

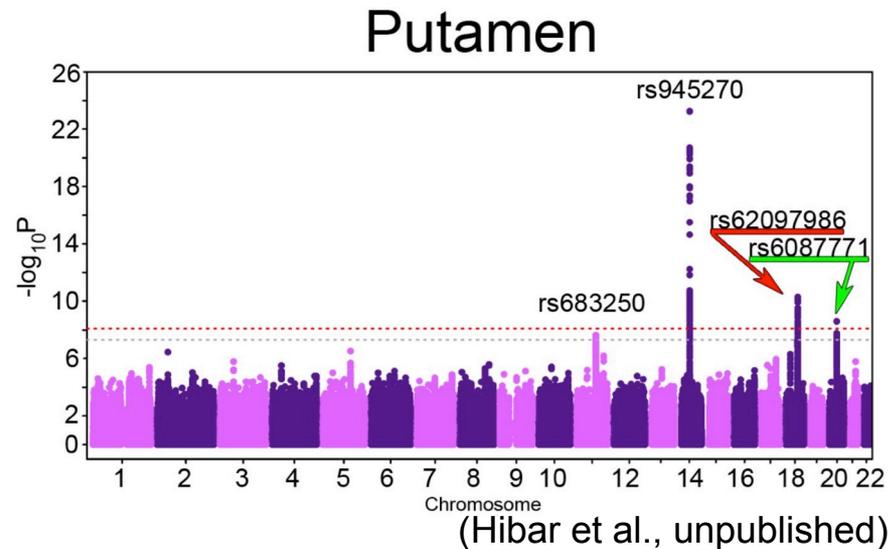


Interpretation of Results

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Organization for Human Brain Mapping
Introduction to Imaging Genetics
Hamburg, Germany
June 8, 2014

A hit is just the beginning...



What you have found

- Variation in a **locus** of the genome which significantly influences your **trait** (brain structure/disease)

What you want to know

- A mechanism by which genetic variation influences brain structure or function and risk for disease?
- Causal variant(s)
- Causal gene(s)
- Causal biological pathway(s)
- Causal brain region(s)

But be wary....

APPLICATIONS OF NEXT-GENERATION SEQUENCING

Sequencing studies in human genetics: design and interpretation

David B. Goldstein¹, Andrew Allen^{1,2}, Jonathan Keebler¹, Elliott H. Margulies⁵,
Steven Petrou^{6,5}, Slavé Petrovski^{1,6} and Shamil Sunyaev⁷

“Human genomes have a high level of ‘**narrative potential**’ to provide compelling but statistically poorly justified connections between mutations and phenotypes.”

“A critical challenge for biologists in [...] will be avoiding premature hypotheses born of biological plausibility and ‘**Just So**’ stories.”

Genome-scale neurogenetics: methodology and meaning

Steven A McCarroll^{1,2}, Guoping Feng^{1,3,4} & Steven E Hyman^{1,5}

ORIGINAL ARTICLES

Spurious Genetic Associations

Patrick F. Sullivan

“Findings from single association studies constitute ‘**tentative knowledge**’ and must be interpreted with exceptional caution.”

Biological plausibility is not a substitute for statistical significance

Exploring biological mechanisms

- Exploring the genetic locus
- Epigenetics & ENCODE
- Move from locus to gene
- Exploring the expression of the gene
- Enrichment in biological pathways

UCSC Genome Browser

Human (*Homo sapiens*) Genome Browser Gateway

The UCSC Genome Browser was created by the [Genome Bioinformatics Group of UC Santa Cruz](#).
Software Copyright (c) The Regents of the University of California. All rights reserved.

group genome assembly position search term

Mammal Human Feb. 2009 (GRCh37/hg19) chr19:45,404,181-45,404,681 enter position, gene symbol or search terms submit

[Click here to reset](#) the browser user interface settings to their defaults.

track search add custom tracks track hubs configure tracks and display

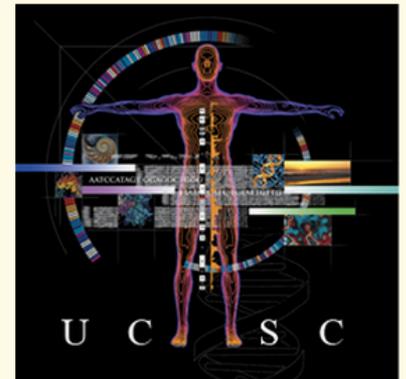
Human Genome Browser – hg19 assembly ([sequences](#))

The February 2009 human reference sequence (GRCh37) was produced by the [Genome Reference Consortium](#). For more information about this assembly, see [GRCh37](#) in the NCBI Assembly database.

Sample position queries

A genome position can be specified by the accession number of a sequenced genomic clone, an mRNA or EST or STS marker, a chromosomal coordinate range, or keywords from the GenBank description of an mRNA. The following list shows examples of valid position queries for the human genome. See the [User's Guide](#) for more information.

Request:	Genome Browser Response:
chr7	Displays all of chromosome 7
chrUn_gl000212	Displays all of the unplaced contig gl000212
20p13	Displays region for band p13 on chr 20
chr3:1-1000000	Displays first million bases of chr 3, counting from p-arm telomere
chr3:1000000+2000	Displays a region of chr3 that spans 2000 bases, starting with position 1000000



Homo sapiens
(Graphic courtesy of [CBSE](#))

<http://genome.ucsc.edu/cgi-bin/hgGateway>

Exploring a hit (rs945270)

UCSC Genome Browser on Human Feb. 2009 (GRCh37/hg19) Assembly

chr14:56,200,223-56,200,723 501 bp.

chr14 (q22.3) 13 12 p11.2 11.2 14q12 21.1 24.3

Scale: 200 bases hg19

chr14: 56,200,300 | 56,200,400 | 56,200,500 | 56,200,600 | 56,200,700

UCSC Genes (RefSeq, GenBank, CCDS, Rfam, tRNAs & Comparative Genomics)

RefSeq Genes

Publications: Sequences in Scientific Articles

Human mRNAs from GenBank

Human ESTs That Have Been Spliced

H3K27Ac Mark (Often Found Near Active Regulatory Elements) on 7 cell lines from ENCODE

Digital DNaseI Hypersensitivity Clusters in 125 cell types from ENCODE

Transcription Factor ChIP-seq (161 factors) from ENCODE with Factorbook Motifs

100 vertebrates Basewise Conservation by PhyloP

Multiz Alignments of 100 Vertebrates

Rhesus
Mouse
Dog
Elephant
Chicken
X_tropicalis
Zebrafish
Lamprey

Simple Nucleotide Polymorphisms (dbSNP 138) Found in >= 1% of Samples

rs870924

Repeating Elements by RepeatMasker

track search default tracks default order hide all add custom tracks track hubs configure reverse resize refresh

