

Discovering new Alzheimer disease
related genes and gene networks
through systems biology methods

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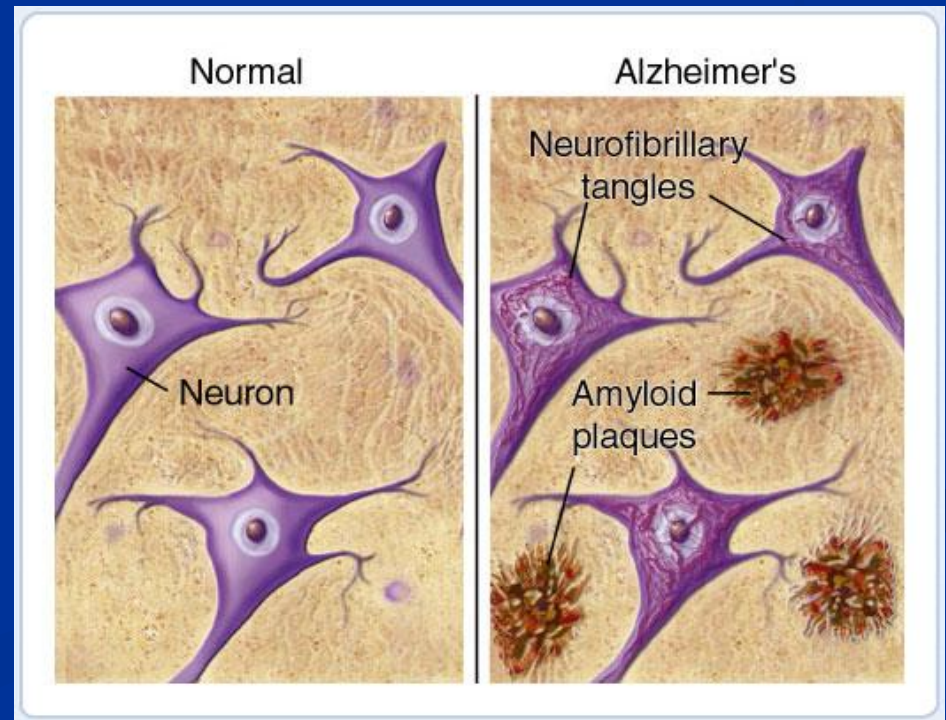
Background of Alzheimer's Disease (AD)



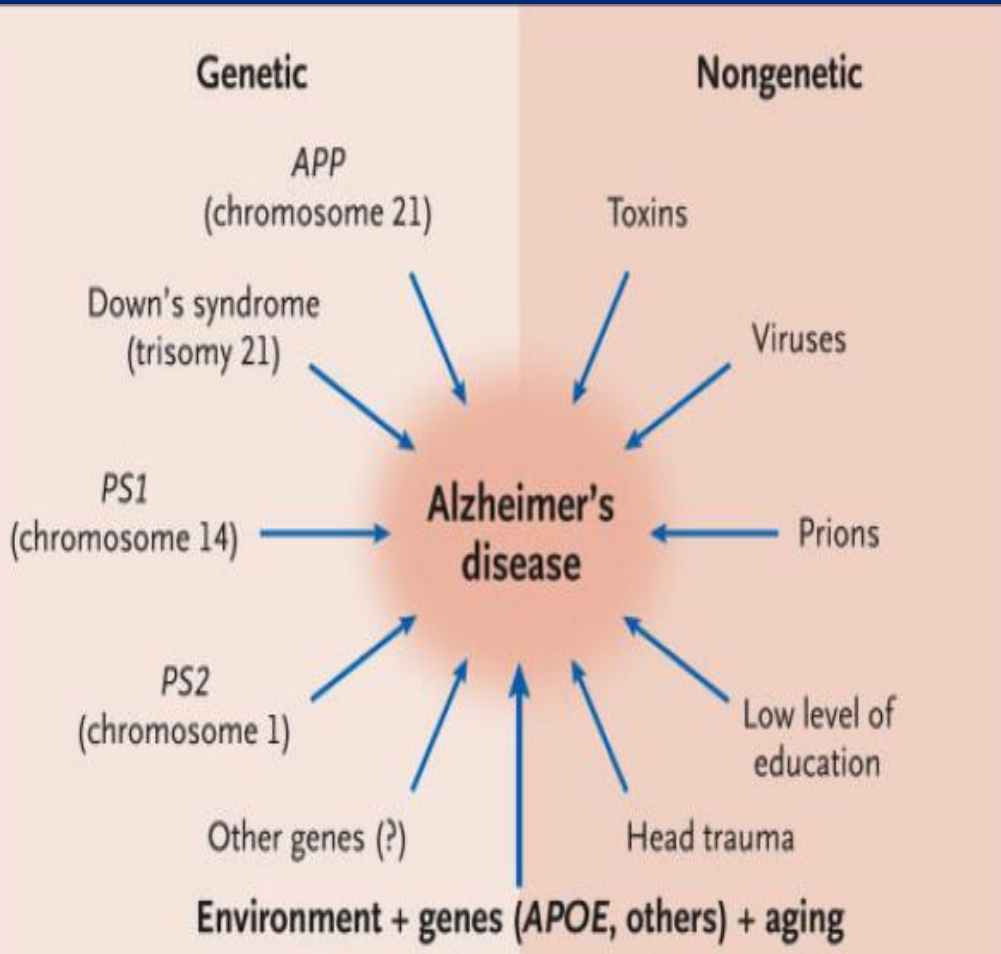
- ◆ One of most common neurodegenerative diseases
- ◆ First described by Alois Alzheimer in 1906 and was named after him
- ◆ There are about 27 million sufferers worldwide
- ◆ AD is predicted to affect 1 in 85 people globally by 2050

Features of Alzheimer's Disease

- ◆ Symptoms: memory loss, cognitive impairment, language breakdown, bodily function loss
- ◆ Neuropathology:
 - Amyloid plaques
 - Neurofibrillary tangles
- ◆ Brain regions:
 - Hippocampus
 - Basal forebrain
 - Cortex



Known causal factors of AD



- ◆ Aging
- ◆ Genetics (APP, APOE, PS1, PS2, etc)
- ◆ Environment (Toxins, Stress, Head trauma, etc)

Several competing hypotheses to explain cause of AD

- ◆ cholinergic hypothesis
- ◆ amyloid hypothesis
- ◆ tau hypothesis
- ◆ myelin hypothesis
- ◆ oxidative stress hypothesis
- ◆ gene mutation hypothesis

Tons of report about AD

The image shows a screenshot of a web browser displaying the PubMed website. The search bar contains the text "alzheimer's disease" and the search button is highlighted. The results page shows "Results: 1 to 20 of 68470". A large orange callout box is overlaid on the page, containing the text "Pubmed 76,800 records". The callout box has a white scroll bar on the left side. The background shows the PubMed interface with various filters and search options.

Search: PubMed
alzheimer's disease

Display Settings: Summary, 20 per page, Sorted by Recently Added

Results: 1 to 20 of 68470

1. [\[VEGF and central nervous system diseases.\]](#)
Zhang LY, Fan YY, Liu Z.
Zhejiang Da Xue Bao Yi Xue Ban. 2009 Nov;38(6):644-648. Chinese.
PMID: 20014493 [PubMed - as supplied by publisher]

2. [\[Germline humanization of a murine Abeta antibody and crystal structure of the humanized antibody.\]](#)
Robert R, Streltsov VA, Newman J, Pearce LA, Wark KL, Dolezal O.
Protein Sci. [Epub ahead of print]
PMID: 20014445 [PubMed - as supplied by publisher]

3. [\[Patient death as a censoring event or competing risk event in models of nursing home placement.\]](#)
Szychowski JM, Roth DL, Clay OJ, Mittelman M.
Stat Med. [Epub ahead of print]
PMID: 20014354 [PubMed - as supplied by publisher]

4. [\[Intracerebral Transplantation of Bone Marrow-Derived Mesenchymal Stem Cells Reduces Amyloid-Beta Deposition and Rescues Memory Deficits in Alzheimer's Disease Mice by Modulation of Immune Responses.\]](#)
Lee JK, Jin HK, Endo S, Schuchman EH, Carter JE, Bae J.
Stem Cells. [Epub ahead of print]
PMID: 20014009 [PubMed - as supplied by publisher]

5. [\[Memory deficit in patients with subcortical vascular cognitive impairment versus Alzheimer-type dementia: the sensitivity of the 'word list' subtest on the Wechsler Memory Scale-III.\]](#)
Suades-Gonzalez E, Jodar-Vicente M, Perdrix-Solas D.
Rev Neurol. 2009 Dec 16;49(12):623-629. Spanish.
PMID: 20013713 [PubMed - as supplied by publisher]

6. [\[Freeze-Fracture Electron Microscopy on Domains in Lipid Mono- and Bilayer on Nano-Resolution Scale.\]](#)
Boschardes-Garcia S, Strohmann D.

Filter your results:
All (68470)
Review (13972)
Free Full Text (10503)
Manage Filters

Also try:
alzheimer's disease review
alzheimer's disease amyloid
models alzheimer's disease
treatment alzheimer's disease
stress alzheimer's disease

Titles with your search terms
ADAS-cog (Alzheimer's Disease Assessment Scale- [Bratisl Lek Listy. 2000]
Effect of dimebon on cognition, activities of daily living, behaviour, and gl [Lancet. 2008]
Cholinesterase inhibitors for Alzheimer's disease [Cochrane Database Syst Rev. 2006]
See more...

4946 free full-text articles in PubMed Central
Apolipoprotein E-mimetics inhibit neurodegeneration and n [PLoS One. 2009]
Coenzyme Q10 effects in neurodegenerative diseases [Neurologist. 2009]

Most of researches are isolated and separated



Systems Biology:

An integrative bioinformatic approach to translate between DNA sequence polymorphism, gene expression, phenotype, genotype and disease susceptibility

Systems Genetics is one kind of Systems Biology

What is Systems Genetics?

