Life is the translation of the information in the genome into the phenotype of the organism:

The organism ‚computes‘ this phenotype from its genotype, given a specific environment

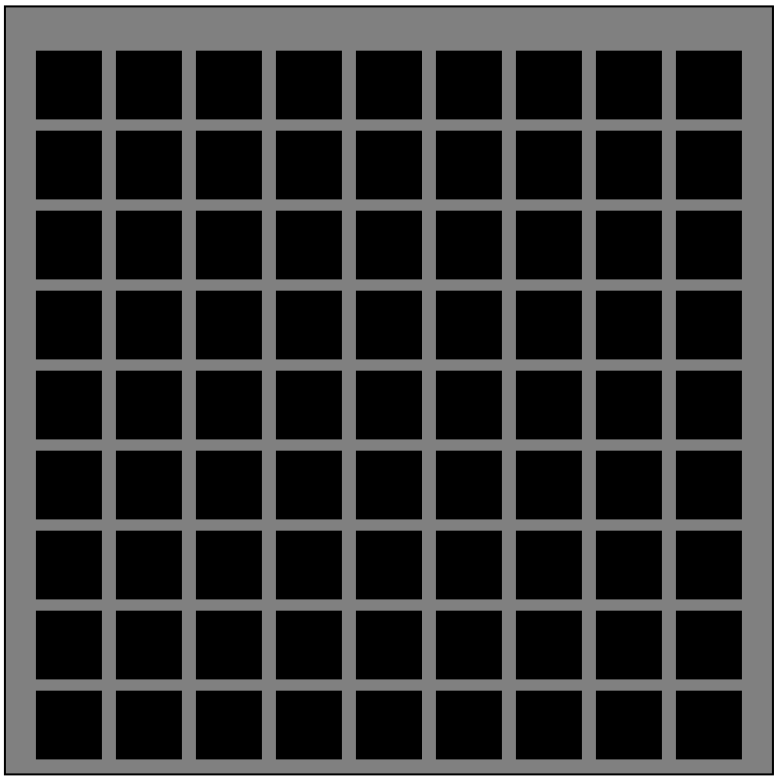
Genome

Environment

Phenotype

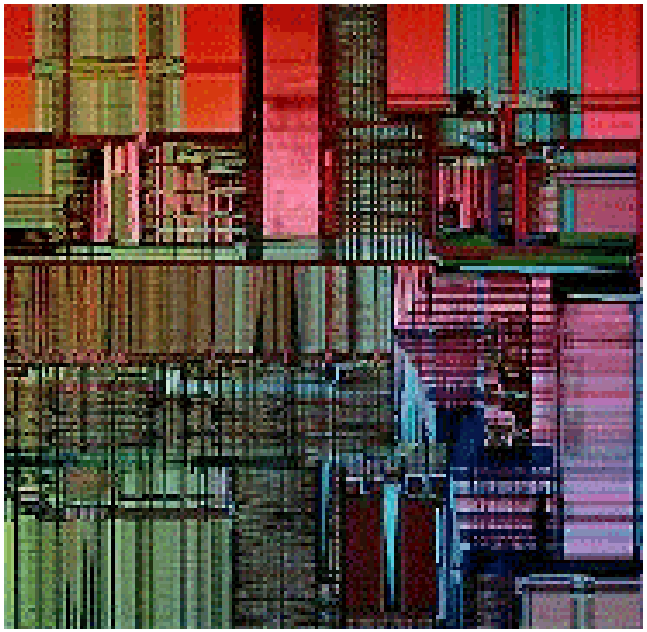
Genome

Environment

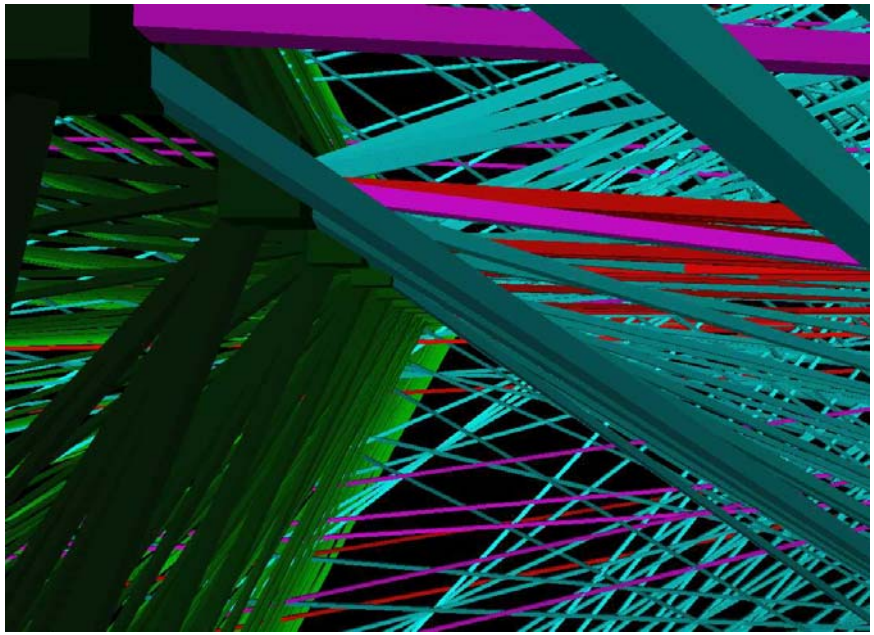


Phenotype

? Genome !



(PentiumV)



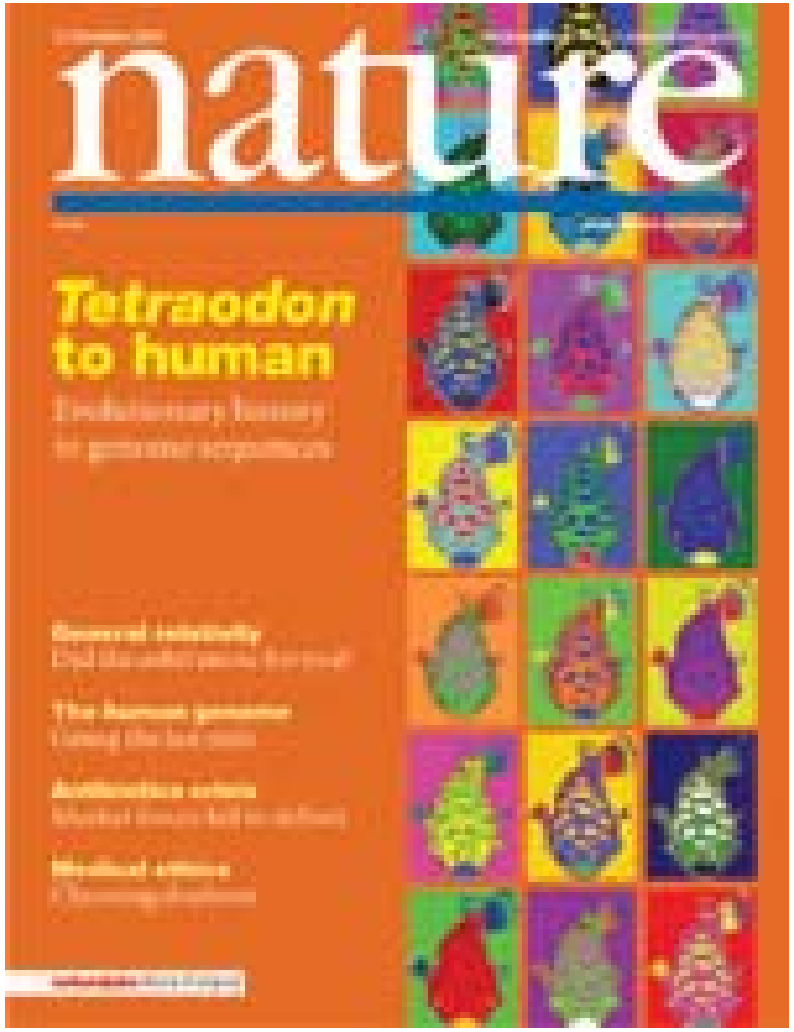
(neuronal net visualisation)

Phenotype

- **What would we do, if we had to ‚cure' a perturbed neural network?**

- Get the list of components: **Genomics**
- Get the information on their interactions: **Genetics**
- Model the network, the disturbance, and possible ways to interfere: **Systems biology**
- Try possible ‚cures' till you succeed.

Genomics



Finishing the euchromatic sequence of the human genome

International Human Genome Sequencing Consortium*

* A list of authors and their affiliations appears in the Supplementary Information

The sequence of the human genome encodes the genetic instructions for human physiology, as well as rich information about human evolution. In 2001, the International Human Genome Sequencing Consortium reported a draft sequence of the euchromatic portion of the human genome. Since then, the international collaboration has worked to convert this draft into a genome sequence with high accuracy and nearly complete coverage. Here, we report the result of this finishing process. The current genome sequence (Build 35) contains 2.85 billion nucleotides interrupted by only 341 gaps. It covers ~99% of the euchromatic genome and is accurate to an error rate of ~1 event per 100,000 bases. Many of the remaining euchromatic gaps are associated with segmental duplications and will require focused work with new methods. The near-complete sequence, the first for a vertebrate, greatly improves the precision of biological analyses of the human genome including studies of gene number, birth and death. Notably, the human genome seems to encode only 20,000–25,000 protein-coding genes. The genome sequence reported here should serve as a firm foundation for biomedical research in the decades ahead.