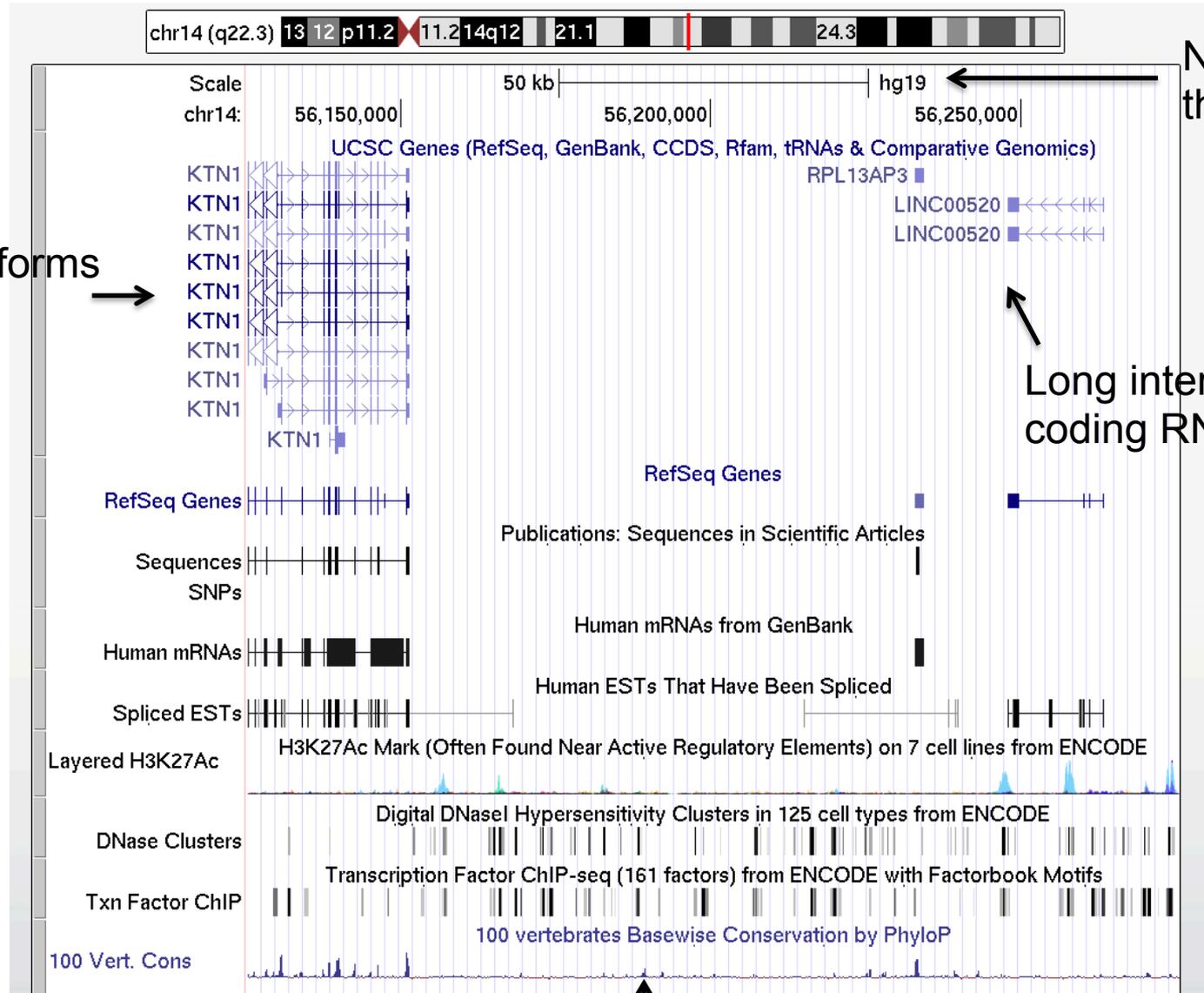
Zoom Out

Click to Shrink Track

Ideogram
Scale
Coordinates

Tracks

Exploring a hit (rs945270)



Multiple isoforms of genes →

Notice the scale ←

Long intergenic non-coding RNAs ↗

↑ The variant initially entered stays in the center

Exploring a hit (rs945270)

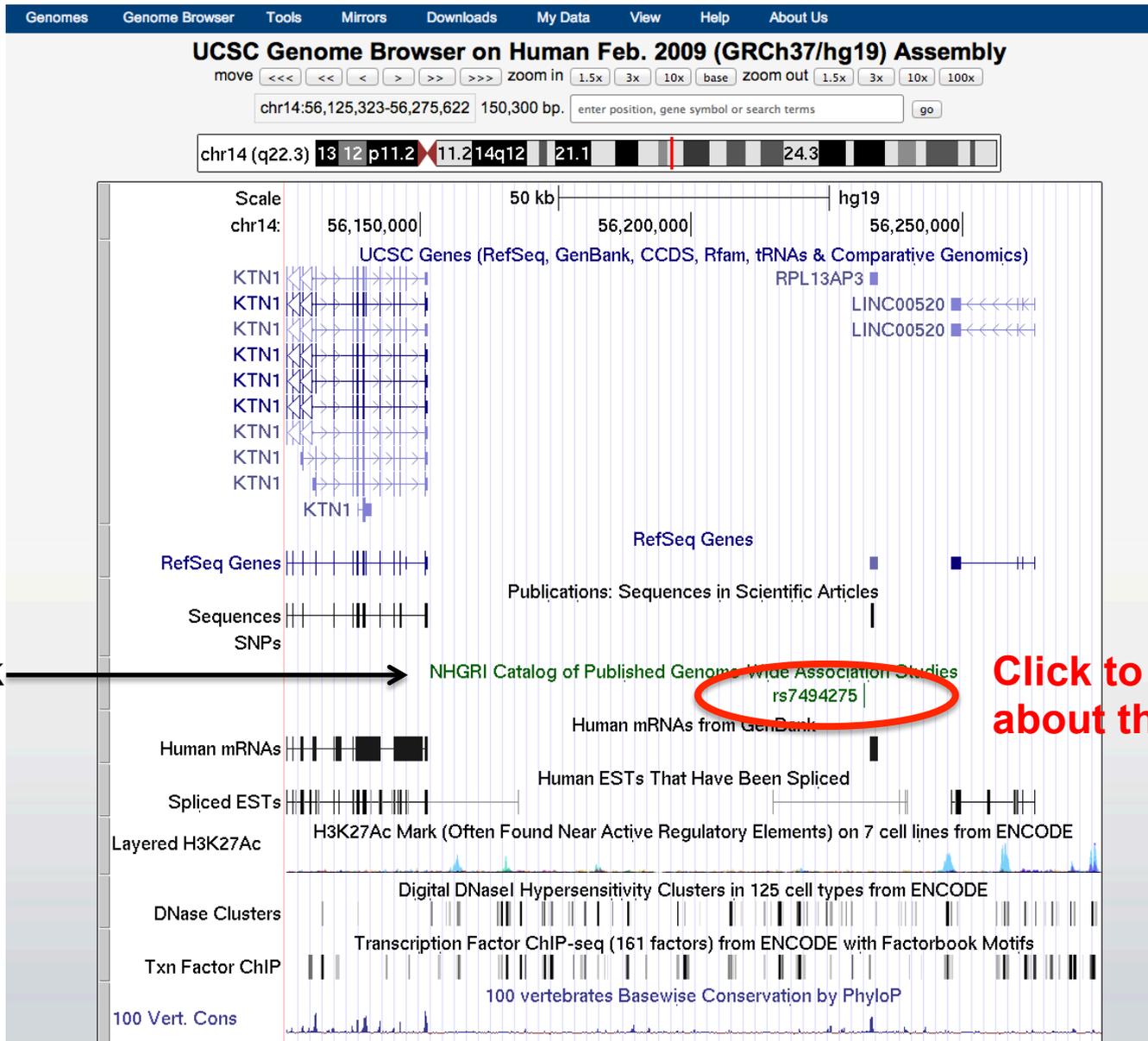
Add a Track

The screenshot displays a genomic data interface with a dark blue header bar labeled "Phenotype and Literature". On the right side of this bar, a "refresh" button is circled in red. Below the header, there are several tracks, each with a title and a "hide" button with a dropdown arrow. The tracks are arranged in a grid:

- Publications (dense)
- ClinVar Variants (hide)
- Coriell CNVs (hide)
- COSMIC (hide)
- DECIPHER (hide)
- GAD View (hide)
- GeneReviews (hide)
- GWAS Catalog (hide)
- HGMD Variants (hide)
- ISCA (hide)
- LOVD Variants (hide)
- MGI Mouse QTL (hide)
- OMIM AV SNPs (hide)
- OMIM Pheno Loci (hide)
- RGD Human QTL (hide)
- RGD Rat QTL (hide)
- UniProt Variants (hide)
- Web Sequences (hide)

A dropdown menu is open for the "GWAS Catalog" track, showing options: "hide", "dense", "squish", "pack", and "full". The "pack" option is currently selected.

Exploring a hit (rs945270)



Exploring a hit (rs945270)

Genomes Genome Browser Tools Mirrors Downloads My Data Help About

NHGRI Catalog of Published Genome-Wide Association Studies (rs7494275)

dbSNP: [rs7494275](#)
Position: [chr14:56231800-56231800](#)
Band: 14q22.3
Genomic Size: 1
[View DNA for this feature](#) (hg19/Human)
Reported region: 14q22.3
Publication: Low SK *et al.* [Genome-wide association study of chemotherapeutic agent-induced severe neutropenia/leucopenia for patients in Biobank Japan](#). *Cancer Sci.* 2013-05-04
Disease or trait: Adverse response to chemotherapy (neutropenia/leucopenia) (all topoisomerase inhibitors)
Initial sample size: 106 Japanese ancestry cases, 187 Japanese ancestry controls
Replication sample size: NA
Reported gene(s): RPL13AP3
Strongest SNP-Risk allele: [rs7494275-C](#)
dbSNP build 137 observed alleles for rs7494275: A/C
Risk Allele Frequency: 0.406
p-Value: 9E-6 (Recessive model)
Odds Ratio or beta: 1.73
95% confidence interval: [1.232-2.433]
Platform: Illumina [733,202]
Copy Number Variant (CNV)?: No

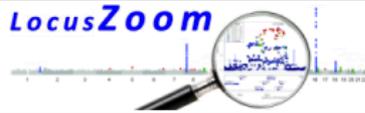
[View table schema](#)

[Go to GWAS Catalog track controls](#)

Data last updated: 2014-05-23

Not super convincing given low sample size and non-genome wide significant P-value.

