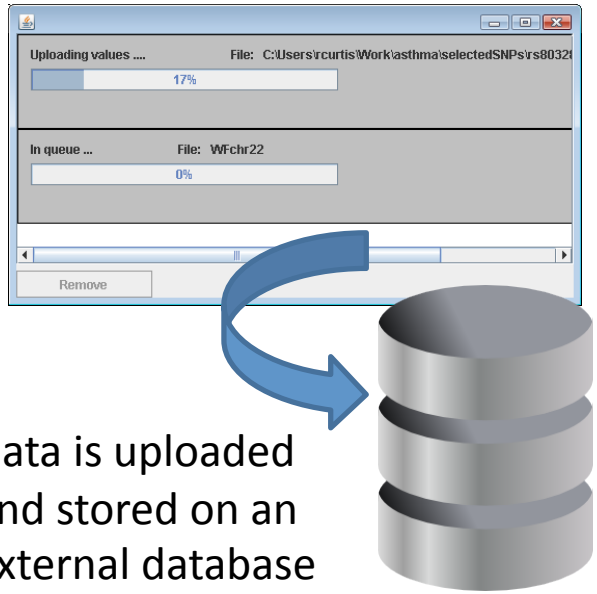


GenAMap automates and replaces many steps in a typical structured association mapping analysis workflow.

GenAMap: Data Management

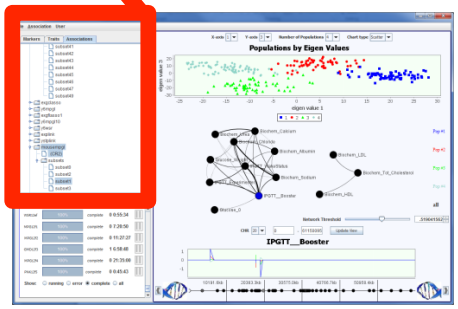
GenAMap organizes genome, phenome, and association data with the corresponding structures.





Data is uploaded and stored on an external database for fast processing and collaborative work.

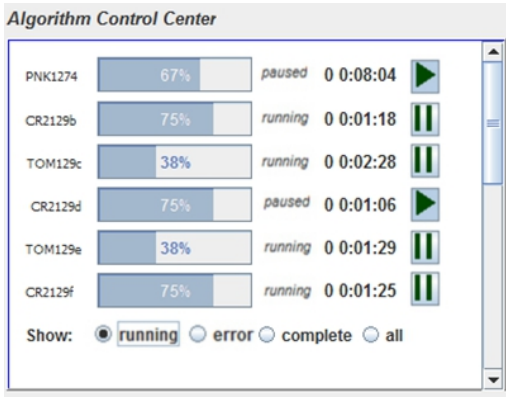
GenAMap supports multiple file formats: delimited text, .PED, and .BED files

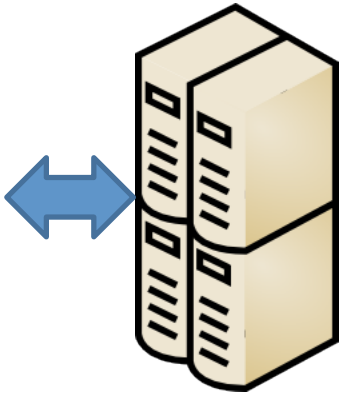


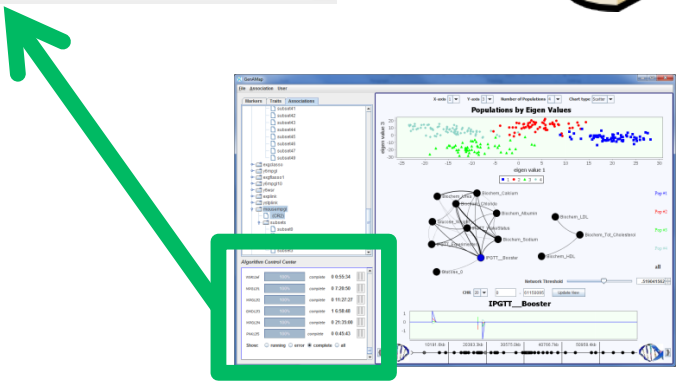
GenAMap: Algorithm Automation

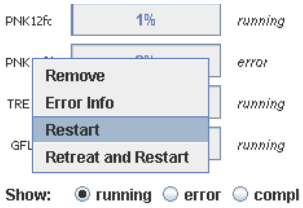
- Association Algorithms
  - PLINK
  - Lasso
  - Wilcoxon-Sum Rank
- Algorithms to create structure
  - Population structure (structure)
  - Network structure (glasso, correlation, scale-free network learning)
  - Tree structure (hierarchical clustering)
- Structured Association Algorithms
  - TreeLasso
  - GFlasso
  - MPGL

Algorithms are automatically run on a cluster in parallel.