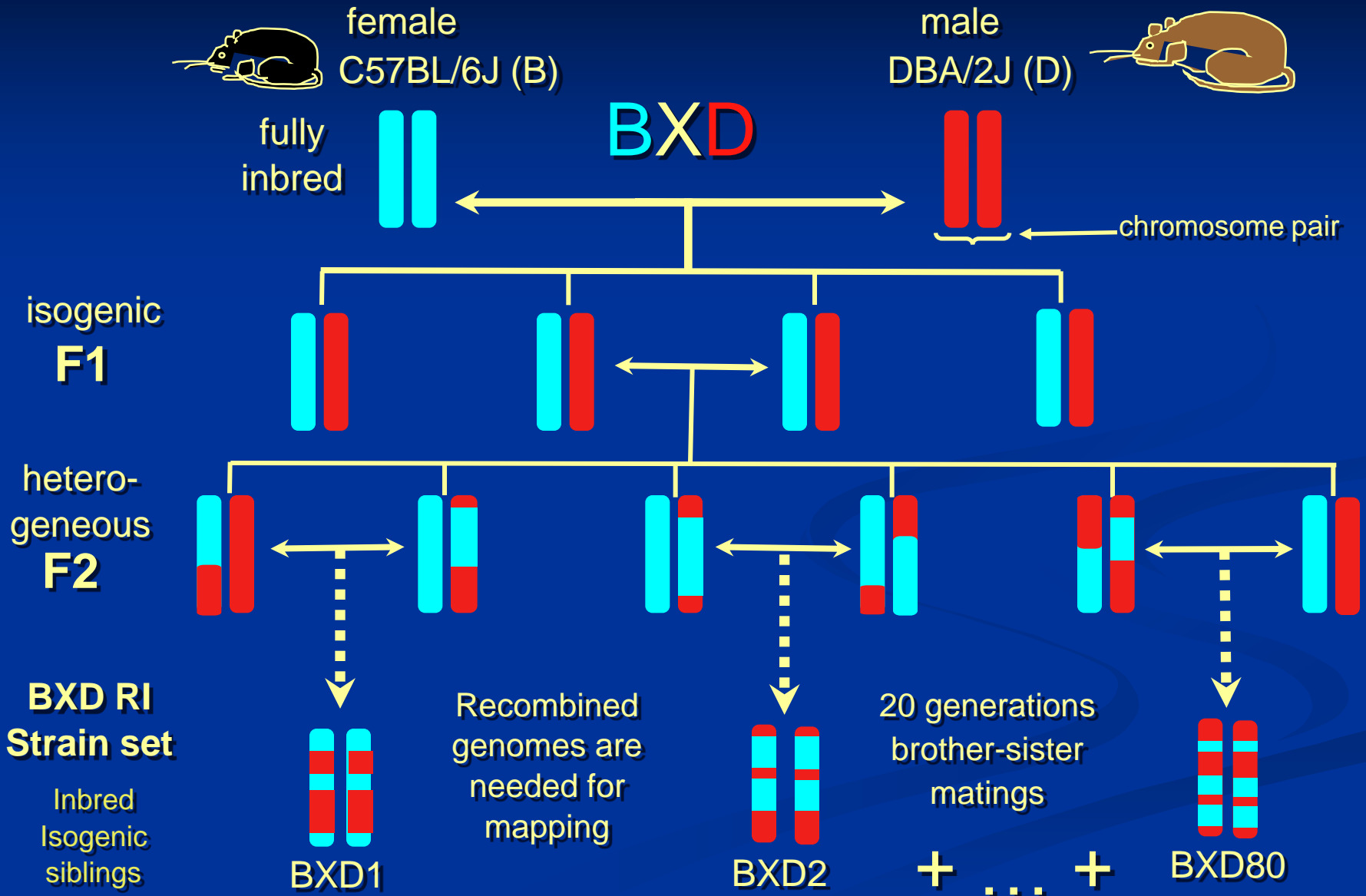
Mendelian Genetics = One gene to one trait
Huntington's disease, albinism, etc.

Complex Trait Genetics = Several genes to one trait
Most of phenotypes or human diseases

Systems Genetics = Many genes, gene pathways
and gene networks to many traits
Advanced approach to study human diseases

Systems Genetics requires:
Dense phenotypes and genotypes
Gene expression data
Genetic Reference Populations

How to make genetic reference population



Multiscale integration & cumulative data

environmental responses

disease resistance or susceptibility

structure

physiology

behavior

GRPs (e.g. BXD)

N genetically defined lines
GENETIC COVARIANCE

epigenetic variation

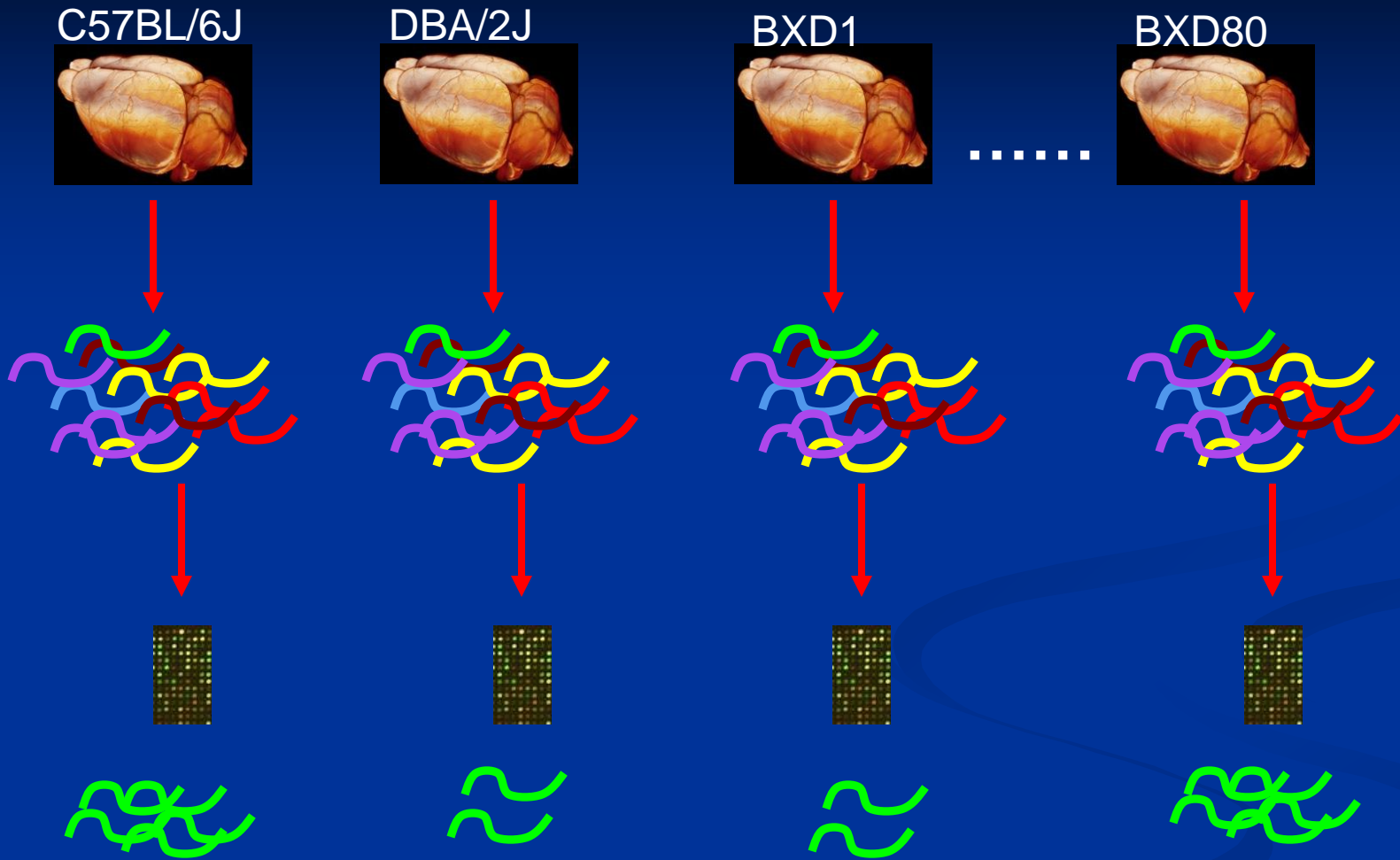
developmental variation

molecular expression variation

Complex (or Quantitative) Traits

- They are determined by multiple gene loci (polygene) and multiple environmental inputs.
- As a result, such traits tend to be normally distributed.
- A quantitative trait locus (QTL) is a site on a chromosome containing a gene or

Gene Expression

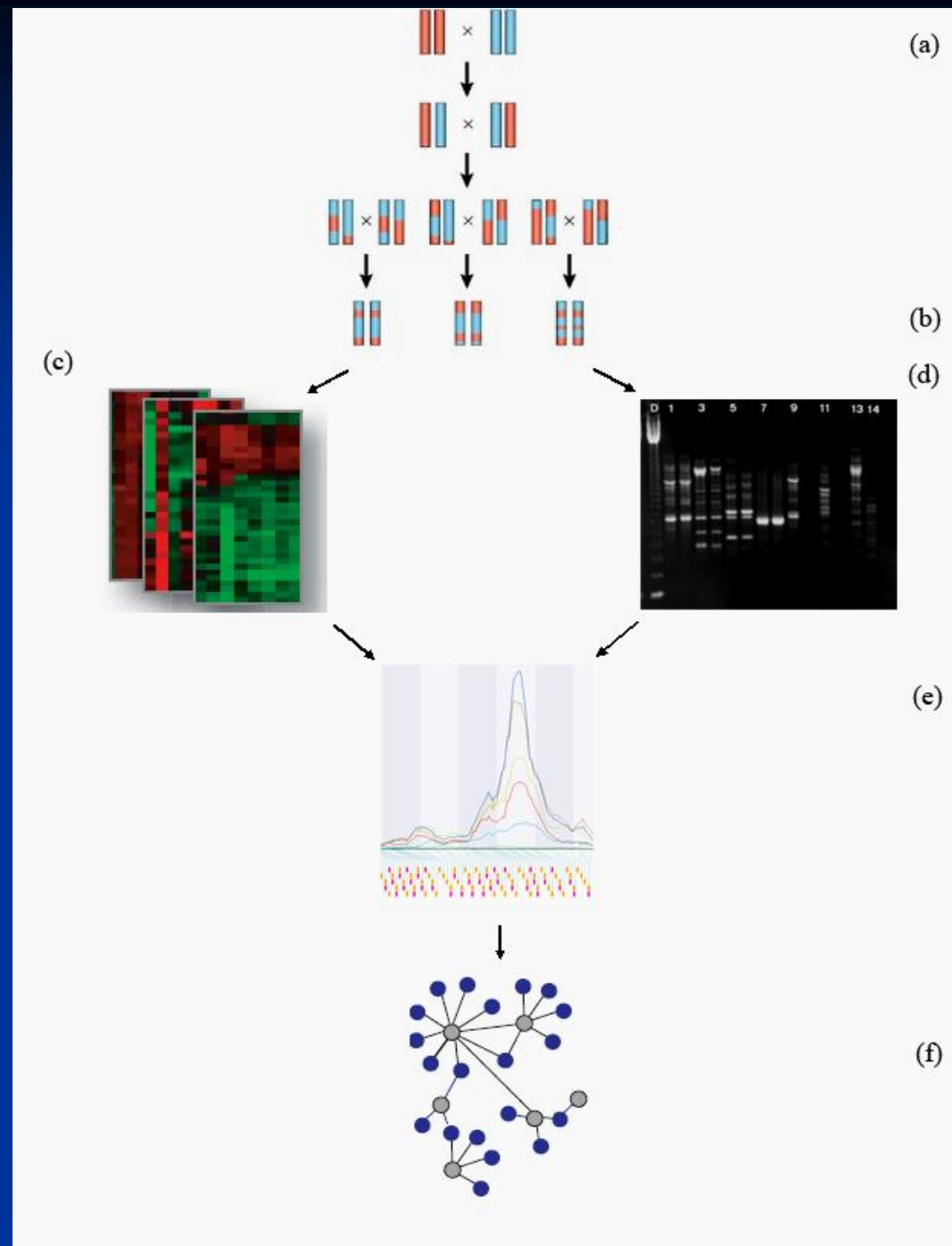


Quantify the amount of specific species of mRNA in each strain

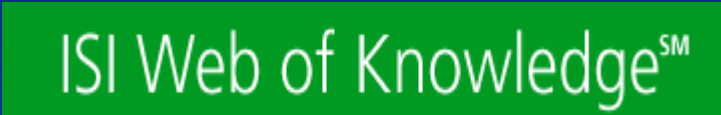
Genetic genomics

Find expression QTL (eQTL) that control gene expression level using linkage analysis

- (a) Inbreeding of animals
- (b) Genetic reference populations (GRP)
- (c) Expression from whole genome microarray
- (d) Genotype
- (e) Transcriptome-QTL mapping
- (f) Gene network building



Collection of AD related genes



There are **366** genes that could be related to AD.

Fresh hippocampus dissection



Gene expression of hippocampus in BXD RI mice

- ◆ There are 29310 genes that present in hippocampus with expression value above 7.
- ◆ 5397 genes have higher expression in hippocampus with expression value above 10.
- ◆ The expression value of top 100 genes in hippocampus is above 14. Some of those genes have been reported to be related to AD directly or indirectly.