LocusZoom: Making Prettier Pictures



LocusZoom - Plot with Your Data

Make sure not too big a file

Plot Your Data

Depending on the size of your data, runs can require 30-60 seconds to generate a plot

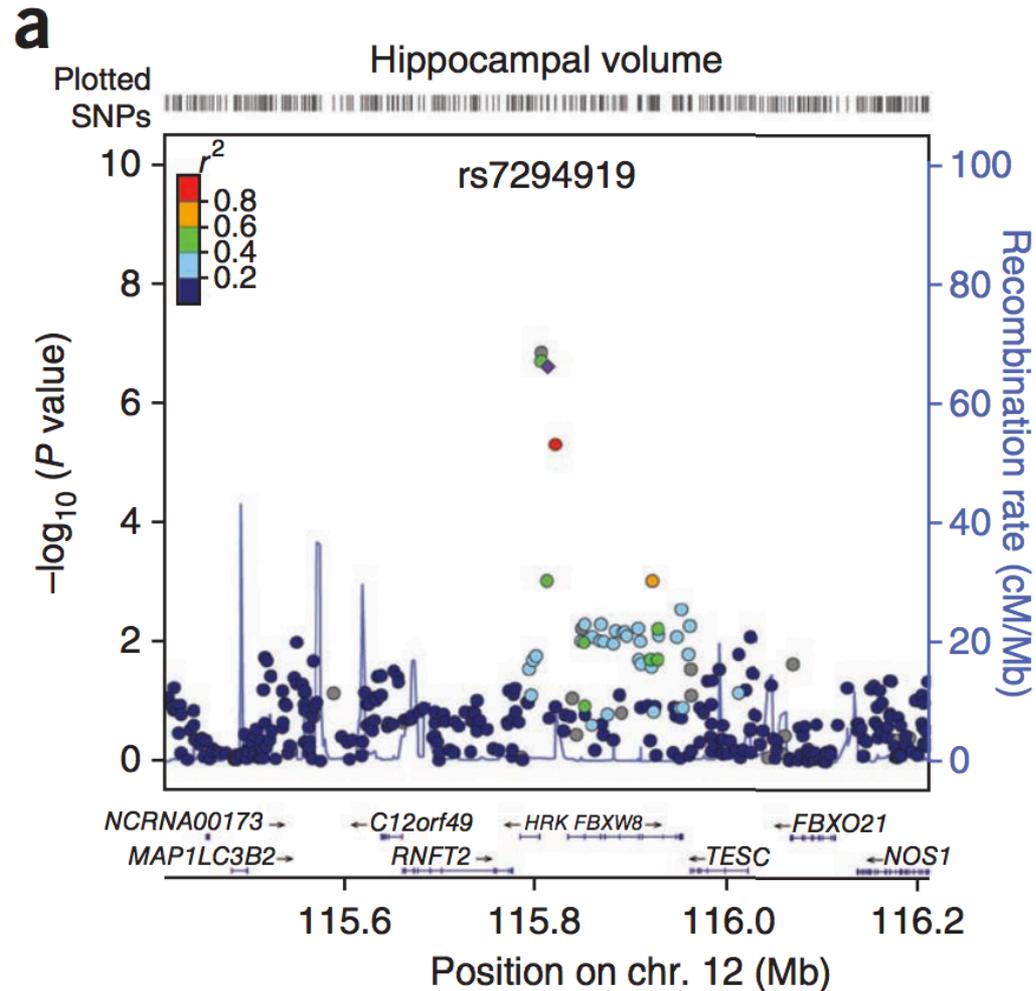
Provide Details for Your Data	Path to Your File	<input type="button" value="Choose File"/> No file chosen File will sent to server and used for plotting (Maximum 200MB) [Help]
	P-Value Column Name	<input type="text"/> Default is P.value
	Marker Column Name	<input type="text"/> Default is MarkerName
	Column Delimiter	<input type="text" value="Tab"/> Default is tab
Specify Region to Display	SNP	<input type="text"/> SNP Reference Name
	Gene	<input type="text"/> Gene Reference Name
	Region	Chr: <input type="text"/> Mb through <input type="text"/> Mb
Custom Annotation	Column Name	<input type="text"/> Name of annotation column
	Category Order	<input type="text"/> Order of annotation categories

Required: Fill in Only ONE of These Three

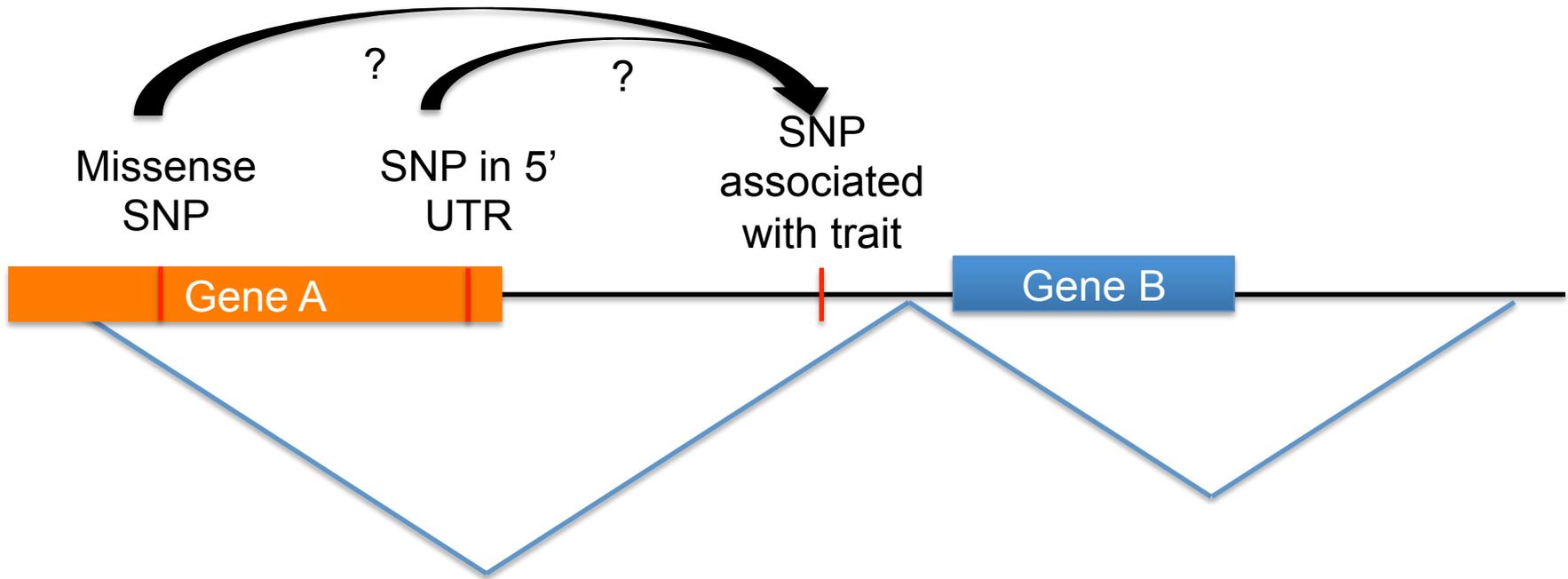
Optional: This overrides Show Annotation below

<https://statgen.sph.umich.edu/locuszoom/genform.php?type=yourdata>

LocusZoom: Making Prettier Pictures



Trying to find possible gene function



We found a genetic variant, but is it in LD with anything of known functionality?

Finding Variants of Known Functionality

The screenshot shows the top navigation bar of the UCSC Genome Browser with the following items: Genomes, Genome Browser, Tools, Mirrors, Downloads, My Data, Help, and About Us. A dropdown menu is open under 'Tools', listing: Blat, Table Browser (circled in red), Variant Annotation Integrator, Gene Sorter, Genome Graphs, In-Silico PCR, LiftOver, VisiGene, and Other Utilities. The text 'Table Browser' is written in red above the dropdown. Below the menu, a search form is visible with fields for 'group' (set to 'Mammal'), 'genome' (set to 'Human'), 'position' (set to 'chr14:56,125,323-56,275,622'), and 'search term' (with a 'submit' button).

Go to the Table Browser in UCSC Genome Browser

The screenshot shows the configuration page for the UCSC Table Browser. The settings are as follows: clade: Mammal, genome: Human, assembly: Feb. 2009 (GRCh37/hg19), group: Variation, track: Common SNPs(138), table: snp138Common, region: position (selected), identifiers (names/accessions): paste list, upload list, filter: create (circled in red), intersection: create, correlation: create, output format: all fields from selected table, Send output to: Galaxy, GREAT, output file: chr14.txt, file type returned: plain text (selected). The text 'Click to create a filter' is written in red next to the 'filter: create' button. At the bottom, there are buttons for 'get output' and 'summary/statistics'.