The Human Genome Project (HGP) was launched in 1990 with the goal of obtaining a highly accurate sequence of the vast majority of the euchromatic portion of the human genome. The initial work followed a two-pronged approach: (1) the mapping of the human and mouse genomes[1–5] to allow the study of inherited disease and provide a crucial scaffold for genome assembly; and (2) the sequencing of organisms with smaller, simpler genomes[6–14] to serve as a testbed for method development and assist in interpreting the human genome. With success along both paths, the sequencing of the human genome itself eventually became feasible. The International Human Genome Sequencing Consortium (IHGSC), an open collaboration involving twenty centres in six countries, was formed to carry out this component of the HGP.

In February 2001, the IHGSC[15] and Celera Genomics[16] each reported draft sequences providing a first overall view of the human genome. These sequences allowed systematic study of the human genome itself, including identification of genes, combinatorial architecture of proteins, regional differences in genome composition, distribution and history of transposable elements, distribution of polymorphism and relationship between genetic recombination and physical distance. Moreover, systematic knowledge of the human genome has enabled new tools and approaches that have markedly accelerated biomedical research.

Both draft sequences, however, had important shortcomings. The IHGSC sequence, for example, omitted ~10% of the euchromatic genome; it was interrupted by ~150,000 gaps; and the order and orientation of many segments within local regions had not been established. The IHGSC thus turned to the challenge of completing the sequence of the euchromatic genome. Operationally, a finished sequence was defined as having an error rate of, at most, one event per 10^4 bases, and the goal for completion was coverage in finished sequence of at least 99% of the euchromatic genome, with the only gaps being those refractory to all available techniques[17] (see http://www.genome.gov/10000923). The goal was challenging because the human genome is replete with such features as dispersed repeats and large segmental duplications, which greatly complicate the determination of genome structure and sequence. In fact, near-complete sequences have been obtained so far only for three multicellular organisms: the nematode[18], mustard weed[19] and the fruitfly[20]. These genomes are all roughly 30-fold smaller than the human genome and have much simpler structure.

We describe here the results of a multiyear effort by the IHGSC towards the goal of a complete human sequence. The number of gaps has been reduced 400-fold to only 341, most of which are associated with segmental duplications and will require new methods for resolution. The assembled near-complete genome sequence has an error rate of only ~1 event per 100,000 bases; it contains 2.85 billion nucleotides and covers ~99% of the euchromatic genome. This paper describes the current genome sequence and the process used to produce it; examines the accuracy and completeness of the sequence; and illustrates biological analyses made possible by the sequence. We do not attempt here a comprehensive analysis of the contents of the human genome. An initial analysis was previously reported[15] and a series of papers is being written describing the individual chromosomes[17,20–38], including annotation of genes and other features.

Current genome sequence

Finishing process

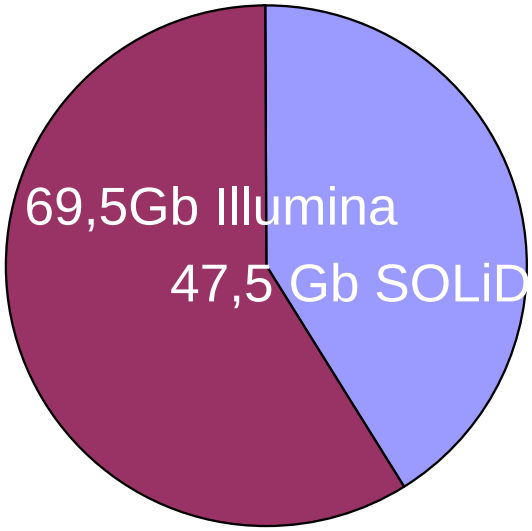
The process of converting the initial draft sequence into a near-complete sequence is referred to as 'finishing'. It is a complex iterative process that proceeds simultaneously at multiple scales, ranging from single nucleotides to the integrity of whole chromosomes. The fundamental challenge is that genomic regions that are not well represented or readily reached through random shotgun sequencing tend to be highly enriched in problematic sequences. Resolving such regions required the development of special approaches, which evolved substantially over time and varied among centres.

Broadly, the finishing process involved two distinct components: (1) producing finished maps, consisting of continuous and accurate paths of overlapping large-insert clones spanning the euchromatic region of each chromosome arm; and (2) producing finished clones, consisting of continuous and accurate nucleotide sequence across each large-insert clone. In practice, these two components were tightly intertwined in that progress in each often depended on results from the other. The components are described in Boxes 1 and 2. Further information about the finishing process and finishing standards can be found in the Supplementary Information (Note 1) and at http://www.genome.gov/10000923.