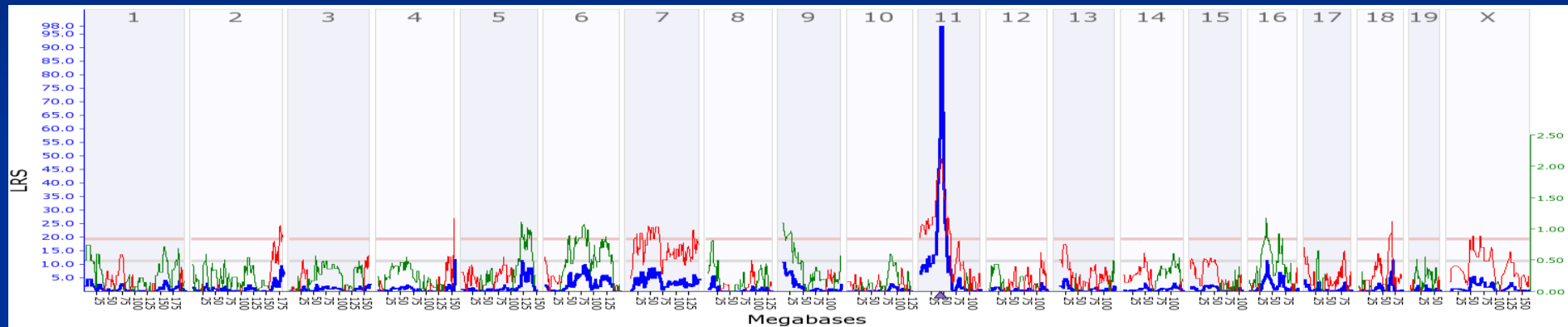
QTL analysis of gene expression in the hippocampus of BXD RI mice

QTL category	QTL number	Percentage of total probesets	Percentage of total QTL
significant QTL	7710	26.3	
cis-eQTLs	3733	12.7	48.4
trans-eQTLs	3977	13.6	51.6
eQTLs with LRS>50	1342	4.6	17.4

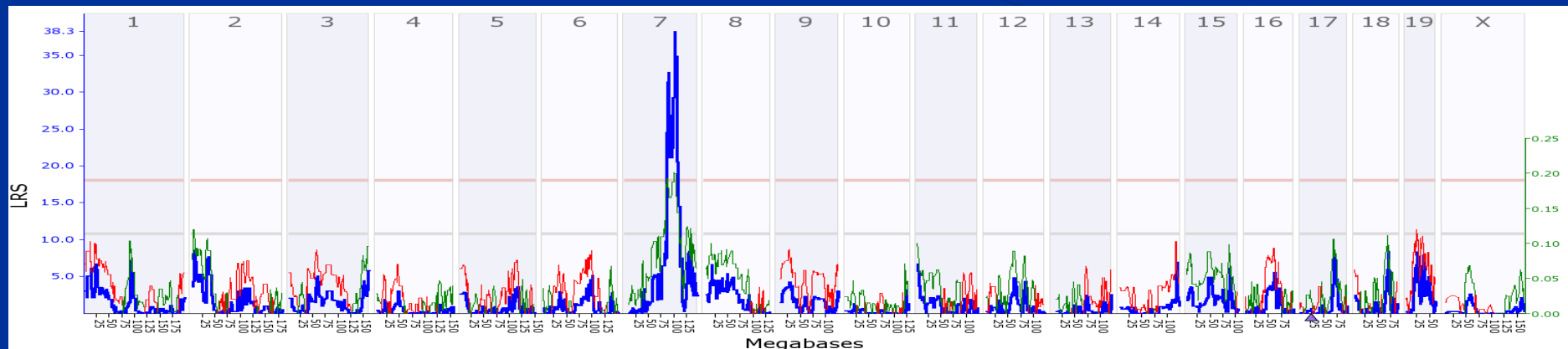
There are total 29310 present probesets

Local vs distant expression linkages

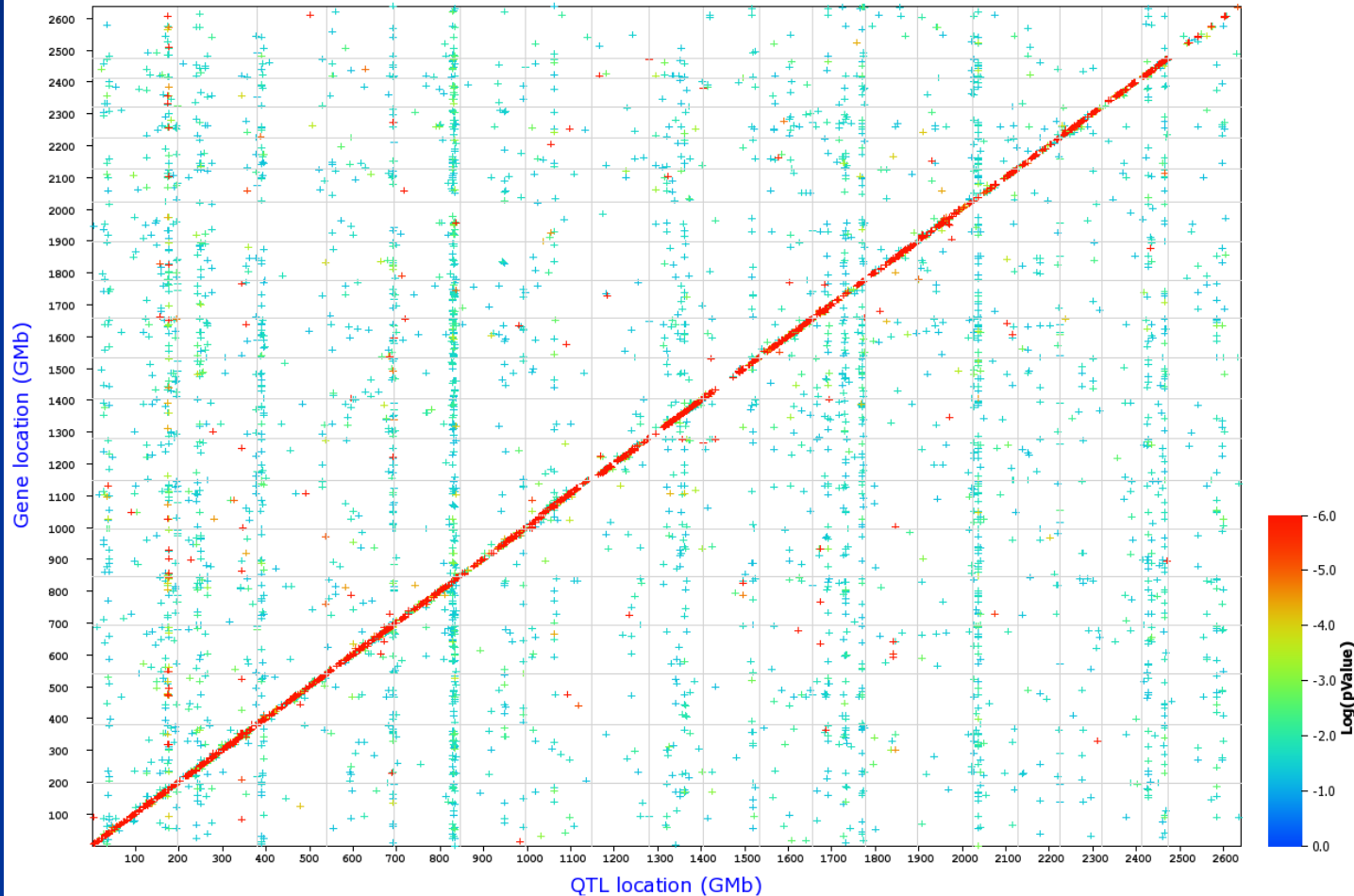
Local linkage or putative cis - modulation (e.g., *Pttg1*)



Distant linkage or putative *trans* - modulation (e.g., *Axin1*)



Distribution of QTLs across the genome



Expression analysis of AD related genes

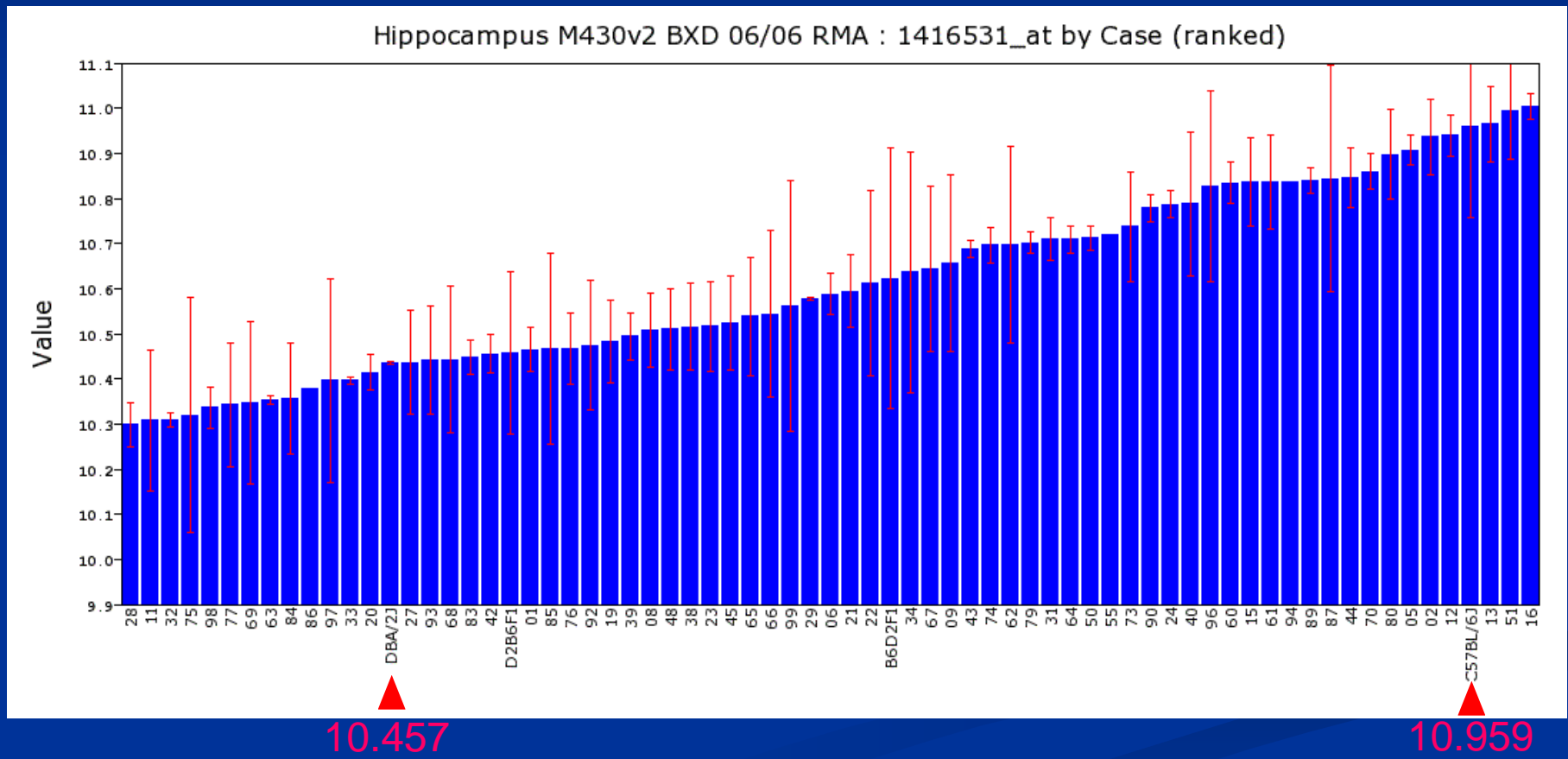
There are total 366 AD related genes found through literature search.