Finding Variants of Known Functionality

Select interpretable functional Variants

func does * unknown coding-synon intron near-gene-3
 near-gene-5 ncRNA nonsense missense stop-loss
 frameshift cds-indel untranslated-3 untranslated-5 splice-3
 splice-5

Click to create a filter

clade: genome: assembly:
group: track:
table:
region: genome ENCODE Pilot regions position
identifiers (names/accessions):
filter:
intersection:
correlation:
output format: Send output to [Galaxy](#) [GREAT](#)
output file: (leave blank to keep output in browser)
file type returned: plain text gzip compressed

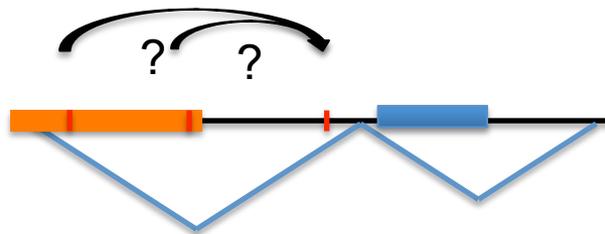
Get output spreadsheet

Finding Variants of Known Functionality

#filter: (FIND_IN_SET('splice-5', snp138Common.func)>0 OR FIND_IN_SET('splice-3', snp138Common.func)>0 OR FIND_IN_SET('untranslat

#bin	chrom	chromStart	chromEnd	name	refNCBI	refUCSC	observed	func
1012	chr14	56068483	56068484	rs116289145	C	C	C/T	intron,ncRNA,untranslated-5
1012	chr14	56068520	56068521	rs10083303	T	T	C/T	intron,ncRNA,untranslated-5
1012	chr14	56078738	56078739	rs1138345	T	T	G/T	ncRNA,untranslated-5
1012	chr14	56079038	56079039	rs34879854	A	A	A/T	coding-synon,ncRNA
1012	chr14	56094725	56094726	rs17128636	C	C	A/C	coding-synon,ncRNA
1012	chr14	56096685	56096686	rs74053638	A	A	A/C	coding-synon,ncRNA
1012	chr14	56096730	56096731	rs2274075	A	A	A/G	coding-synon,ncRNA
1013	chr14	56146356	56146357	rs11546	G	G	A/G	coding-synon,ncRNA

Variants of known function



Are variants of known function in LD with our top hit?

Finding Variants of Known Functionality

Query SNPs

Input SNPs: [Example](#)

One snp per line:

Search Options

SNP data set: r^2 threshold:

Population panel: Distance limit:

Output Options

Download to: Include each query snp as a proxy for itself
 Suppress warning messages in output

<http://www.broadinstitute.org/mpg/snap/ldsearch.php>

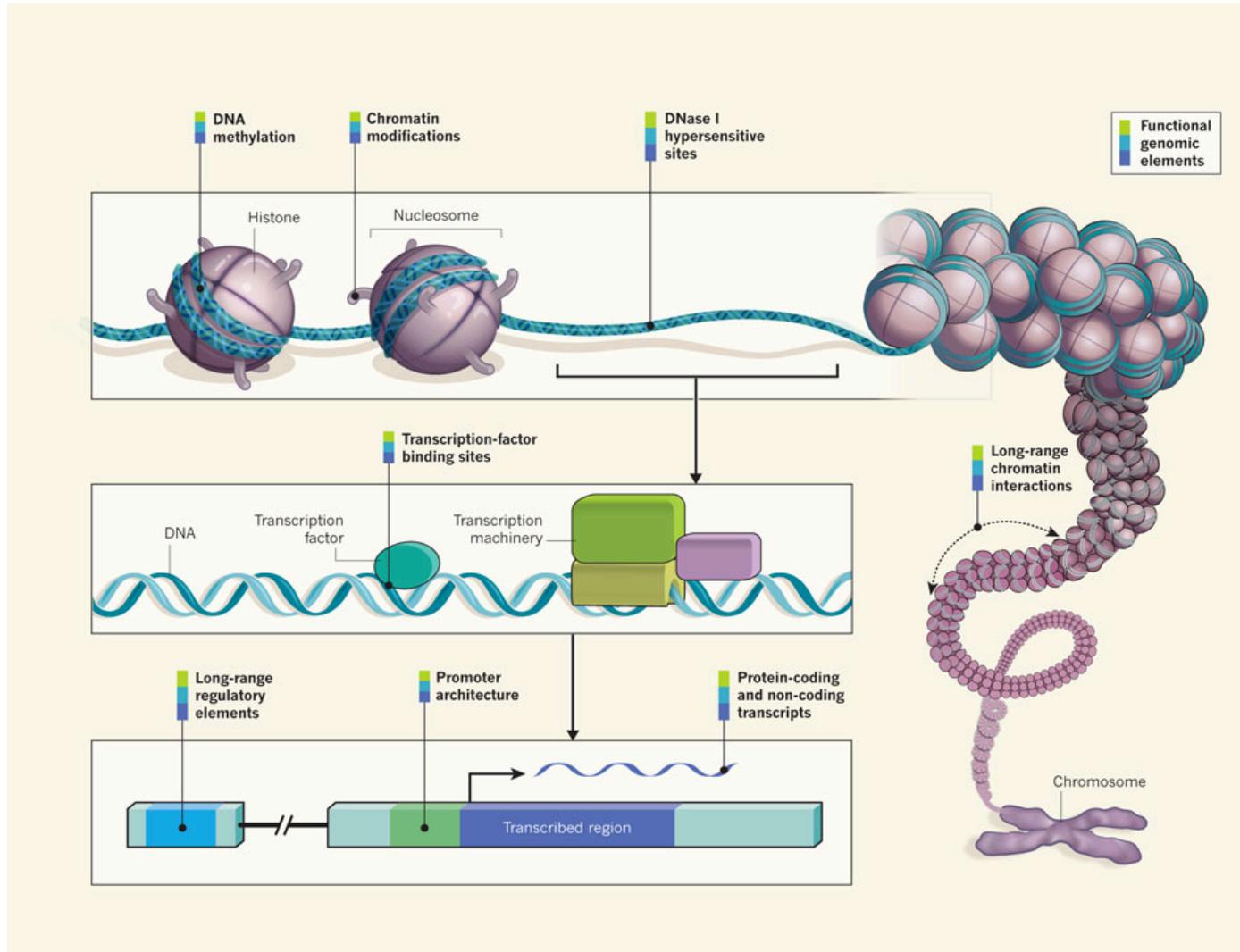
Finding Variants of Known Functionality

SNP	Proxy	Distance	RSquared	DPrime	Arrays	Chromosome	Coordinate_HG18
rs945270	rs945270	0	1	1	None	chr14	55270226
rs945270	rs8017172	1425	1	1	I2,I5,I6,I6	chr14	55268801
rs945270	rs1959089	2636	0.875	1	None	chr14	55267590
rs945270	rs1953350	3199	0.875	1	None	chr14	55267027
rs945270	rs1953351	3248	0.875	1	None	chr14	55266978
rs945270	rs1953352	3314	0.875	1	I3,I5,I6,I6	chr14	55266912
rs945270	rs2342589	3405	0.875	1	None	chr14	55266821
rs945270	rs2342588	3434	0.875	1	None	chr14	55266792
rs945270	rs868202	4711	0.875	1	None	chr14	55265515
rs945270	rs10129414	7201	0.875	1	None	chr14	55263025
rs945270	rs8012377	9060	0.875	1	AN,A5,A6	chr14	55261166
rs945270	rs10145631	11143	0.875	1	A6,OQ	chr14	55259083
rs945270	rs8014725	13520	0.875	1	None	chr14	55256706
rs945270	rs7157327	8023	0.84	0.964	None	chr14	55262203
rs945270	rs8021018	22965	0.807	0.929	I2,I5,I6,I6	chr14	55247261

Are any of the proxy SNPs in the list of functional SNPs?... Nope.

Our hit cannot be explained by known functional variants

Epigenetics & ENCODE



(Ecker et al., 2012)