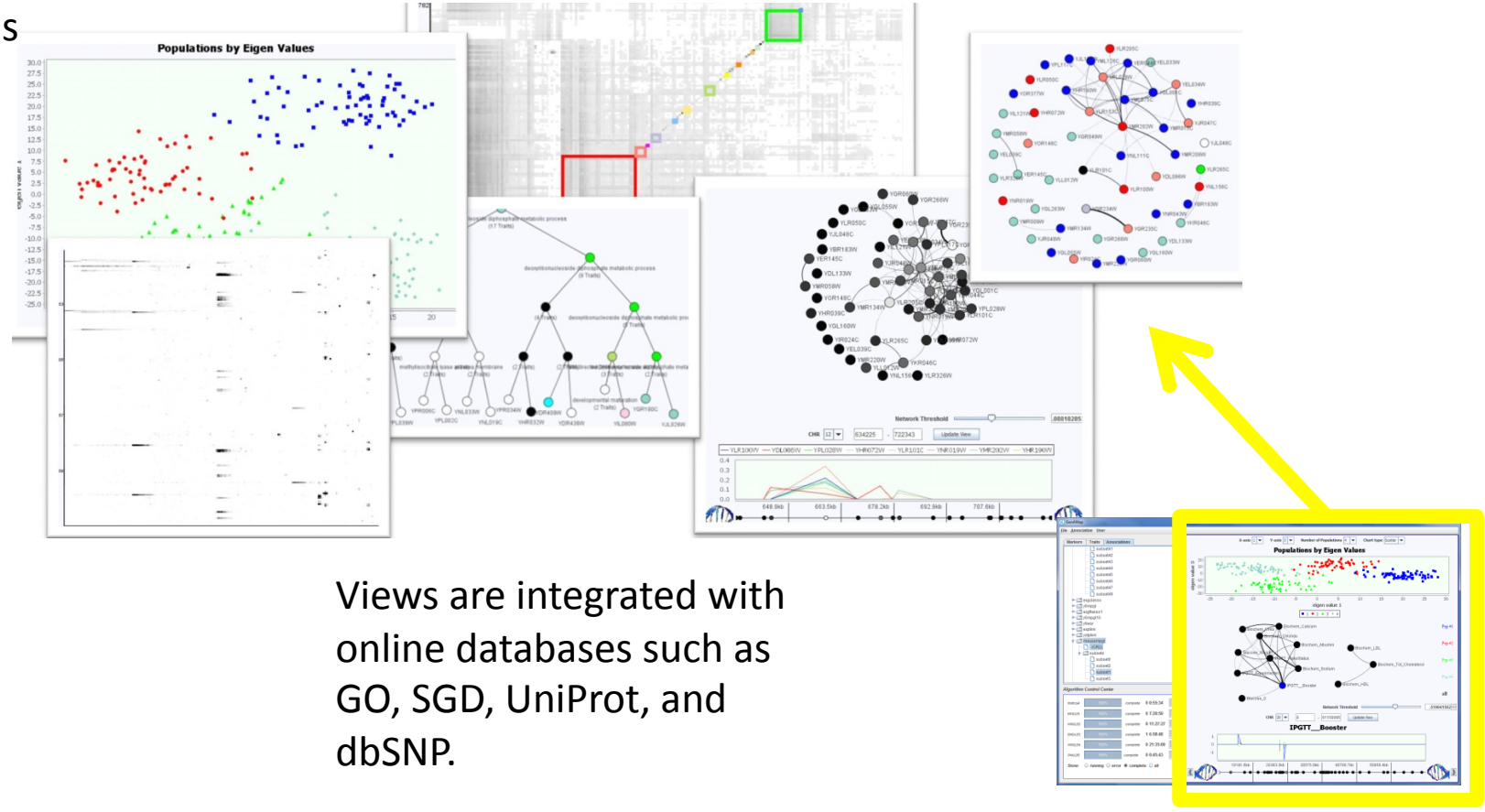




User monitors and interacts with algorithms through GenAMap.