There are 130 genes whose expression are controlled by eQTL

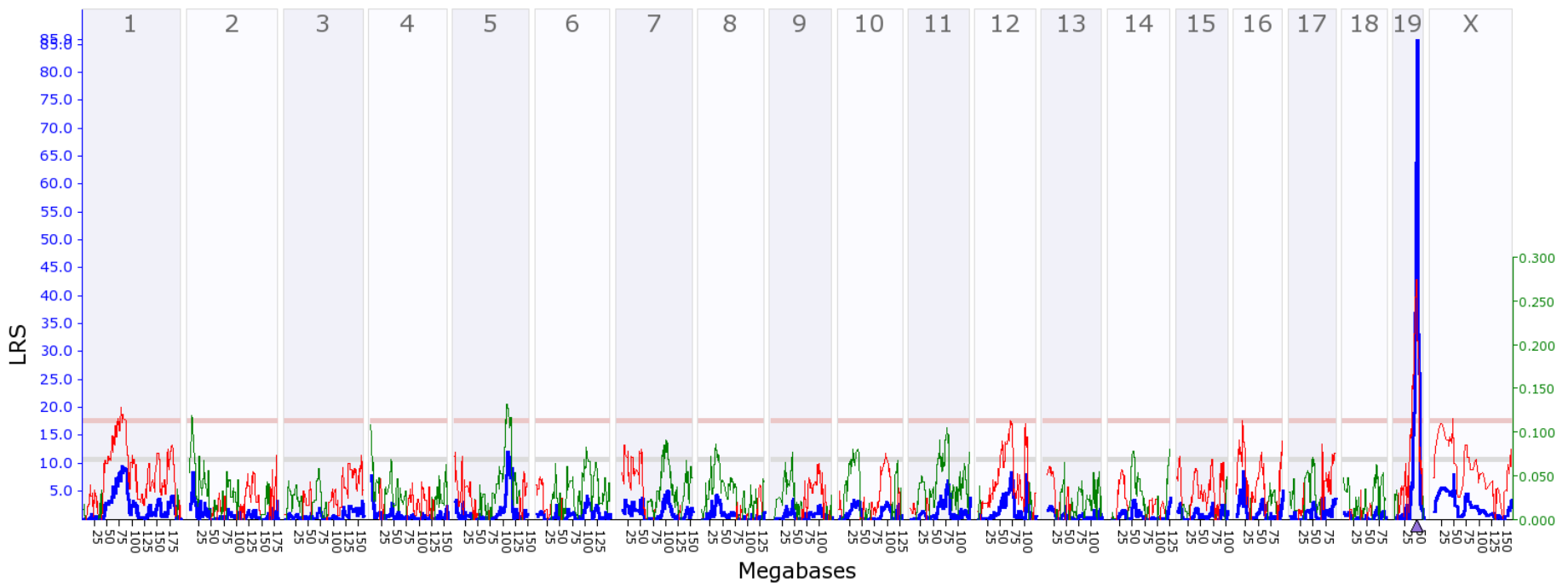
Expression of 64 genes is controlled by local sequence variants (cis-eQTL)

Expression of 66 genes is controlled by other region of the genome (trans-eQTL)

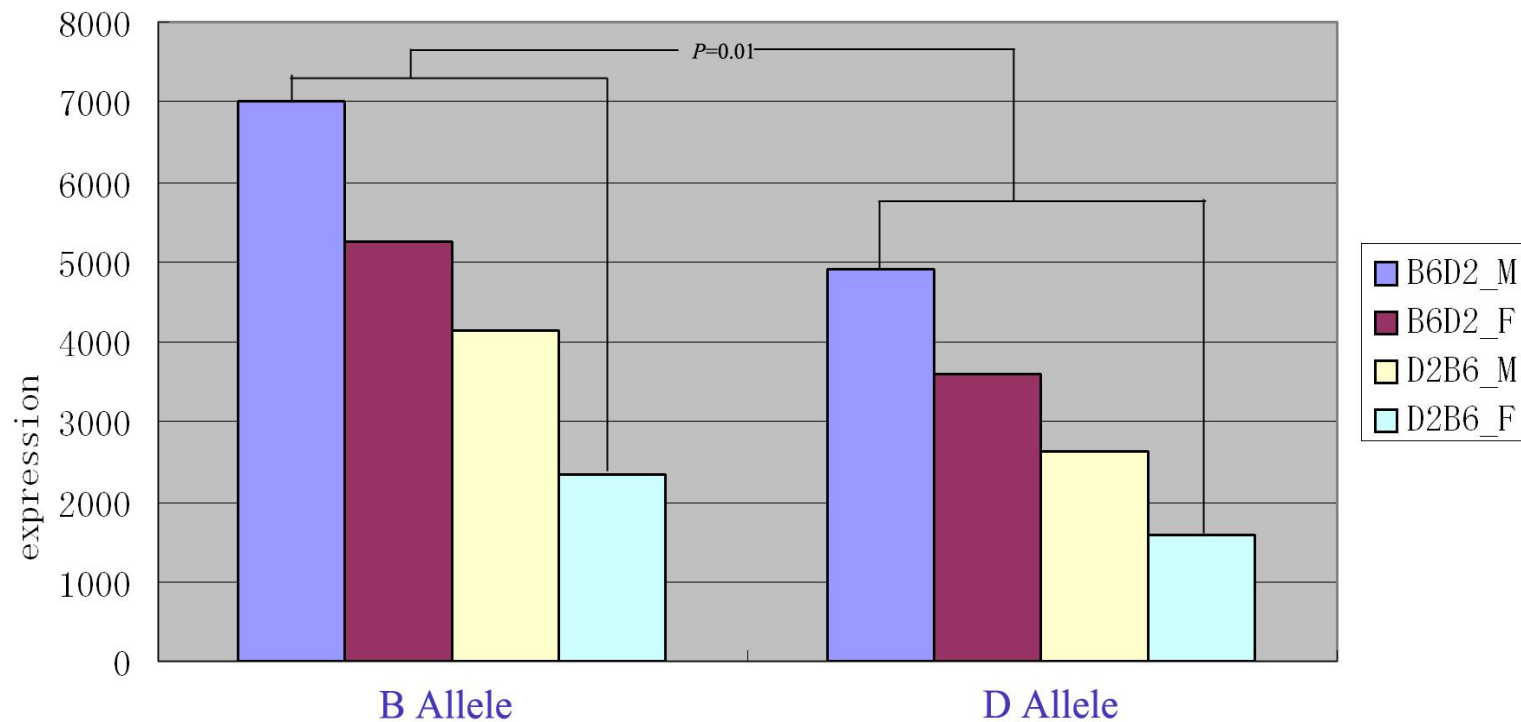
Expression of *Gsto1* gene (Probeset 1416531) in the hippocampus of BXD RI mice