ENCODE in UCSC Genome Browser

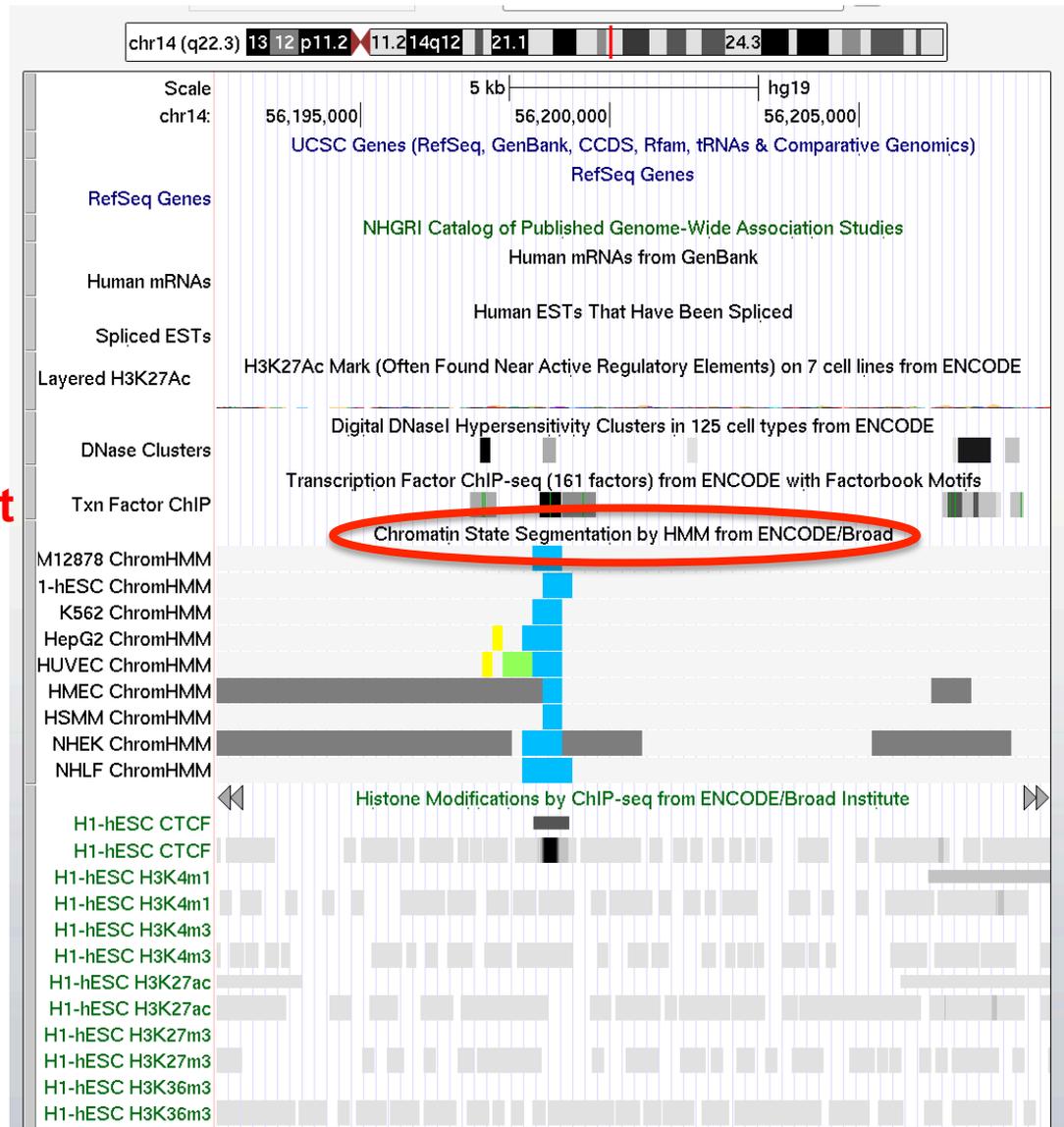
Regulation refresh

<input checked="" type="checkbox"/> ENCODE Regulation... show	<input type="checkbox"/> 18 CD34 DnaseI hide	<input type="checkbox"/> CpG Islands... hide	<input type="checkbox"/> ENC Chromatin... hide	<input type="checkbox"/> ENC DNA Methyl... hide	<input type="checkbox"/> ENC DNase/FAIRE... hide
<input checked="" type="checkbox"/> ENC Histone... hide show	<input type="checkbox"/> ENC RNA Binding... hide	<input type="checkbox"/> ENC TF Binding... hide	<input type="checkbox"/> FSU Repli-chip hide	<input type="checkbox"/> Genome Segments hide	<input type="checkbox"/> 18 NKI Nuc Lamina... hide
<input type="checkbox"/> 18 ORegAnno hide	<input type="checkbox"/> Stanf Nucleosome hide	<input type="checkbox"/> SUNY SwitchGear hide	<input type="checkbox"/> 17 SwitchGear TSS hide	<input type="checkbox"/> TFBS Conserved hide	<input type="checkbox"/> TS miRNA sites hide
<input type="checkbox"/> UCSF Brain Methyl hide	<input type="checkbox"/> UMMS Brain Hist hide	<input type="checkbox"/> UW Repli-seq hide	<input type="checkbox"/> Vista Enhancers hide		