GenAMap: Visualization

Multiple coordinated views allow for exploration of data structure and association signals



Views are integrated with online databases such as GO, SGD, UniProt, and dbSNP.

GenAMap: User Study

- Preliminary qualitative user study
  - 8 participants, experts in genetics
  - Semi-structured tasks to explore GenAMap
- Survey results
  - GenAMap is better than other tools that explore association results: average score 5.0/5
  - GenAMap led to insight not available using other tools: average score 4.71/5
  - Would recommend GenAMap to other researchers: average score 4.75/5
- Comments
  - 6 users commented that GenAMap was more convenient than using MATLAB
  - 5 users specifically mentioned that using GenAMap was easier, more convenient, and saved time over how they normally do association analysis.
  - *"By myself, I would have to go back and forth between tools. It is really nice that this is integrated into this software."*
  - *"The ability to interact with the network and the genome is excellent."*
  - *"GenAMap's visualizations really put the associations into perspective."*

Part IV

Association Analysis and Next Generation Sequencing

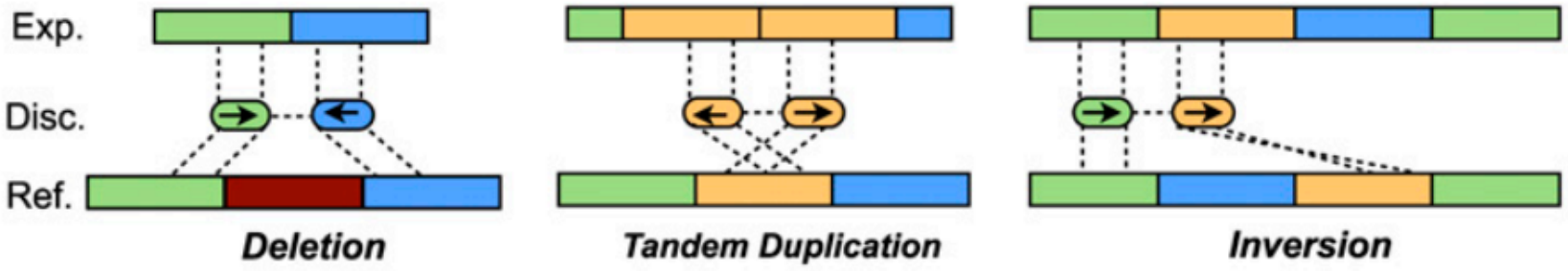
The case of the missing heritability

When scientists opened up the human genome, they expected to find the genetic components of common traits and diseases. But they were nowhere to be seen. **Brendan Maher** shines a light on six places where the missing loot could be stashed away.

Explaining Missing Heritability

- Undetected epistasis
- Going beyond SNPs
  - Structural variants: insertions, deletions, duplication, copy number variants
- From common variants to rare variants

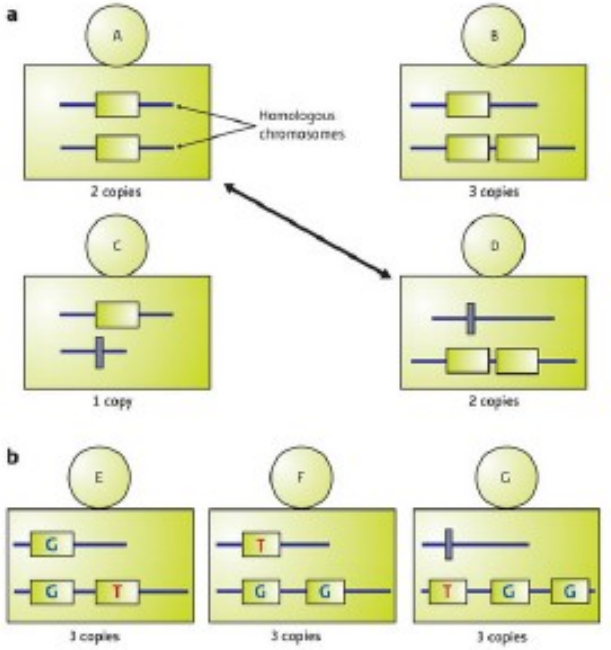
Other Genetic Variations



Quinlan et al., Genome Research 2010

Other Genetic Variations

- Copy Number Variation
  - DNA segment whose numbers differ in different genomes
    - Kilobases to megabases in size
  - Usually two copies of all autosomal regions, one per chromosome
  - Variation due to deletion or duplication



Copy-number variation (CNV) can occur in ambiguous patterns. (a) Individuals in a population may have different copy numbers on homologous chromosomes at CNV loci. For example, here individual A and D have two copies, although the patterns are different: A has one copy on each chromosome, whereas D has two on one chromosome and zero on the other. (b) Individuals may also have CNVs that contain SNPs. For example, individuals E, F, and G each have three copies, but the patterns can be distinguished by the numbers of copies on each chromosome and variations defined by SNPs.