eQTL Mapping for *Gsto1* in Hippocampus of BXD mice

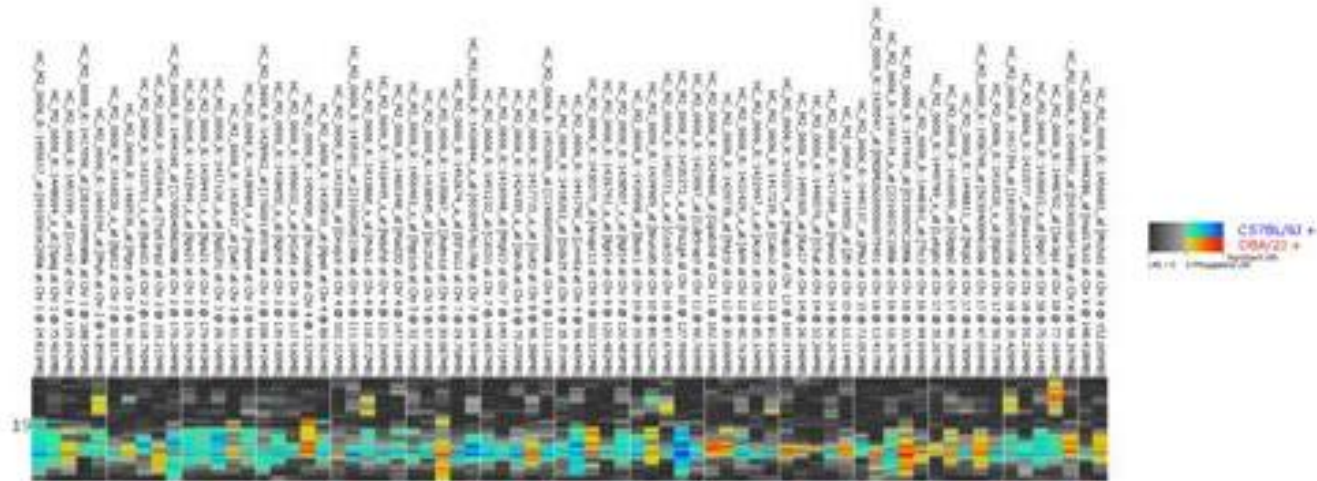


Allele-specific expression assay (ASE) analysis of *Gsto1* gene



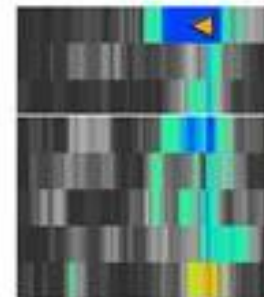
Downstream gene analysis of Gsto1

A

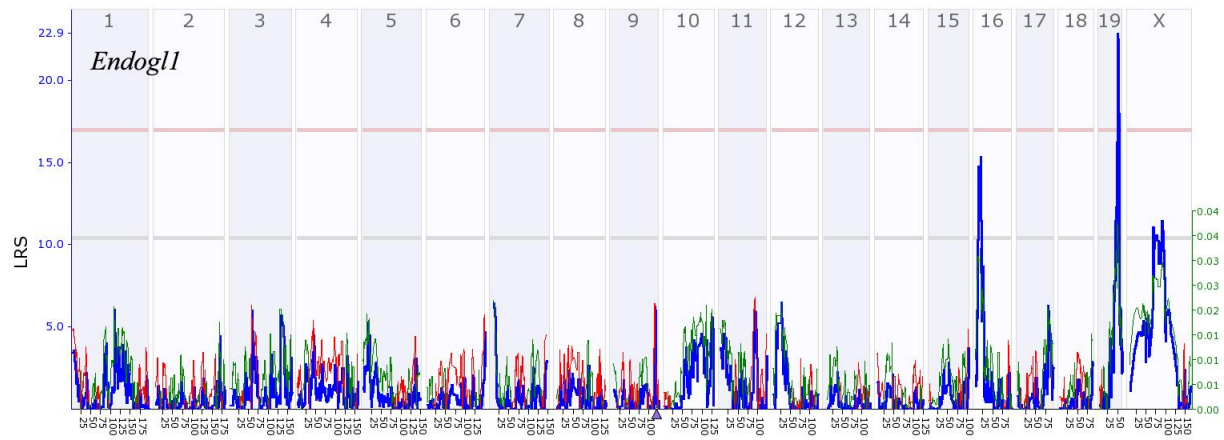
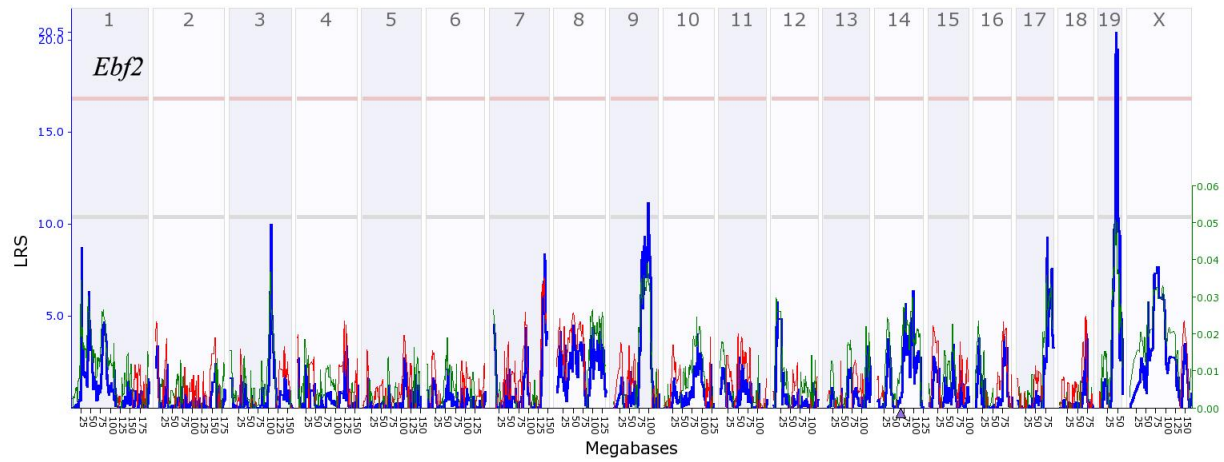
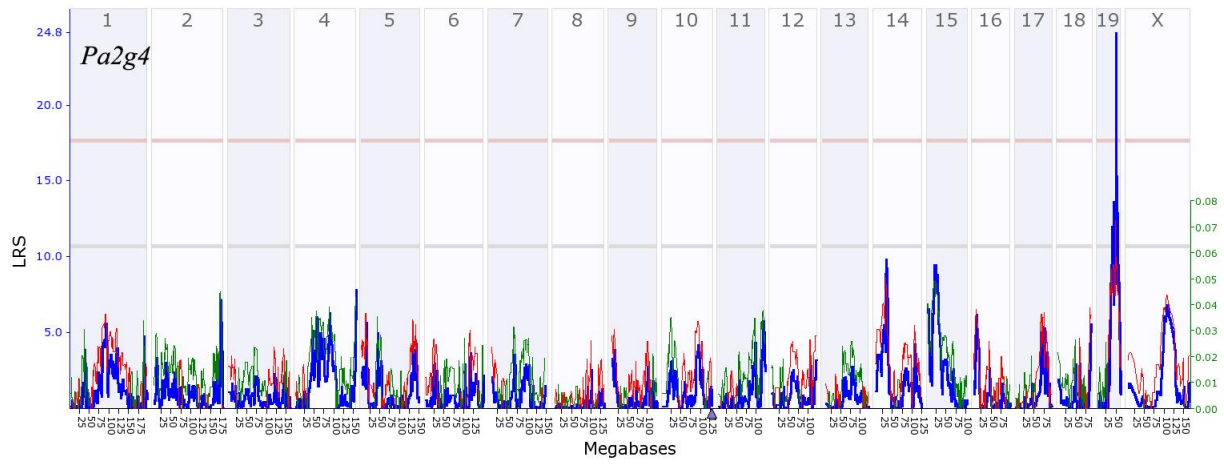


B

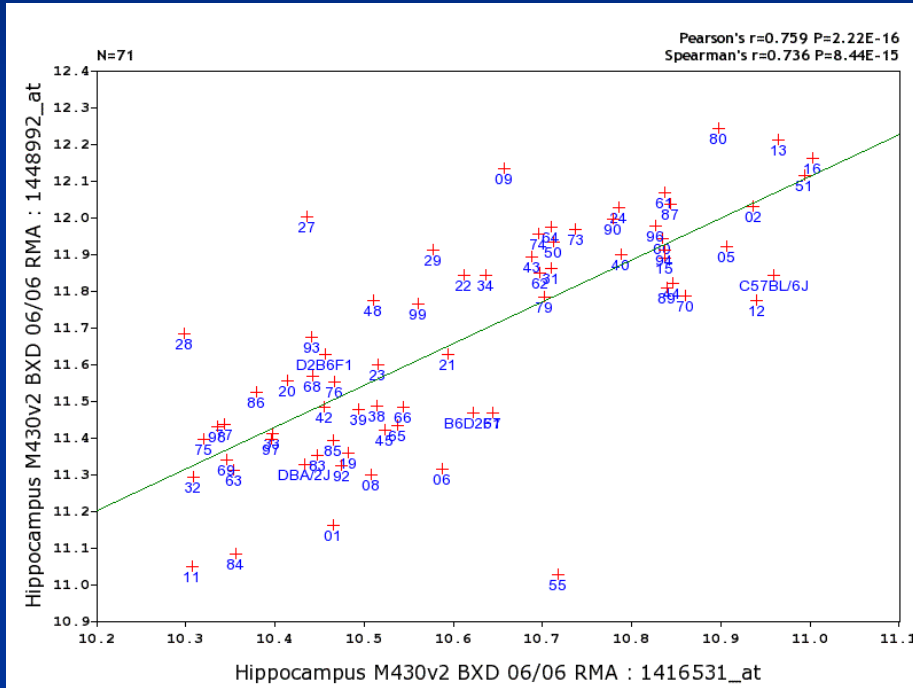
HC_M2_0606_R::1416531_at [Gsto1 at Chr 19 @ 47.939MB]
 HC_M2_0606_R::1417189_at [Psme2 at Chr 14 @ 56.207MB]
 HC_M2_0606_R::1416948_at [Mirpl23 at Chr 7 @ 149.721MB]
 HC_M2_0606_R::1426844_a_at [6030457N17Rik at Chr 7 @ 34.974MB]
 HC_M2_0606_R::1456462_x_at [Ppp1cb at Chr 5 @ 32.795MB]
 HC_M2_0606_R::1460348_at [Mad2l2 at Chr 4 @ 147.518MB]
 HC_M2_0606_R::1428962_at [1700013F07Rik at Chr 3 @ 108.341MB]
 HC_M2_0606_R::1460536_at [Ptptr at Chr 2 @ 90.360MB]