Comparative Genomics refresh

Add some tracks that may help us explore function

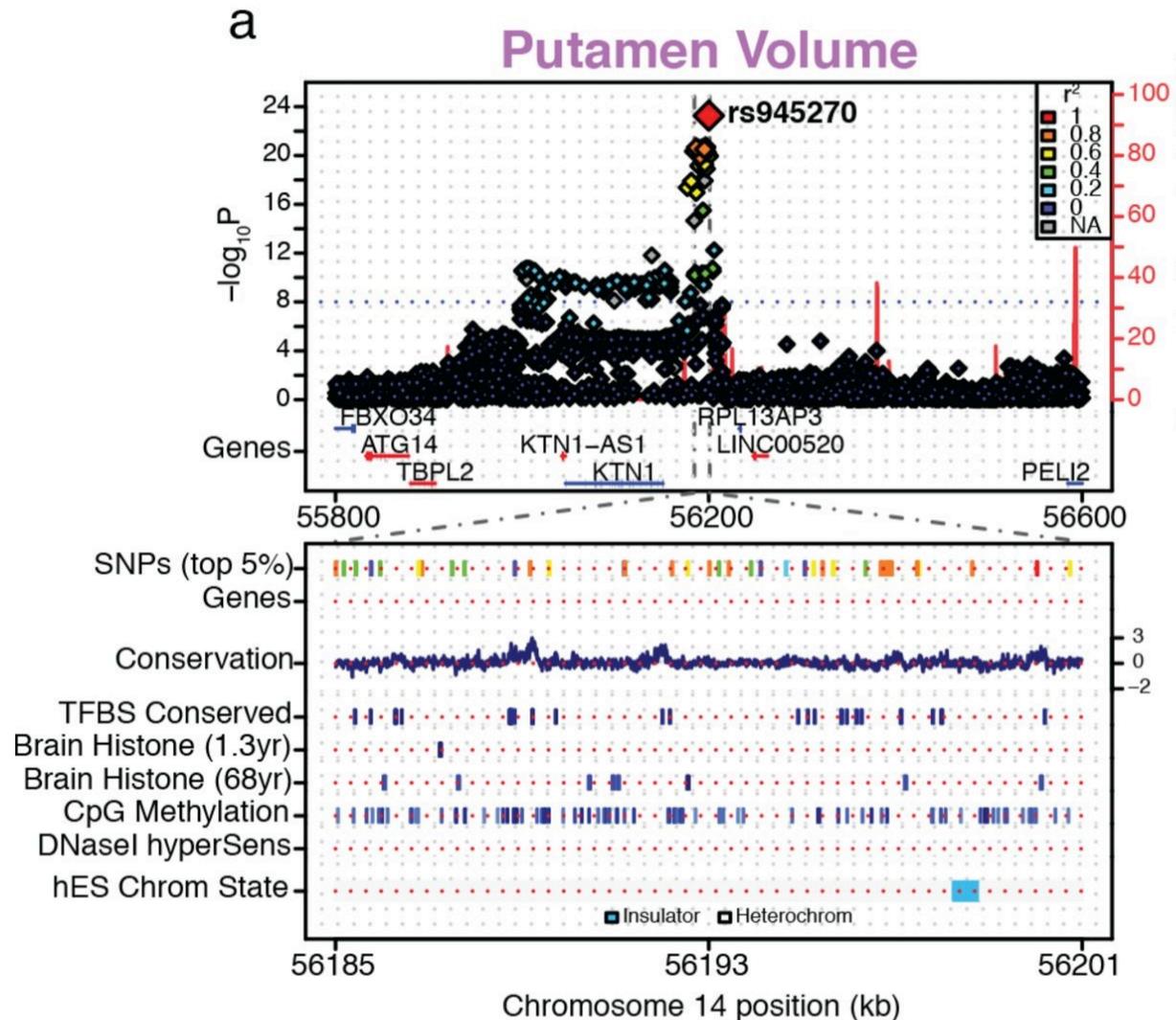
Epigenetics & ENCODE



Click to see what the colors mean

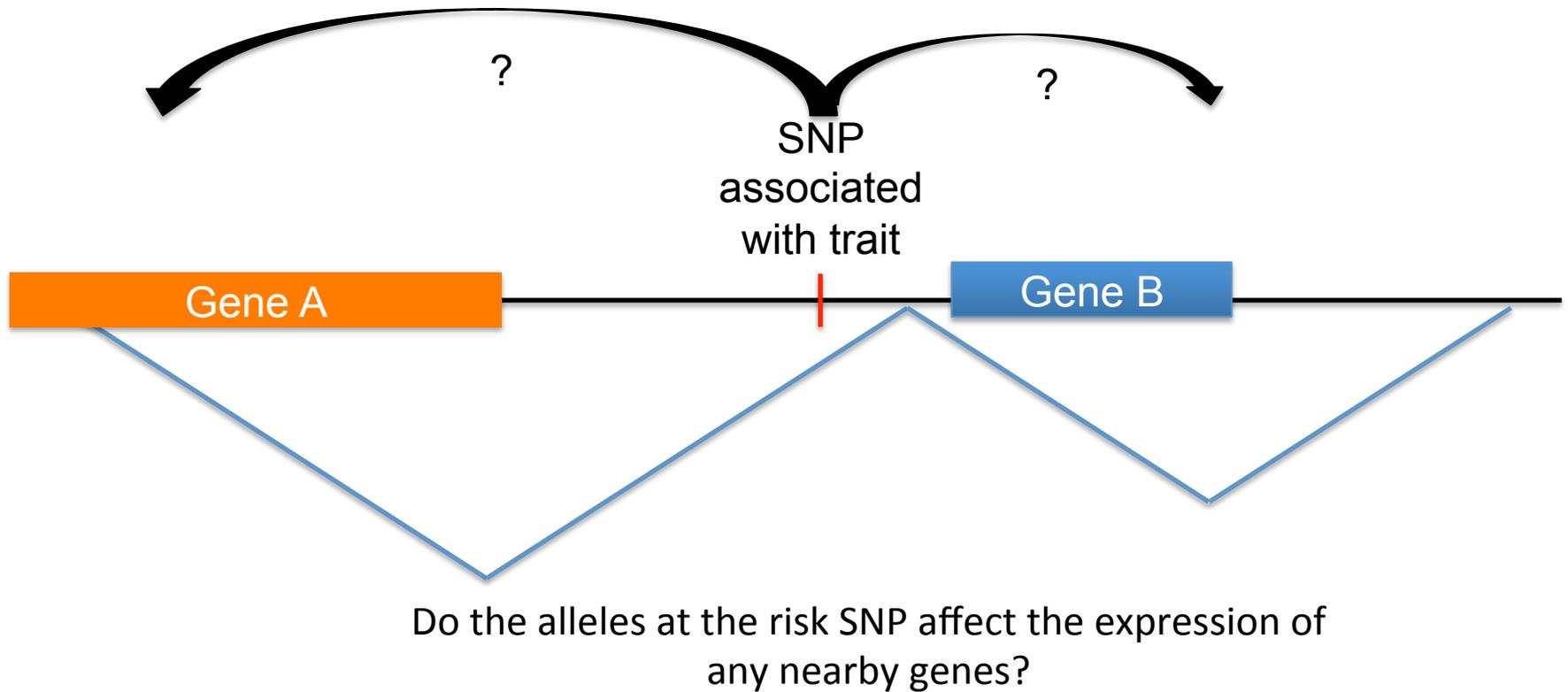
Appears to be a CTCF binding site (insulator) very close to the locus!

LocusTrack: Other ways to visualize



<http://gump.qimr.edu.au/general/gabrieC/LocusTrack/index.html>

expression QTLs (eQTLs)



A way to move from variant to gene.

eQTL databases

Pritchard eQTL database

Welcome to eqtl.uchicago.edu/

Instructions
Search using a sequence name, gene name, locus, or other landmark. The wildcard character * is allowed. To center on a location, click the ruler. Use the Scroll/Zoom buttons to change magnification and position.

Examples RPS26, chr12:54655000..54680000, *RPS26*

Search
To return to the homepage, and for documentation click here. This site was last updated in June 2010. Recent updates have included DNase-sensitivity eQTLs (Degner et al. 2012), eQTLs from an article under review (Mangravite, Engelhardt, et al.), Estimates of probability of causal SNPs from Galthey et al. 2012, and eQTLs from liver in Innocenti et al. 2011. For the cisQTL track, each QTL is now linked to a set of summary plots. You can download all of the data contained in this browser here.

Landmark or Region: **Reports & Analysis:**

Data Source
Welcome to eqtl.uchicago.edu/

Tracks
 Overview All on All off

Ideogram

General All on All off

- Degner, Pat, Pope-Heggi et al. (2012). -log10(P), LCLs, 70 Nigerian HAPMAP ids, DNase sensitivity eQTLs (sEQTLs) by DNase-seq
- Veyrieras et al. (2008). posterior probability, LCLs, 210 HAPMAP ids, multipopulation
- Pickrell et al. (2010). -log10(P), LCLs, 69 Nigerian HAPMAP ids, RNA-Seq for splicing eQTLs
- Omas et al. (2009). -log10(P), LCLs, 75 Europeans
- Schadt et al. (2007). -log10(P), liver, 427 ids, European descent
- Mangravite, Engelhardt, et al. (in review). Bayes Factor, LCLs, 480 ids from Cholesterol And Pharmacogenetics (CAP) study
- Montgomery et al. (2010). -log10(P), LCLs, 60 European HAPMAP ids, RNA-Seq for transcript eQTLs
- Omas et al. (2009). -log10(P), T-cells, 75 Europeans
- Myers et al. (2007). -log10(P), cortex from control brain, 270 ids, European descent
- Pickrell et al. (2010). -log10(P), LCLs, 69 Nigerian HAPMAP ids, RNA-Seq for eQTLs
- Zeller et al. (2010). -log10(P), LCLs, 69 Nigerian HAPMAP ids, Monocytes, 1,490 ids recruited in RNA-Seq for eQTLs
- Stranger et al. (2007). -log10(P), LCLs, 210 HAPMAP ids, 4 single populations
- Galthey et al. (2012). Posterior probability causal, LCLs, 210 multi-log10(P), LCLs, 60 European population HAPMAP ids, RNA-ChIP/HAPMAP ids, RNA-Seq for exon for eQTLs
- Montgomery et al. (2010). -log10(P), LCLs, 60 European HAPMAP ids, RNA-Seq for exon for eQTLs
- Veyrieras et al. (2008). -log10(Bayes Factor), Liver, 266 ids, RNA-ChIP for eQTLs
- Innocenti et al. (2011). -log10(Bayes Factor), Liver, 266 ids, RNA-ChIP for eQTLs
- Omas et al. (2009). -log10(P), Fibroblasts, 75 Europeans

Genes All on All off

<http://eqtl.uchicago.edu/cgi-bin/gbrowse/eqtl/>

Blood eQTL browser

Blood eQTL browser

This web page accompanies the manuscript titled *Systematic identification of trans-eQTLs* which has been published in Nature Genetics. If you want to use any of the cis- or trans-eQTLs as indicated below. For further questions, contact the corresponding author: lude@ludesign.nl

Download eQTL Results

You can download the full cis- and trans-eQTLs, detected at a false-discovery rate of 0.50:
Cis-eQTLs (FDR 0.5)
Trans-eQTLs (FDR 0.5)

How to cite

If you use the eQTLs present on this website in your paper or research, please cite our work: <http://dx.doi.org/10.1038/ng.1000>

Query eQTL Results

Or, you can query the cis- and trans-eQTLs below (examples: rs7807018 or VWCE):

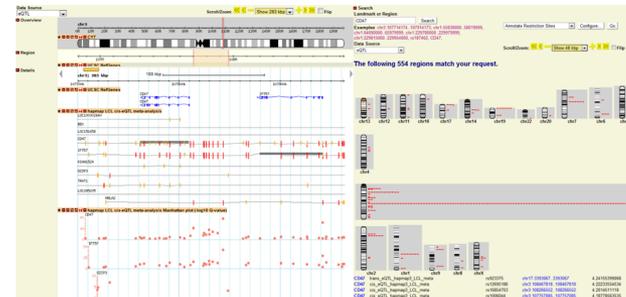
Gene or SNP name:

<http://genenetwork.nl/bloodeqtlbrowser/>

seeQTL

seeQTL: A searchable human eQTL browser and database

Department of Biostatistics, Computer Sciences and Genetics
University of North Carolina at Chapel Hill