Common Variants vs. Rare Variants

- First-generation genome-wide association study (GWAS): common variant common disease hypothesis

- Common variants with minor allele frequency (MAF)>5%
  - dbGap: ~11 million SNPs
  - HapMap: 3.5 million SNPs
  - A successful GWAS requires a more complete catalogue of genetic variations

- Rare variants (MAF<0.5%), low-frequency variants (MAF:0.5%~5%)
  - Captured by sequencing with next-generation sequencing technology
  - Possibly significant contributors to the genetic architecture of disease
    - Causal variants are subject to negative selection

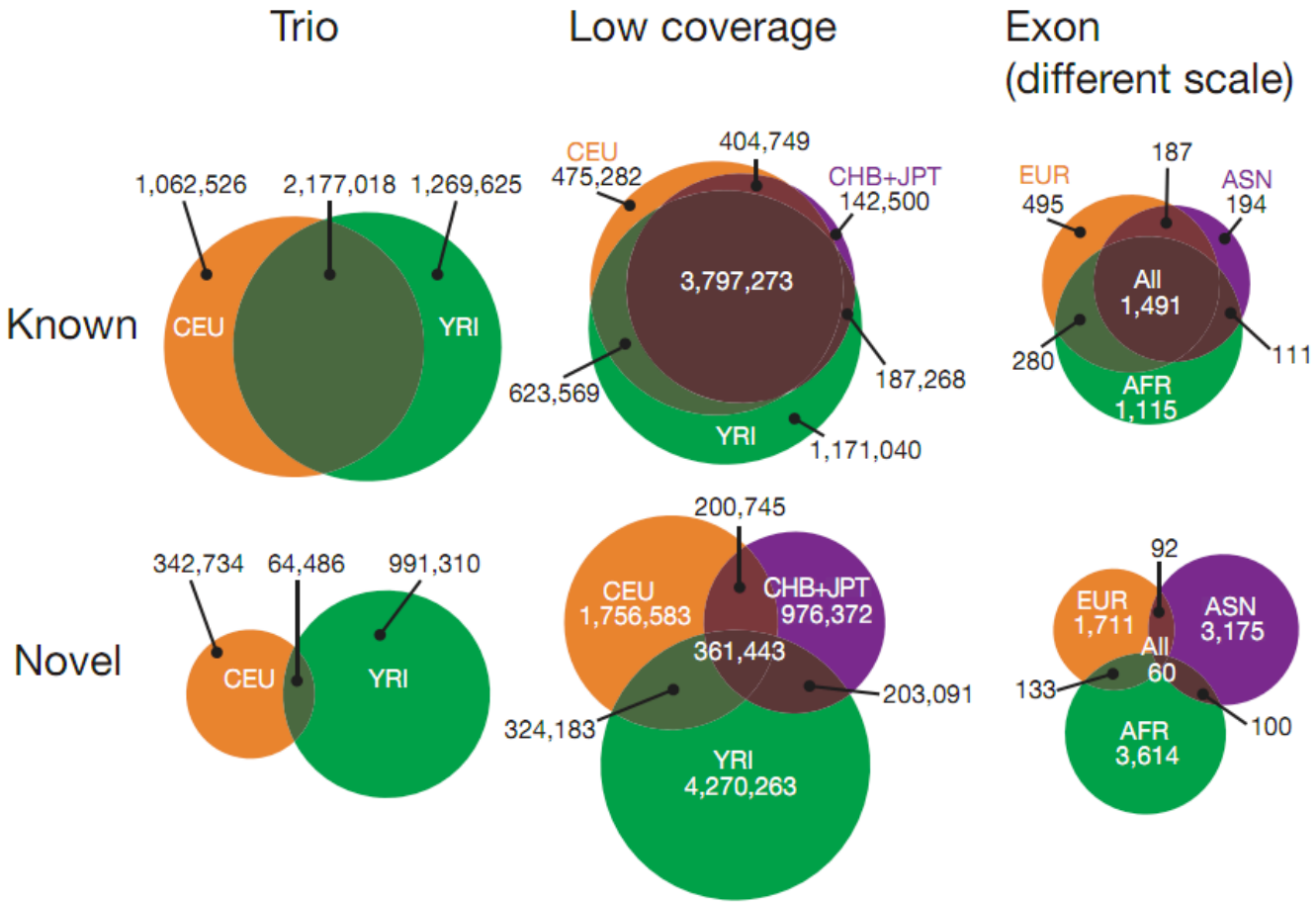
1000 Genome Project

(The 1000 Genome Project Consortium, Nature 2010)

The **goal** is to characterize over **95% of variants** that are in genomic regions accessible to current high-throughput sequencing technologies and that have **allele frequency of 1% or higher** (the classical definition of polymorphism) in each of **five major population groups** (populations in or with ancestry from Europe, East Asia, South Asia, West Africa and the Americas)

- 179 individuals (low coverage)
- 6 individuals in two trios (deep sequencing)
- 697 individuals (exon sequencing of 8,140 exons)

1000 Genome Projects: Known vs. Novel Variants



Associations to Rare Variants

- Often GWA studies are underpowered for functional rare variants

Common Variant Association

	Case	Control
Allele a	60	20
Allele A	40	80

Rare Variant Association