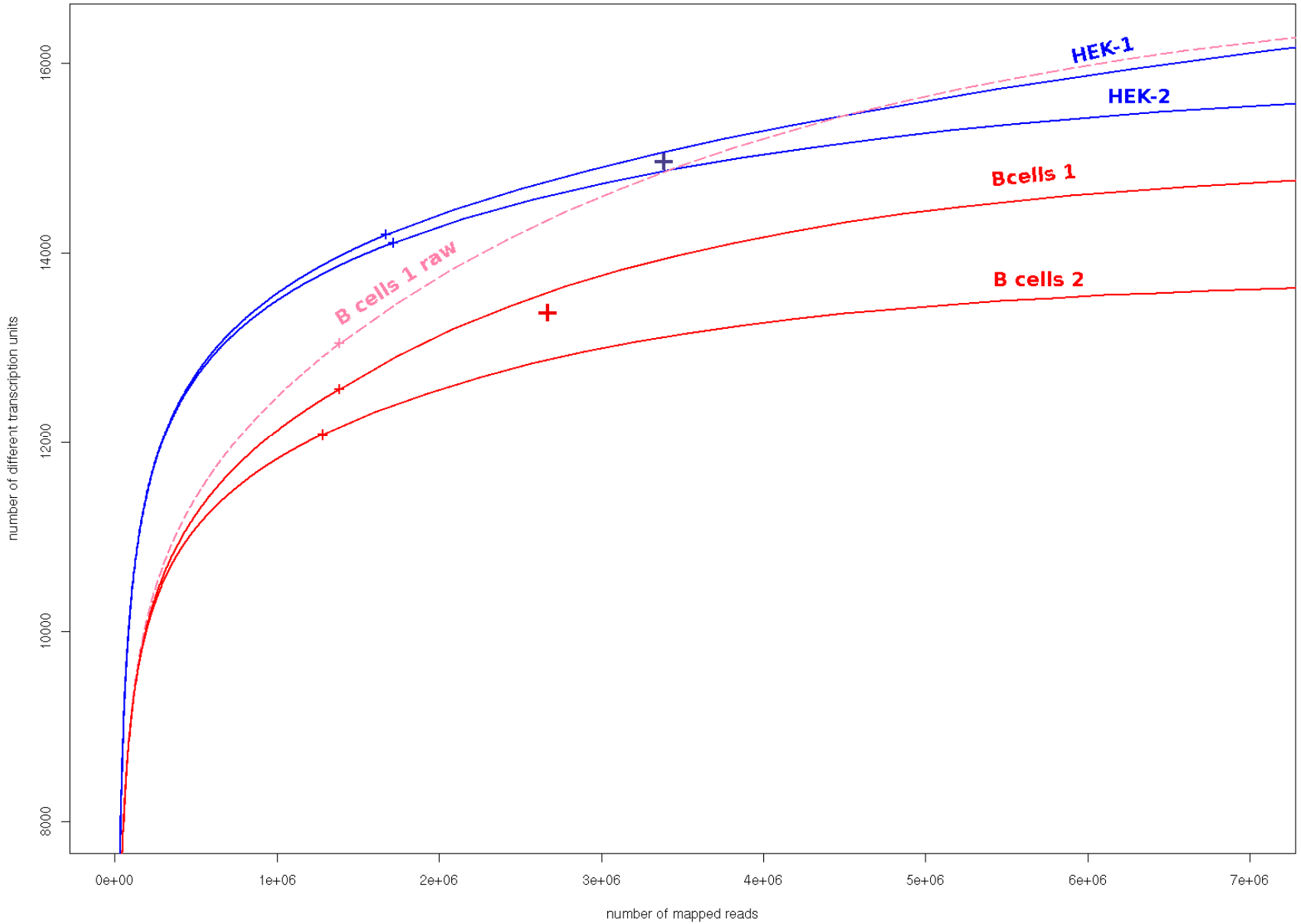
In total, we generated a shotgun sequence from 99,208 large-insert clones (total length ~5.84 gigabases (Gb)) and finished the sequence from 45,742 of these clones (total length ~3.67 Gb). The clones consisted primarily of bacterial artificial chromosomes