<http://gbrowse.csbio.unc.edu/cgi-bin/gb2/gbrowse/seeqtl/>

NCBI eQTL Browser

Search Parameters

Analysis ID

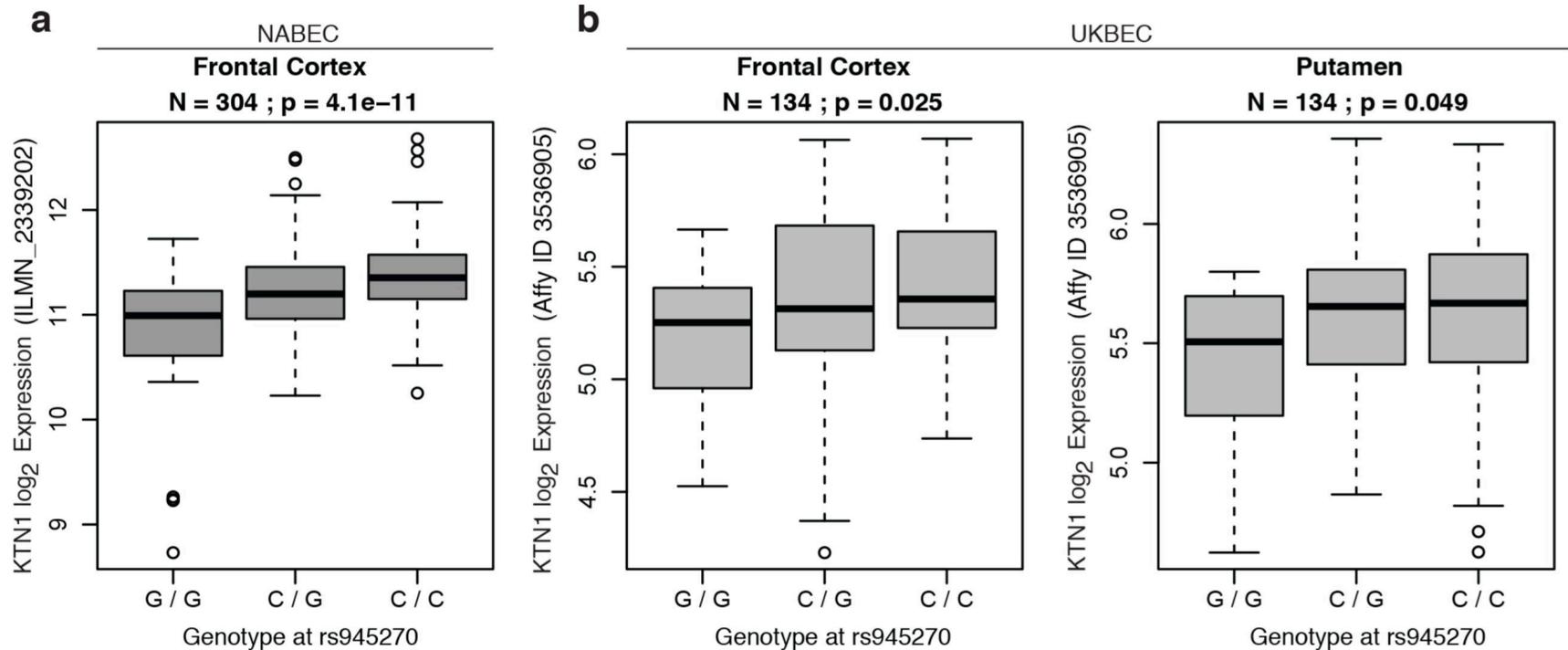
ID	Tissue	Title
<input type="checkbox"/>	1 Lymphoblastoid	Transcriptome genetics using second generation sequencing in a Caucasian population.
<input type="checkbox"/>	2 Liver	Mapping the genetic architecture of gene expression in human liver
<input type="checkbox"/>	3 Brain Cerebellum	Abundant quantitative trait Loci exist for DNA methylation and gene expression in human brain
<input type="checkbox"/>	4 Brain Frontal Cortex	Abundant quantitative trait Loci exist for DNA methylation and gene expression in human brain
<input type="checkbox"/>	5 Brain Temporal Cortex	Abundant quantitative trait Loci exist for DNA methylation and gene expression in human brain
<input type="checkbox"/>	6 Brain Pons	Abundant quantitative trait Loci exist for DNA methylation and gene expression in human brain
<input type="checkbox"/>	7 Lymphoblastoid	Population genomics of human gene expression

SNP filters
RS numbers

Gene Expression Filters
Gene symbols, gene IDs, RefSeq IDs, and/or Pr

<http://www.ncbi.nlm.nih.gov/projects/gap/eqtl/index.cgi>

eQTL phone a friend

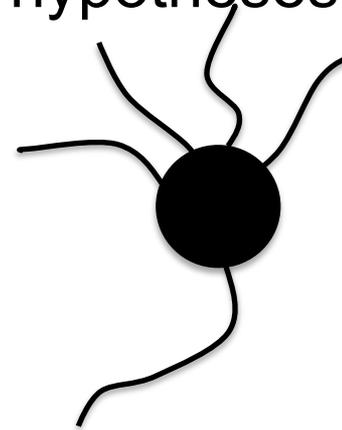


This SNP affects a gene (replicated in brain),
we now have a gene!

When and Where is Gene Expressed?

- 86-95% of genes are expressed in the brain at some point during the lifespan and 90% of those were differentially regulated across region or time (Kang et al., 2011; Miller et al., 2014).
- Expression of a gene in brain does little to implicate it as causal.
- However, finding the time period or region of gene expression may lead us to cell type hypotheses.

Gene A



When and Where is Gene Expressed?

BRAINSPAN
ATLAS OF THE DEVELOPING HUMAN BRAIN

Home **Developmental Transcriptome** Prenatal LMD Microarray ISH Reference Atlas Download Documentation Help

Enter Gene Name, Gene Symbol, Entrez Gene ID or Ensembl ID

Gene Search
 Differential Search

KTN1

Search

Expression by time →

1 - 2 of 2

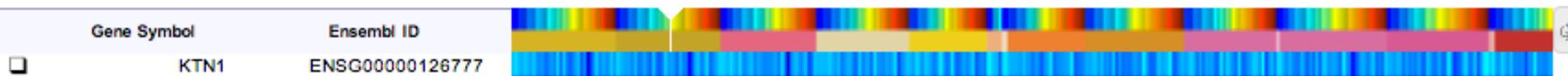
Donor H376.IIA.51 Age: 8 pcw dorsolateral prefrontal cortex (DFC)



Expression by region →

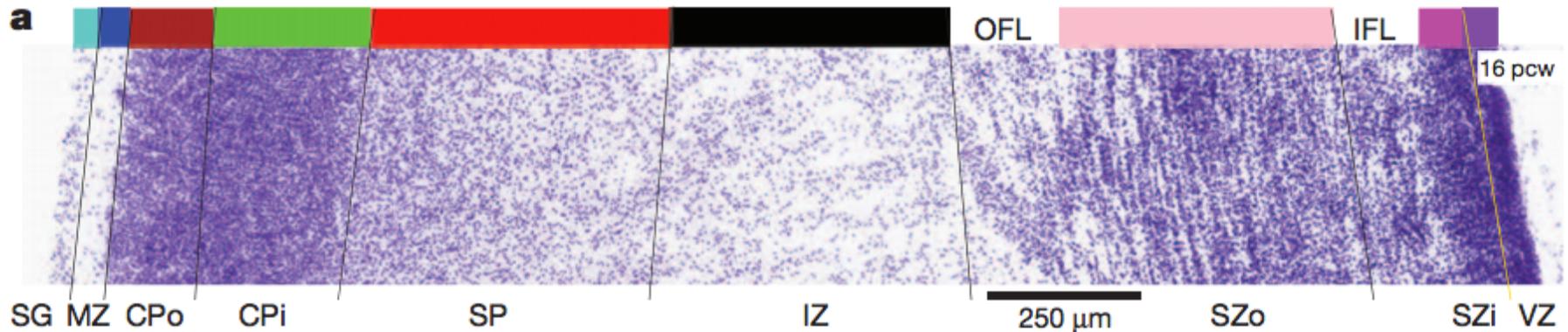
1 - 2 of 2

Donor H376.IIA.51 Age: 8 pcw dorsolateral prefrontal cortex (DFC)



<http://brainspan.org/rnaseq/search/index.html>

Where in Fetal Development is Gene Expressed?



BRAINSPAN
ATLAS OF THE DEVELOPING HUMAN BRAIN

Home Developmental Transcriptome **Prenatal LMD Microarray** ISH Reference Atlas Download Documentation Help

Gene Search Differential Search Gene Classification

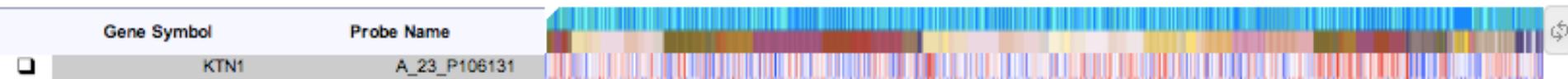
Enter Gene Name, Gene Symbol, NCBI Accession Number or Entrez Gene ID

Show exact matches only

Expression by lamina →

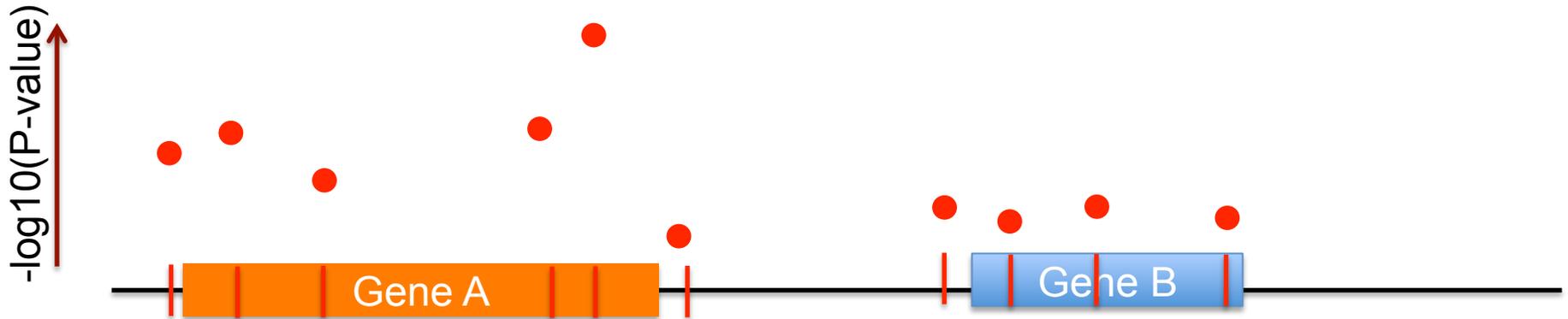
1 - 5 of 5

Donor H376.IV.02 Age: 21 pcw SG in frontal polar cortex (fSGfp)