	Case	Control
Allele a	7	2
Allele A	93	98

- Common variant GWA approaches are appropriate only for common variants

Recent Methods for Detecting Rare Variant Associations

- Test combined effect of multiple rare variants
- Fixed-Threshold Approach (Li & Leal, AJHG 2008)
  - Include only the SNPs with allele frequency below a fixed threshold
  - For SNP $i=1,\ldots,m$ in a genomic region or a gene,

$$Score = \sum_{i=1}^{m} \varepsilon_i C_i$$

» C_i : The allele frequency of SNP i in cases

» $\varepsilon_i = \begin{cases} 1 & \text{If the allele frequency of SNP } i \text{ is below a specified threshold} \\ 0 & \text{Otherwise} \end{cases}$

  - Evaluate the significance of $Score$ by permutation test

Recent Methods for Detecting Rare Variant Associations

- Weighted Approach (Madson & Browning, PLoS Genetics 2009)
  - Instead of fixed threshold, weight each SNP with the inverse square root of the variance at each SNP locus
  - For SNP $i=1,\ldots,m$ in a genomic region or a gene,

$$Score = \sum_{i=1}^{m} \varepsilon_i C_i$$

» C_i : The allele frequency of SNP i in cases

» $\varepsilon_i = 1/\sqrt{p_i(1-p_i)}$ p_i : allele frequency

  - Evaluate the significance of $Score$ by permutation test

Recent Methods for Detecting Rare Variant Associations

- Incorporating computational predictions of functional effects

  (Price et al., AJHG 2010)

  – PolyPhen-2 : a probabilistic scoring system for neutral and functional amino acids