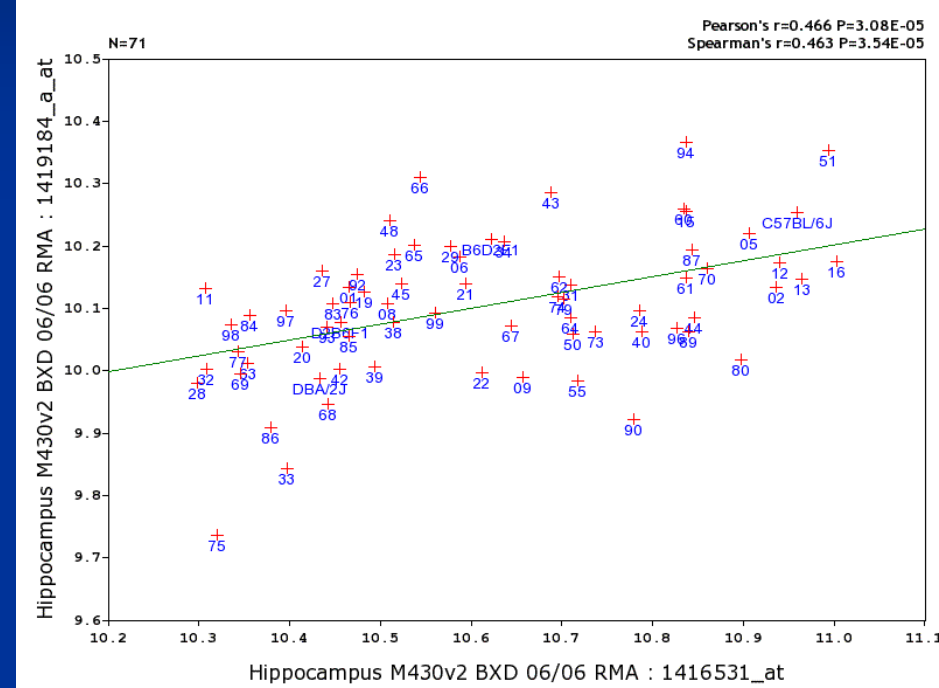
Chromosome 19



Correlation plot

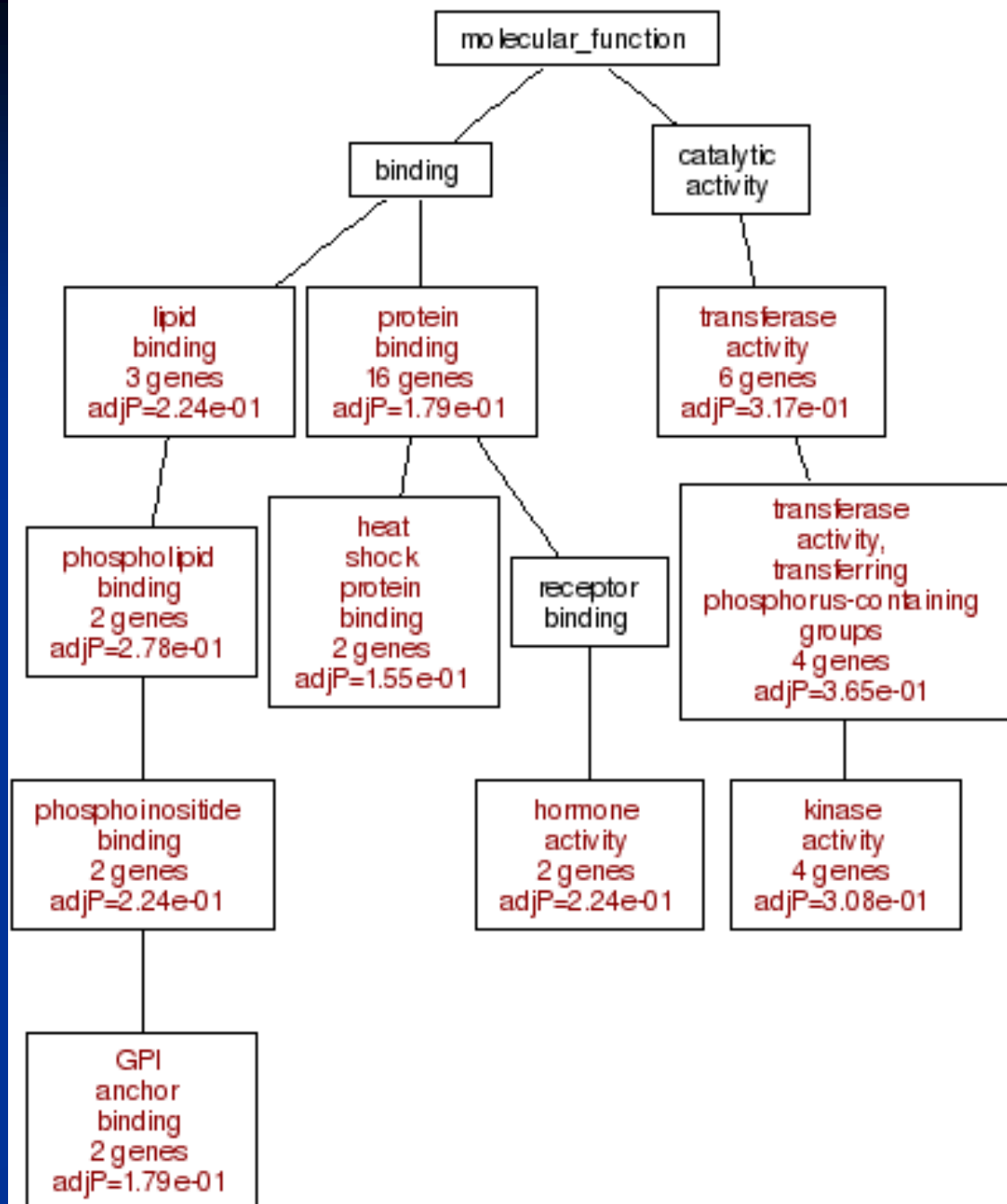


Gsto1 & *Ina*

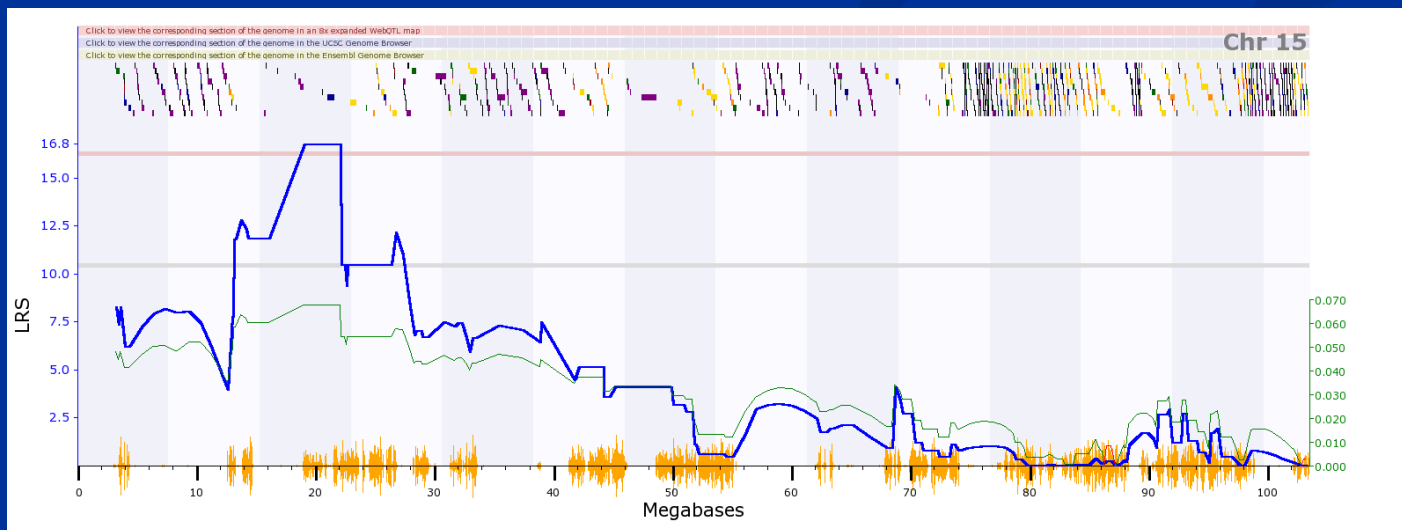
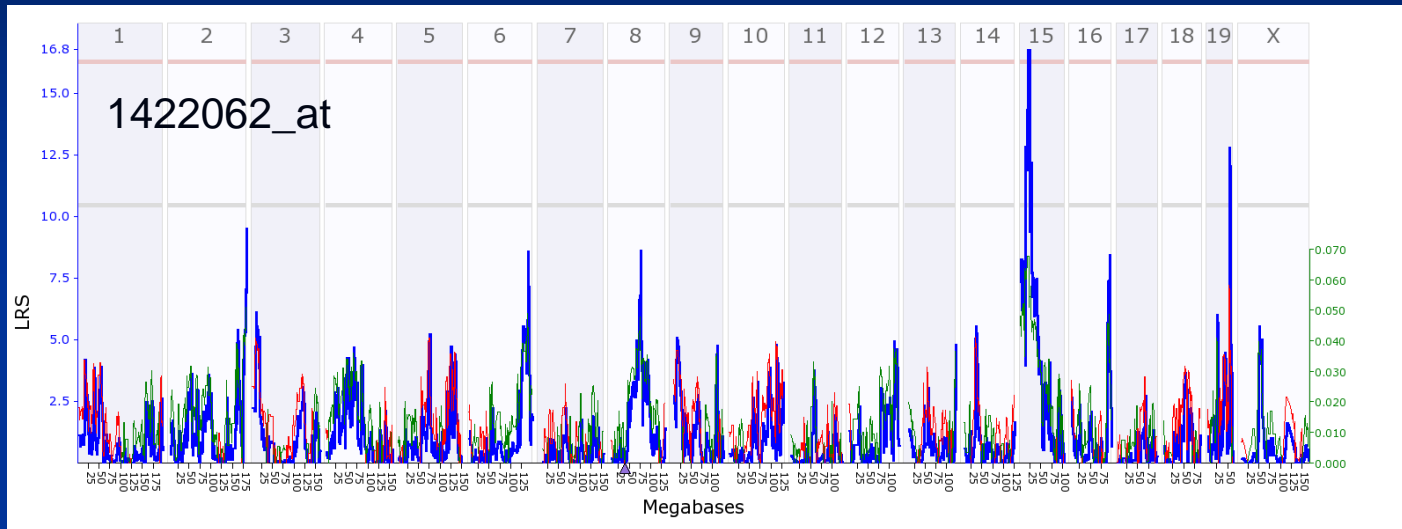


Gsto1 & *Fhl2*

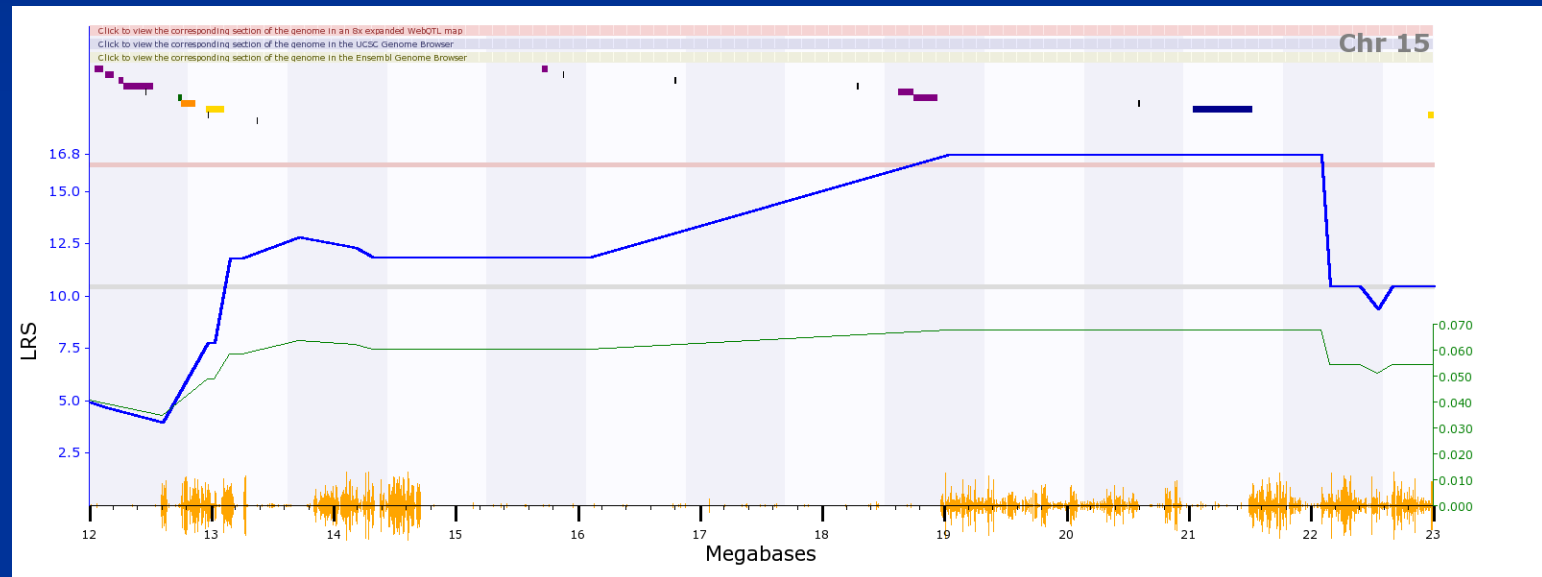
**Gene ontology analysis
for the top 500 genes
whose expression is high
significantly correlated
with Gsta1 gene**



Expression QTL analysis of macrophage scavenger receptor 1 (*Msr1*) gene



The location of Msr1 expression QTL



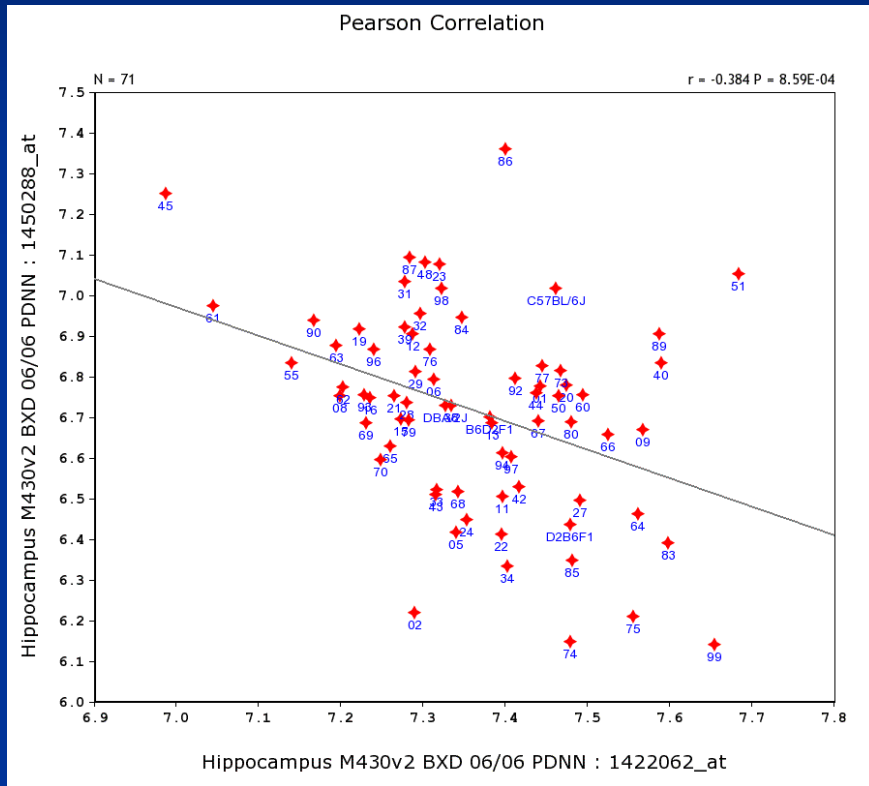
Candidate genes that regulate the expression of *Msr1*

Index	Gene Symbol	Mb Start (mm9)	Gene Length (Kb)	SNP Count	SNP Density (SNP/Kb)	Gene Description
1	Zfr	12.05	67.60	3	0.04	zinc finger RNA binding protein
2	Mtmr12	12.13	67.15	4	0.06	myotubularin related protein 12
3	Golph3	12.25	29.77	1	0.03	golgi phosphoprotein 3
4	Pdzd2	12.29	235.50	5	0.02	PDZ domain containing 2
5	5033430J17Rik	12.47	1.21	0	0.00	RIKEN cDNA 5033430J17 gene
6	6030458C11Rik	12.74	16.23	6	0.37	RIKEN cDNA 6030458C11 gene
7	Rnasen	12.75	110.48	343	3.10	ribonuclease III, nuclear
8	Cdh6	12.96	139.44	230	1.65	cadherin 6
9	B130021B11Rik	12.98	0.05	0	0.00	RIKEN cDNA B130021B11 gene
10	LOC239338	13.38	0.04	0	0.00	similar to CDK105
11	4930557F08Rik	15.71	43.43	3	0.07	RIKEN cDNA 4930557F08 gene
12	EG239341	15.89	0.05	0	0.00	predicted gene, EG239341
13	Cdh9	16.80	0.05	0	0.00	cadherin 9
14	4921515E04Rik	18.29	10.85	0	0.00	RIKEN cDNA 4921515E04 gene
15	C030047K22Rik	18.63	121.09	10	0.08	RIKEN cDNA C030047K22 gene
16	Cdh10	18.75	193.91	3	0.02	cadherin 10
17	Acot10	20.59	1.54	0	0.00	acyl-CoA thioesterase 10
18	Cdh12	21.04	478.08	93	0.19	cadherin 12
19	Cdh18	22.97	437.96	968	2.21	cadherin 18