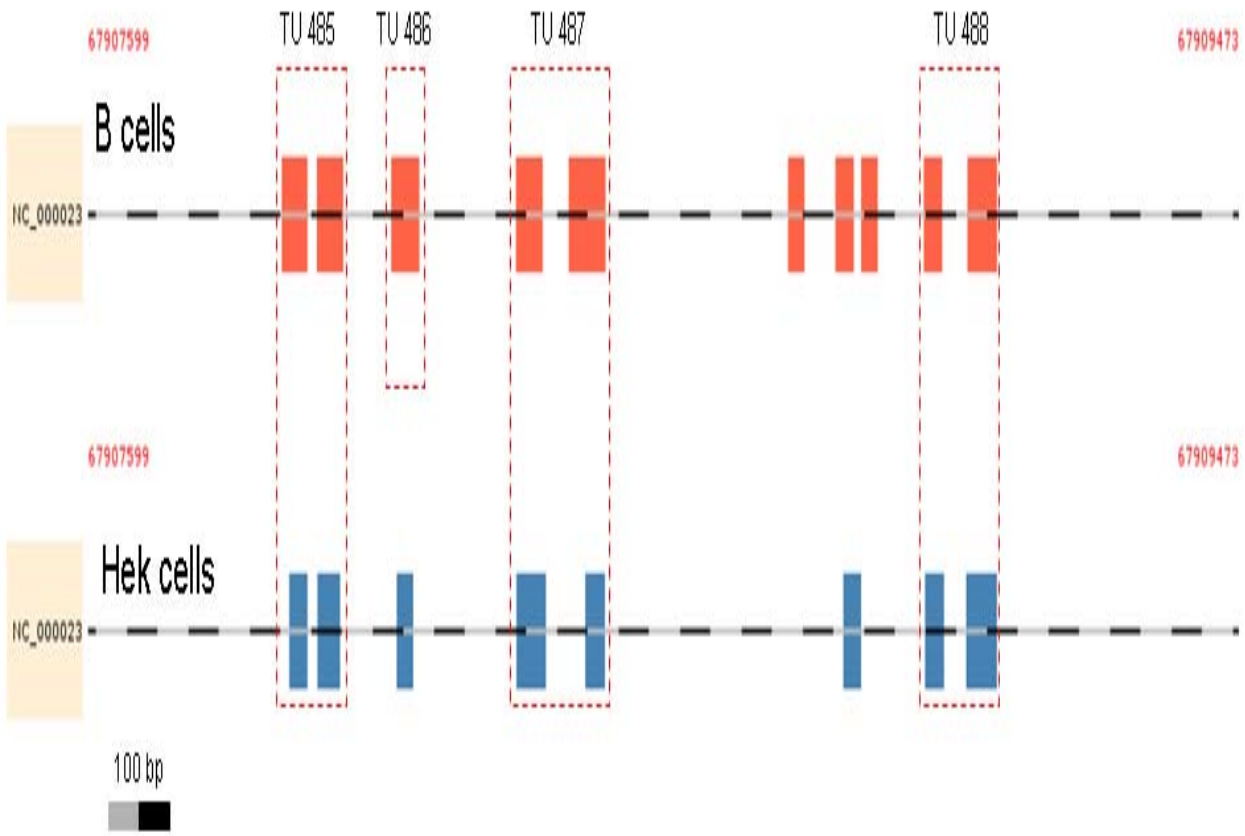
The 1000 genomes project: a catalogue of human polymorphism created using next generation sequencing