  – For SNP $i=1,\ldots,m$ in a genomic region or a gene,

$$Score = \sum_{i=1}^{m} \varepsilon_i C_i$$

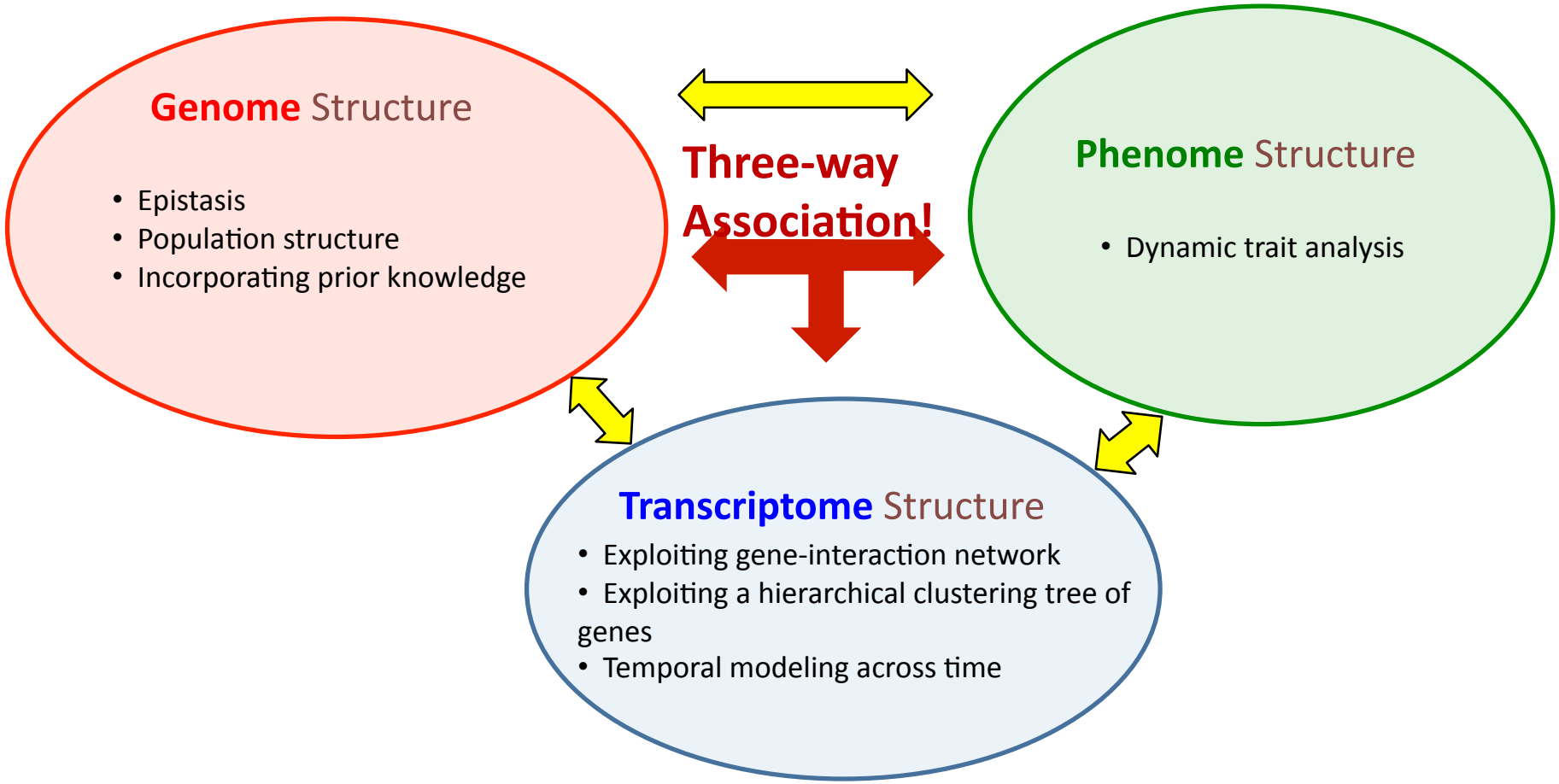
  » C_i : The allele frequency of SNP i in cases

  » $\varepsilon_i = P(S_i)$

  $P(S_i)$: score for SNP i being functional, given PolyPhen-2 score S_i

  – Evaluate the significance of $Score$ by permutation test

Summary: Structured Genome-Transcriptome-Phenome Association Analysis



Publicly Available Software

- Haplotyper: http://www.people.fas.harvard.edu/~junliu/Haplo/docMain.htm
- PHASE, FastPHASE: http://stephenslab.uchicago.edu/software.html
- Structure: http://pritch.bsd.uchicago.edu/structure.html
- EigenStrat: http://genepath.med.harvard.edu/~reich/Software.htm
- mStruct: http://cogito-b.ml.cmu.edu/mstruct/
- Plink: http://pngu.mgh.harvard.edu/~purcell/plink/
- Lasso: http://cran.r-project.org/web/packages/glmnet/index.html
- Strat: http://pritch.bsd.uchicago.edu/software/STRAT.html
- Genomic Control: http://www.wpic.pitt.edu/wpiccompgen/software.htm
- Gflasso: http://cogito-b.ml.cmu.edu/gflasso/
- Structured IO Lasso: http://cogito-b.ml.cmu.edu/epistaticQTL/
- Lirnet: http://www.cs.washington.edu/homes/suinlee/lirnet/
- GenAMap: http://cogito-b.ml.cmu.edu/genamap/

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  - Judie Howrylak
  - Kyung-Ah Sohn
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- University of Pittsburgh Medical Center
  - Sally Wenzel (MD)
- Harvard Medical School
  - Scott Weiss (MD)
  - Benjamin Raby (MD)

Acknowledgement

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