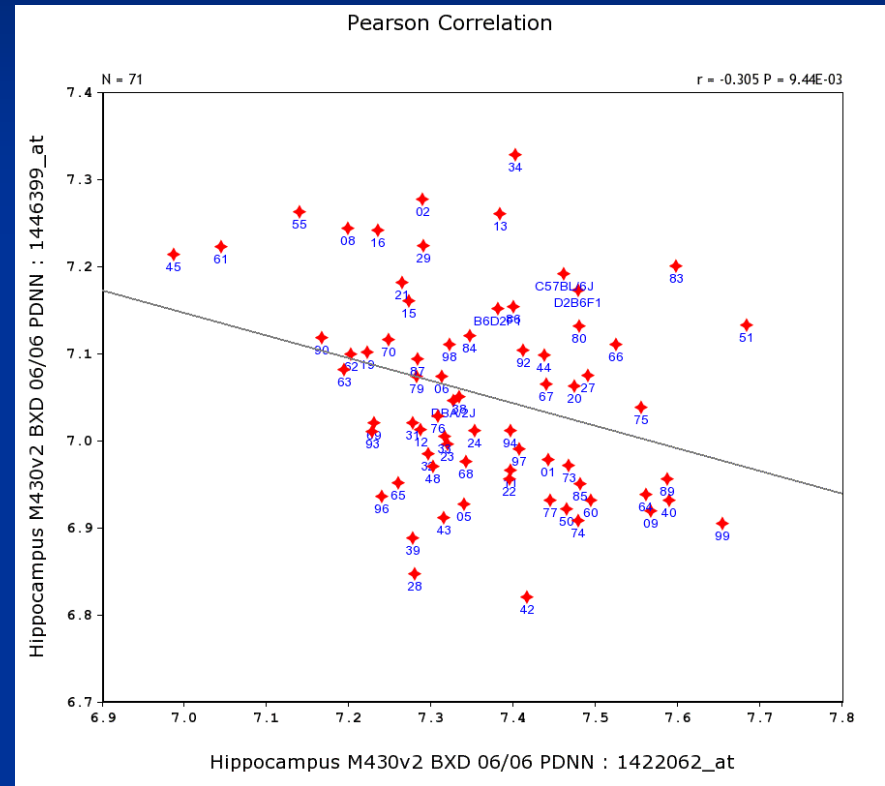
Selection of candidate genes that regulate the expression of *Msr1*

Index	Gene Symbol	Correlation P value	Mean Expression	Max LRS	Max LRS Location (Chr: Mb)
1	Zfr	0.000647488	7.00	11	Chr5: 133.538653
2	Mtmr12	#N/A	#N/A	#N/A	#N/A
3	Golph3	1.2211E-07	8.00	11.9	Chr9: 81.753446
4	Pdzd2	#N/A	#N/A	#N/A	#N/A
5	5033430J17Rik	3.3522E-05	6.56	18	Chr6: 140.066609
6	6030458C11Rik	0.000127752	5.53	10.1	Chr2: 180.825581
7	Rnasen	#N/A	#N/A	#N/A	#N/A
8	Cdh6	0.000859319	7.90	111.7	Chr15: 12.972088
9	B130021B11Rik	#N/A	#N/A	#N/A	#N/A
10	LOC239338	#N/A	#N/A	#N/A	#N/A
11	4930557F08Rik	#N/A	#N/A	#N/A	#N/A
12	EG239341	#N/A	#N/A	#N/A	#N/A
13	Cdh9	#N/A	#N/A	#N/A	#N/A
14	4921515E04Rik	#N/A	#N/A	#N/A	#N/A
15	C030047K22Rik	#N/A	#N/A	#N/A	#N/A
16	Cdh10	3.2451E-10	8.20	10.9	ChrX: 112.637353
17	Acot10	#N/A	#N/A	#N/A	#N/A
18	Cdh12	#N/A	#N/A	#N/A	#N/A
19	Cdh18	#N/A	#N/A	#N/A	#N/A

Correlation plot



Msr1 & *Cdh6*



Msr1 & *Cdh10*

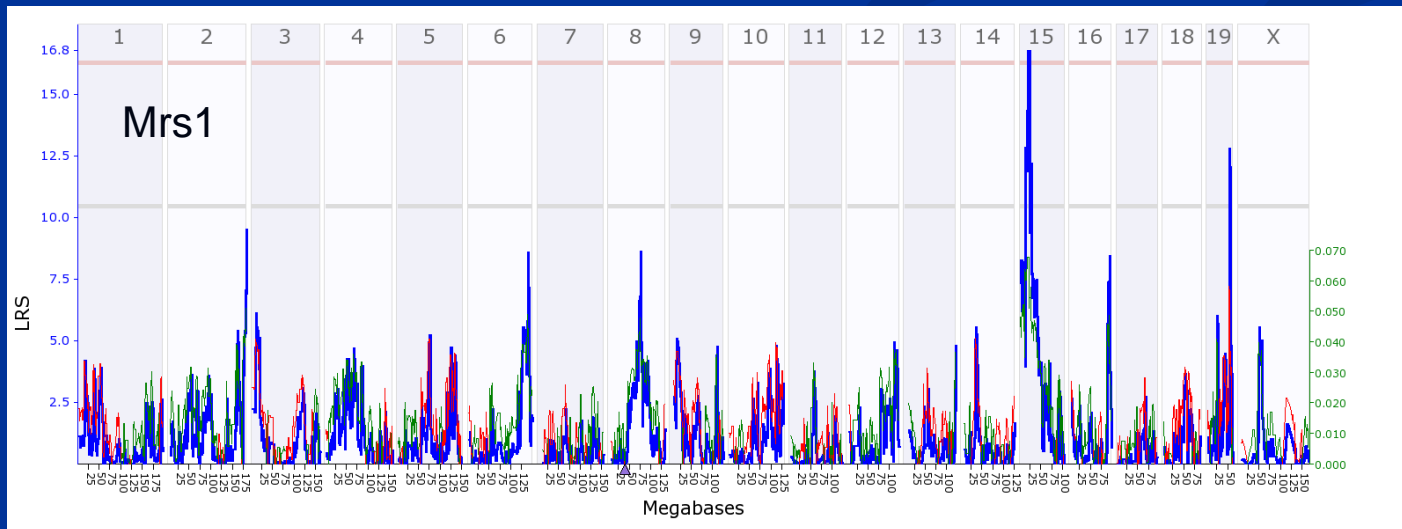
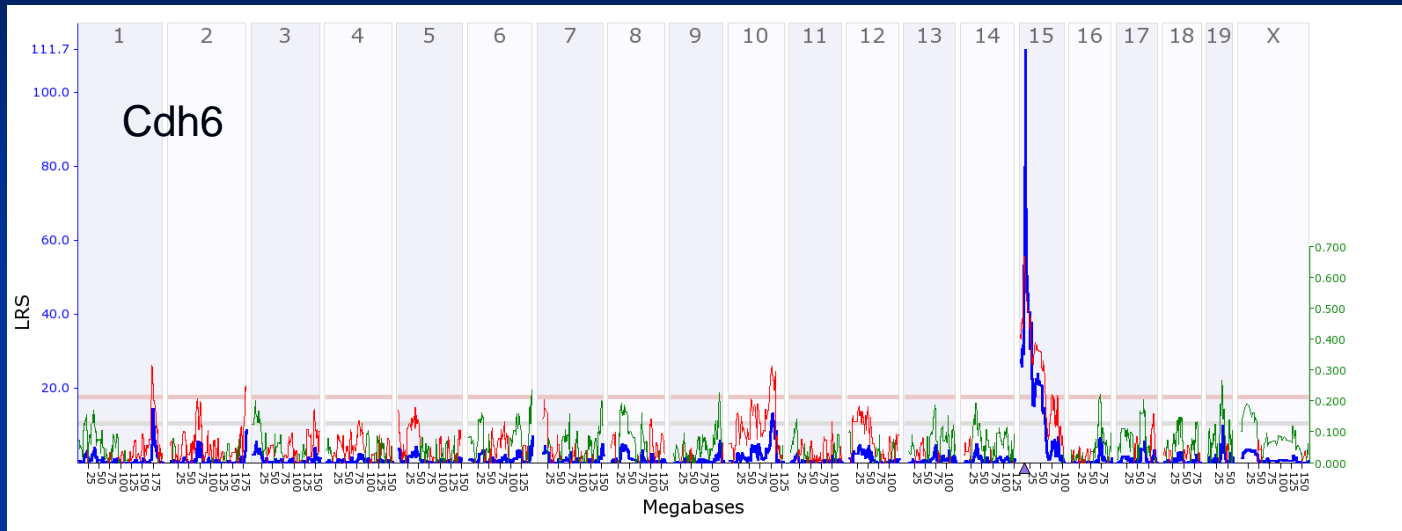
Polymorphism analysis of candidate genes that regulate the expression of *Msr1*

chromosome	position	B6 allele	D2 allele	gene	exon
15	12747846	C	T	6030458C11Rik	4
15	12747971	C	T	6030458C11Rik	4
15	12751199	A	G	6030458C11Rik	3
15	12754260	T	G	6030458C11Rik	1
15	12971132	T	C	<i>Cdh6</i>	10

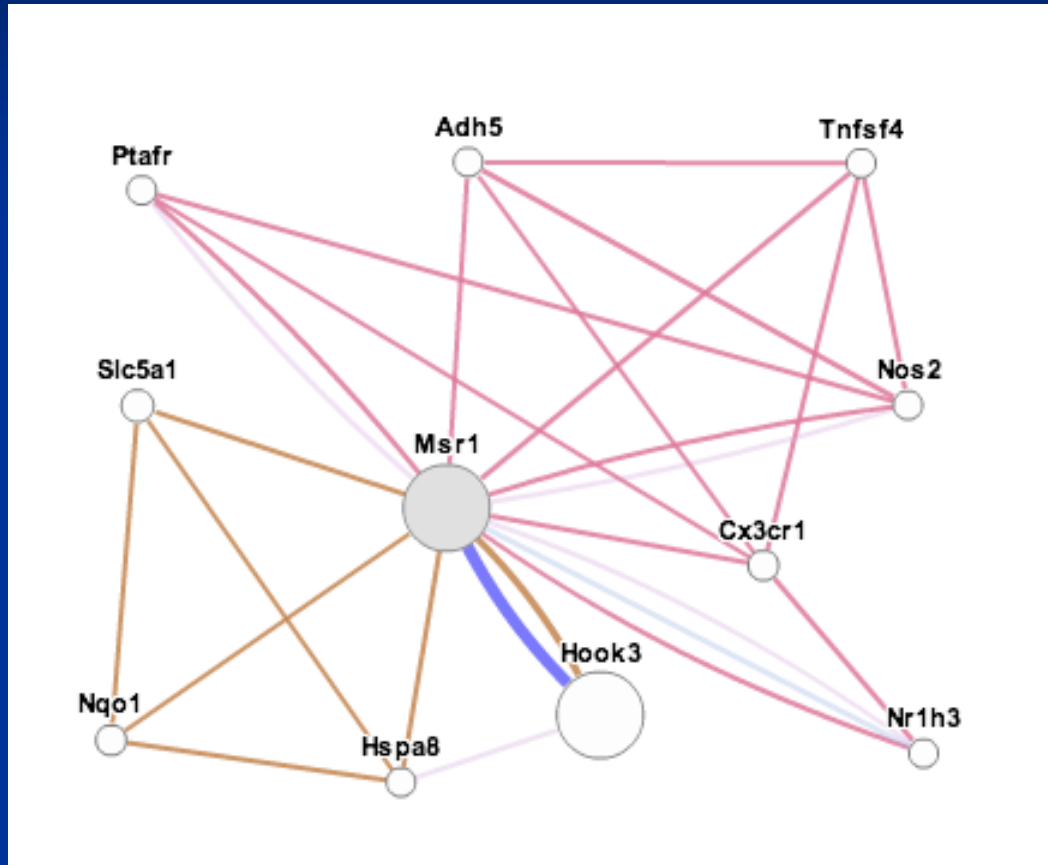
Candidate genes that regulate the expression of *Msr1*