<http://www.brainspan.org/lcm/search/index.html>

Gene-based tests



Combines SNP associations across genes to form a gene based p-value

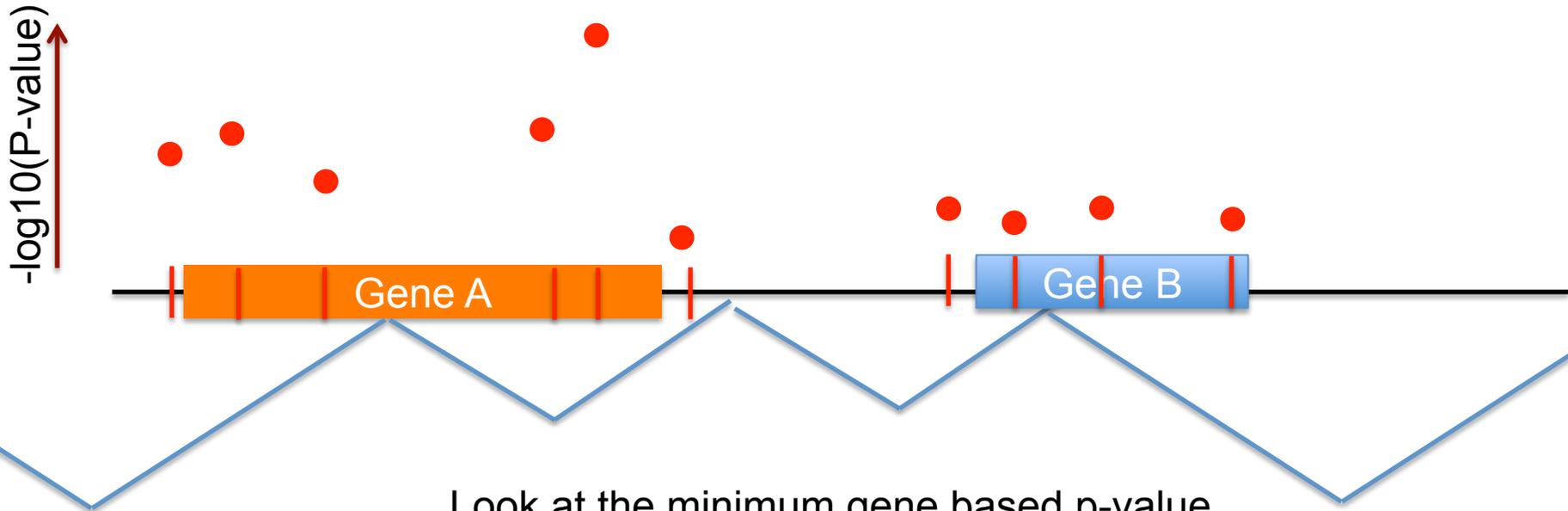
Advantages

- Greater interpretability
- Fewer multiple comparisons
- Can feed into pathway based approaches

Disadvantages

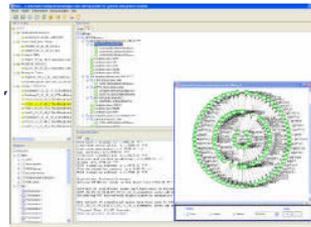
- Ignores intergenic variation
- Generally ignores direction of association
- Ignores that a variant within the intron of one gene may be affecting a totally different gene

Tools for Gene Based Analyses



Look at the minimum gene based p-value accounting for the number of independent SNPs

See GATES algorithm implemented in KGG toolbox (Li et al., 2011)



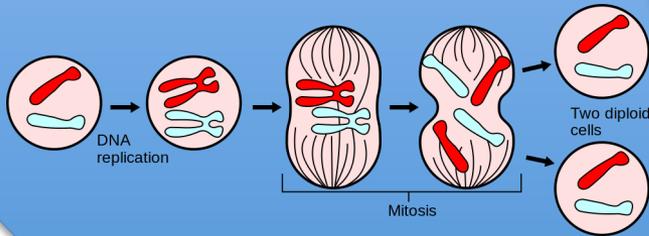
Pathway Analysis

Look for enrichment of your SNPs in known pathways

Genes involved in Mitosis

ASPM
KI67
NES
CHK1

....
(300 genes)



Advantages

- Amazing interpretability – exactly what you're looking for

Genes Associated with my trait by gene based test

Gene A
Gene B
Gene C

...
(100 genes)

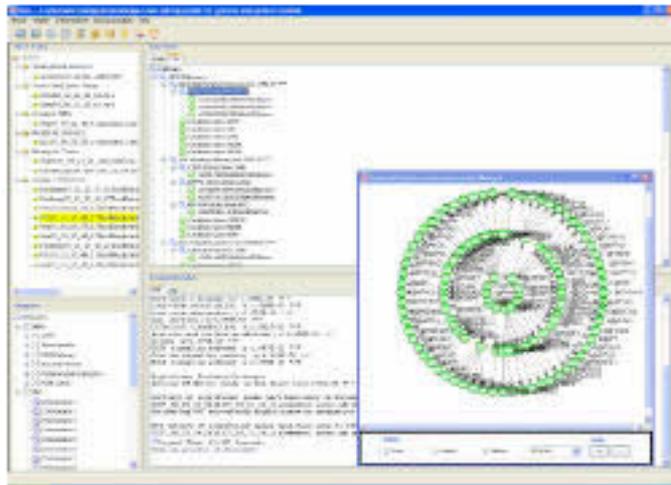
Gene D
Gene E
Gene F
...
(10 genes)

Disadvantages

- Uses gene based tests
- Pathway gene lists are generally not well known

Tools for Pathway Based Analyses

Knowledge-Based Mining System for Genome-Wide Genetic Studies (KGG)



<http://statgenpro.psychiatry.hku.hk/limx/kgg/index.html>

MAGENTA

MAGENTA: Meta-Analysis Gene-set Enrichment of variant Associations



<http://www.broadinstitute.org/mpg/magenta/>

Mouse QTLs

GeneNetwork

University of Tennessee: www.genenetwork.org

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Select and Search

Species:

Group: [Info](#)

Type:

Data Set: [Info](#)

Databases marked with ** suffix are not public yet.
Access requires [user login](#).

Get Any:

Enter terms, genes, ID numbers in the **Get Any** field.
Use * or ? wildcards (Cyp*a?, synap*).
Use **Combined** for terms such as *tyrosine kinase*.

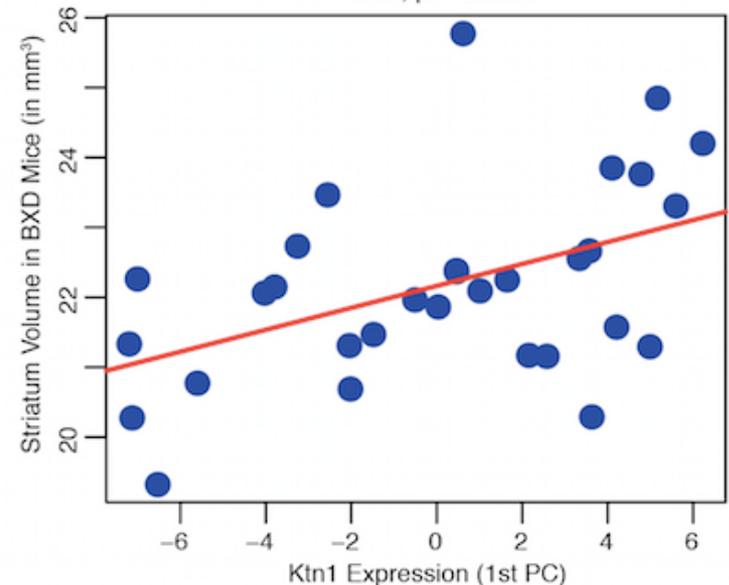
Combined:

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Striatal volume vs Ktn1 expression in BxD mouse
 $r = 0.47$; $p = 0.0071$



Conclusions

- Identifying the genetic locus is a causal foothold into understanding novel biological mechanisms.
- There are many databases and tools that will allow you to form hypotheses about the biological mechanisms.
- If you are characterizing one known variant in brain, these tools should still be useful for understanding the genome.
- It's easy to make a story! Let the evidence guide you.

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