1000 Genome project



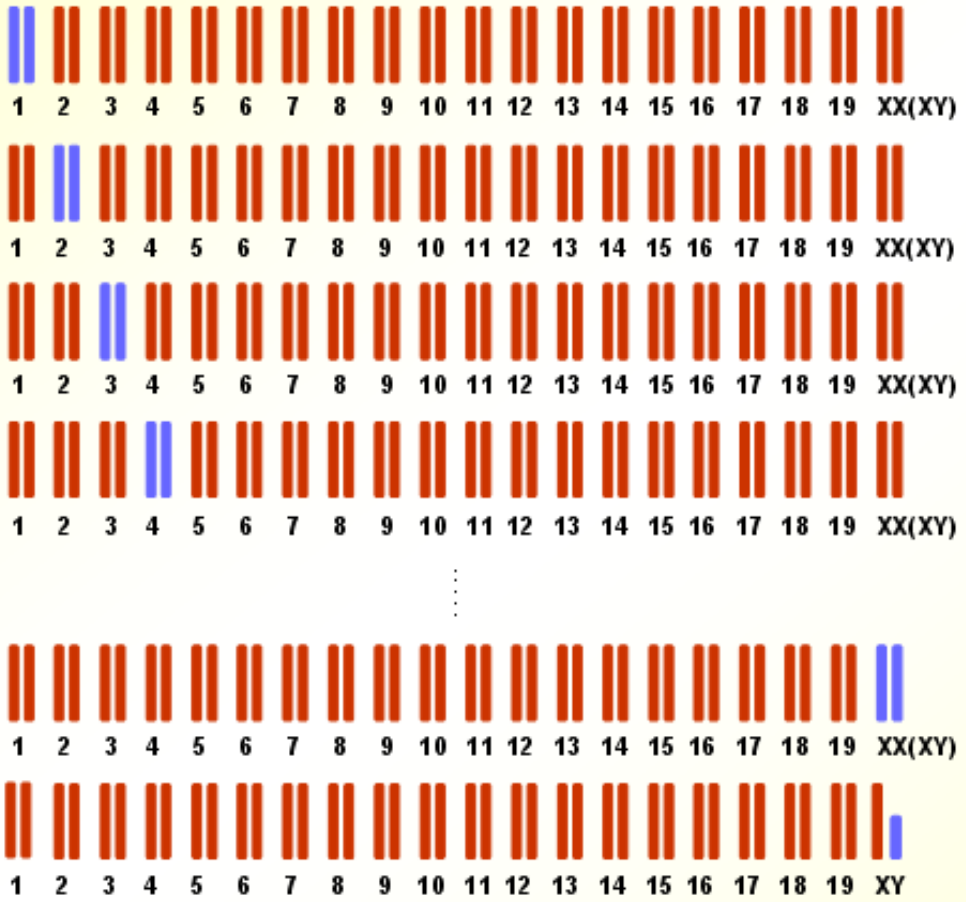
117 Gb, two sequencing platforms


HEK-1
HEK-2
Bcells 1
B cells 2
B cells 1 raw
number of different transcription units
number of mapped reads
8000
10000
12000
14000
16000
0e+00
1e+06
2e+06
3e+06
4e+06
5e+06
6e+06
7e+06


67907599
TU 485
TU 486
TU 487
TU 488
67909473
B cells
NC_000023
67907599
67909473
Hek cells
NC_000023
100 bp

Genetics

A panel of 21 inter-species consomic strains



B6-1^{PWD}

B6-2^{PWD}

B6-3^{PWD}

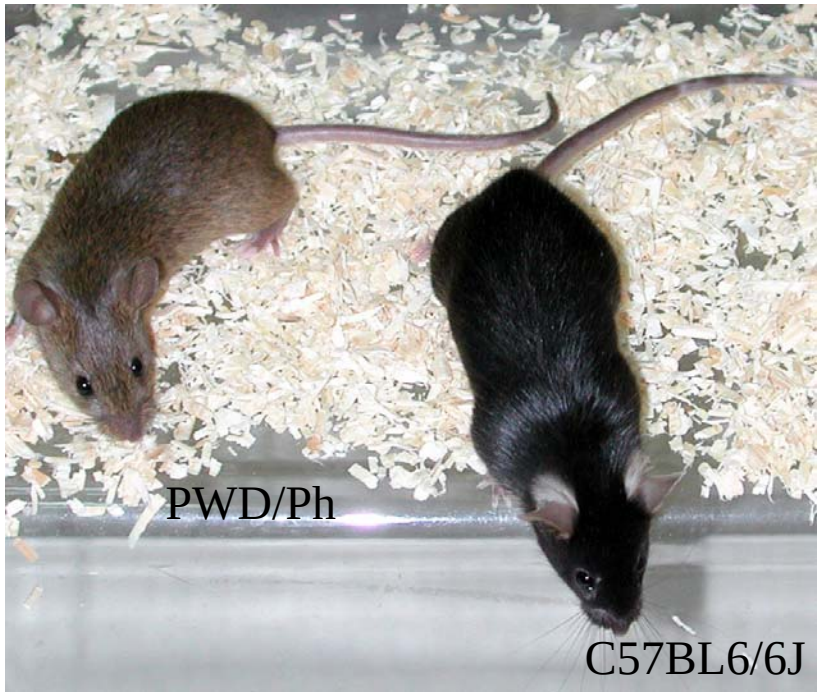
B6-4^{PWD}

B6-X^{PWD}

B6-Y^{PWD}

donor strain: PWD/Ph (*Mus musculus musculus*)

Mouse model



Mus mus musculus ***Mus mus domesticus***

1 million years of separate evolution

<u>PWD characteristics</u>:

captured in Prague in the 1970s

Inbred for > 60 generations (J. Forejt)