Index	Gene Symbol	Correlation P value	Mean Expression	Max LRS	Max LRS Location (Chr: Mb)	non- synonymous mutation
1	Zfr	0.000647488	7.00	11	Chr5: 133.538653	
2	Mtmr12	#N/A	#N/A	#N/A	#N/A	
3	Golph3	1.2211E-07	8.00	11.9	Chr9: 81.753446	
4	Pdzd2	#N/A	#N/A	#N/A	#N/A	
5	5033430J17Rik	3.3522E-05	6.56	18	Chr6: 140.066609	
6	6030458C11Rik	0.000127752	5.53	10.1	Chr2: 180.825581	yes
7	Rnasen	#N/A	#N/A	#N/A	#N/A	
8	Cdh6	0.000859319	7.90	111.7	Chr15: 12.972088	yes
9	B130021B11Rik	#N/A	#N/A	#N/A	#N/A	
10	LOC239338	#N/A	#N/A	#N/A	#N/A	
11	4930557F08Rik	#N/A	#N/A	#N/A	#N/A	
12	EG239341	#N/A	#N/A	#N/A	#N/A	
13	Cdh9	#N/A	#N/A	#N/A	#N/A	
14	4921515E04Rik	#N/A	#N/A	#N/A	#N/A	
15	C030047K22Rik	#N/A	#N/A	#N/A	#N/A	
16	Cdh10	3.2451E-10	8.20	10.9	ChrX: 112.637353	
17	Acot10	#N/A	#N/A	#N/A	#N/A	
18	Cdh12	#N/A	#N/A	#N/A	#N/A	
19	Cdh18	#N/A	#N/A	#N/A	#N/A	

Cadherin 6 (*Cdh6*) QTL Mapping



Known working partner of *Msr1* gene

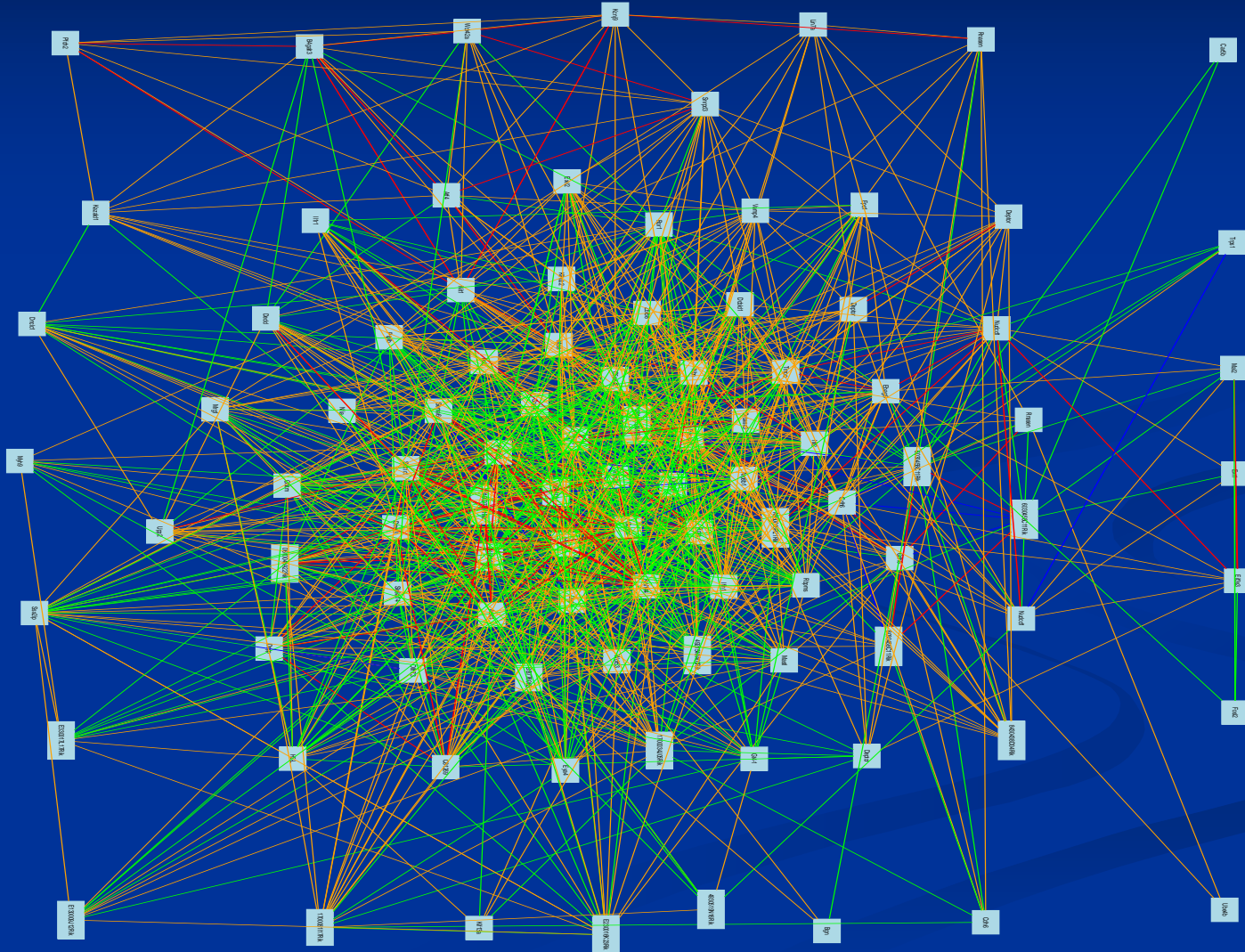


<http://genemania.org>

Confirmed working partner of *Msr1* gene in our expression data

Index	Gene Symbol	Gene Description	Correlation P value
1	Msr1	macrophage scavenger receptor 1 Gene	0
2	Hook3	hook homolog 3 (Drosophila)(curated)	0.002039967
3	Slc5a1	solute carrier family 5 (sodium/glucose cotransporter), member 1 Gene	1.1373E-07
4	Nqo1	NAD(P)H dehydrogenase, quinone 1 Gene	#N/A
5	Cx3cr1	chemokine (C-X3-C) receptor 1 Gene	0.002811294
7	Hspa8	heat shock protein 8 Gene	3.58904E-06
8	Nr1h3	nuclear receptor subfamily 1, group H, member 3 Gene	2.12208E-07
9	Ptafr	platelet-activating factor receptor Gene	4.20329E-05
10	Adh5	alcohol dehydrogenase 5 (class III), chi polypeptide Gene	1.53053E-09
11	Tnfsf4	tumor necrosis factor (ligand) superfamily, member 4 Gene	0.002117561

Gene Network of *Msr1*



Top 30 working partners of *Msr1* gene

Record	Symbol	Description	Location (Chr, Mb)	Mean Expr	Sample p(r)
1422062_at	<i>Msr1</i>	macrophage scavenger receptor 1	Chr8: 40.691029	7.40	0
1439437_x_at	Cpe	carboxypeptidase E	Chr8: 67.071407	8.87	0
1419222_at	Tbxa2r	thromboxane A2 receptor	Chr10: 80.797325	8.37	0
1426121_at	Mrgpra3	MAS-related GPR, member A3	Chr7: 54.844713	8.26	0
1447668_x_at	Efemp2	epidermal growth factor-containing fibulin-like extracellular matrix protein 2	Chr19: 5.481717	7.83	0
1418989_at	Ctse	cathepsin E	Chr1: 133.571532	7.69	0
1442869_at	A930013K19	hypothetical protein A930013K19	Chr5: 35.429889	7.57	0
1447300_at	Vwa5a	von Willebrand factor A domain containing 5A	Chr9: 39.398309	7.55	0
1431634_at	4930455C13Rik	RIKEN cDNA 4930455C13	Chr10: 21.044230	7.25	0
1450670_at	Dbh	dopamine beta-hydroxylase (dopamine beta-monoxygenase, dopamine to norepinephrine)	Chr2: 27.037106	7.19	0
1418765_at	Timd2	T-cell immunoglobulin and mucin domain containing 2	Chr11: 46.490707	7.10	0
1430398_at	4921517O11Rik	RIKEN cDNA 4921517O11 gene	Chr18: 22.331255	7.06	0
1416396_at	Snx4	sorting nexin 4	Chr16: 33.299890	7.51	2.22045E-16
1426507_at	Il1f5	interleukin 1 family, member 5 (delta)	Chr2: 24.138353	7.32	2.22045E-16
1422963_at	Sprr2i	small proline-rich protein 2I	Chr3: 92.212874	7.20	2.22045E-16
1431750_at	Ush2a	usherin basement membrane protein (Usher syndrome 2A, retinitis pigmentosa and hearing loss)	Chr1: 190.180888	7.13	2.22045E-16
1449924_at	Prg3	proteoglycan 3	Chr2: 84.829551	7.11	2.22045E-16
1420206_at	5730494M16Rik	RIKEN cDNA 5730494M16	Chr18: 25.297204	7.07	2.22045E-16
1459044_at	AU015558	ESTs	Chr7: 37.901095	7.03	2.22045E-16
1421608_at	Il20	interleukin 20	Chr1: 132.803773	8.13	4.44089E-16
1445961_at	BG071636	BG071636	Chr17: 53.427689	8.00	4.44089E-16
1441962_at	Alox5	arachidonate 5-lipoxygenase (leukotriene synthesis)	Chr6: 116.360136	7.80	4.44089E-16
1443828_x_at	5031400M07Rik	5031400M07Rik (putative protein processing and translation related)	Chr9: 24.953623	7.68	4.44089E-16
1447518_at	Tpx2	targeting protein of Xklp2 (spindle pole microtubule-associated)	Chr2: 152.719414	7.50	4.44089E-16
1457629_at	Atmin	ATM interactor (ATM/ATR-substrate Chk2-interacting Zn2+-finger protein)	Chr8: 119.481822	7.05	4.44089E-16
1451292_at	Zfp212	Zinc finger protein 212	Chr6: 47.882108	9.59	6.66134E-16
1417805_at	Xpnpep2	X-prolyl aminopeptidase (aminopeptidase P) 2, membrane-bound	ChrX: 45.489257	7.49	6.66134E-16
1433189_at	4933433N18Rik	RIKEN cDNA 4933433N18 gene	Chr13: 50.760886	7.37	6.66134E-16
1443599_at	A930031F18Rik	ESTs	Chr3: 89.158425	7.78	8.88178E-16
1421338_at	Elf4	E74-like factor 4 (ets domain transcription factor)	ChrX: 45.765520	7.27	8.88178E-16

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