Smaller; lower body weight

Circadian and sleep rhythms different

Marginally more anxious in open field test

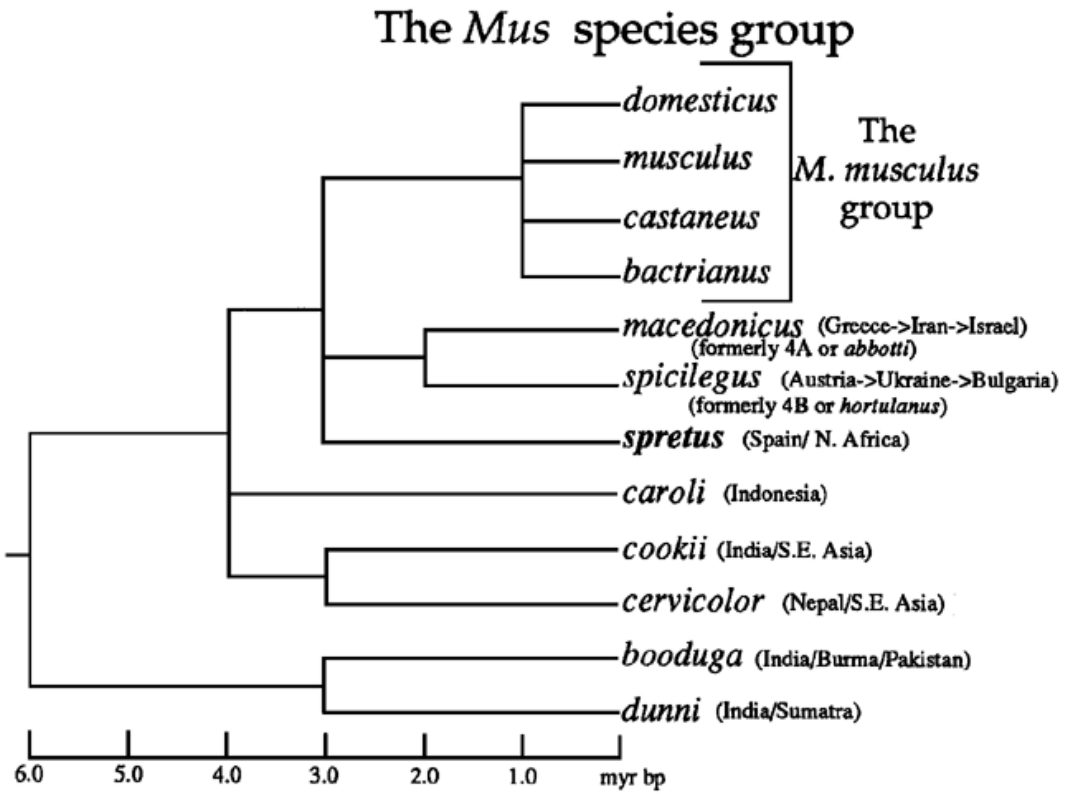
Greater awareness of test environment

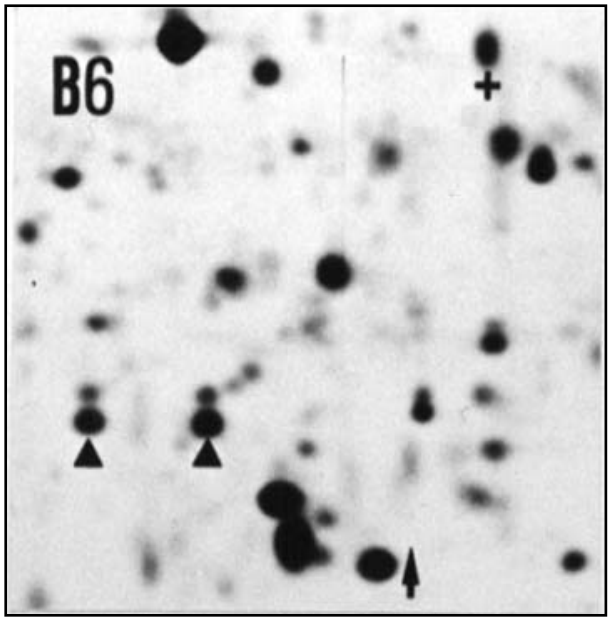
In high-glucose tolerance test:

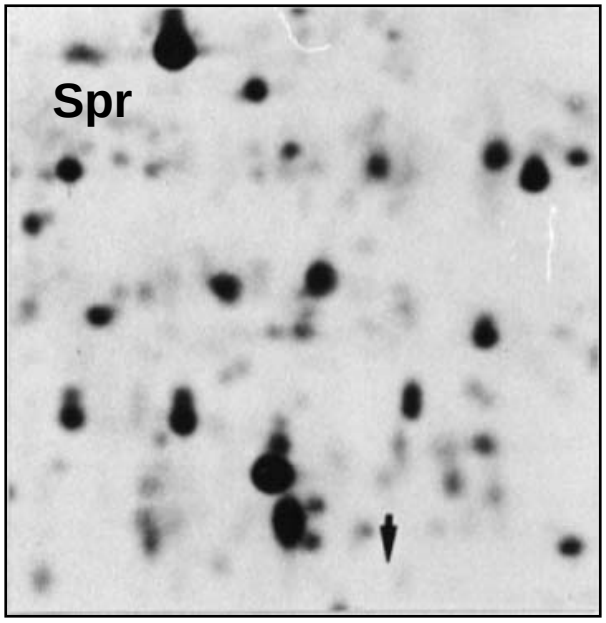
clear glucose faster

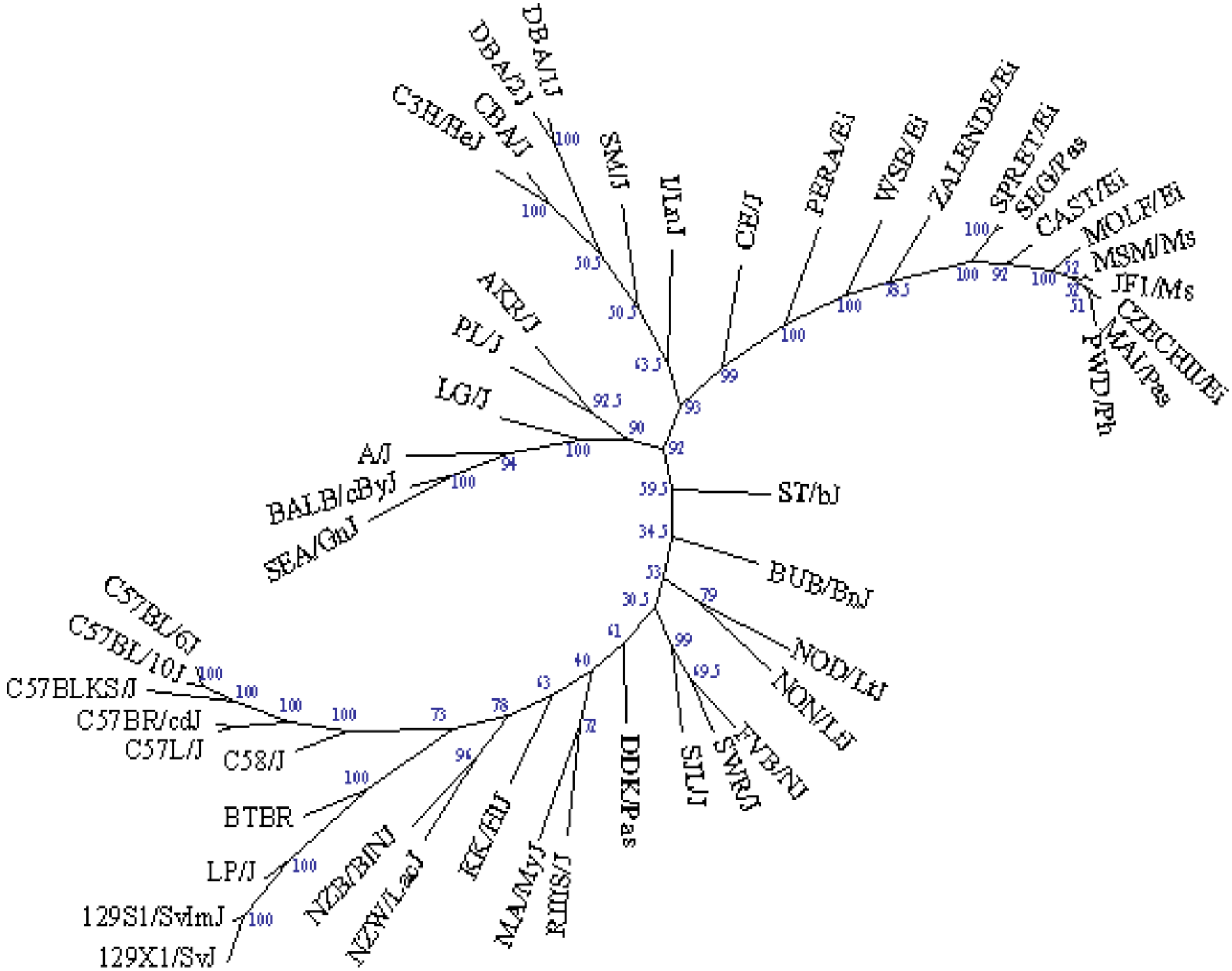
1% difference in genomic sequence vs. B6 (BAC clone sequencing) – frequency of SNPs ~ 2-fold compared to classical inbred strains (1/330 bp vs. 1/600 bp)

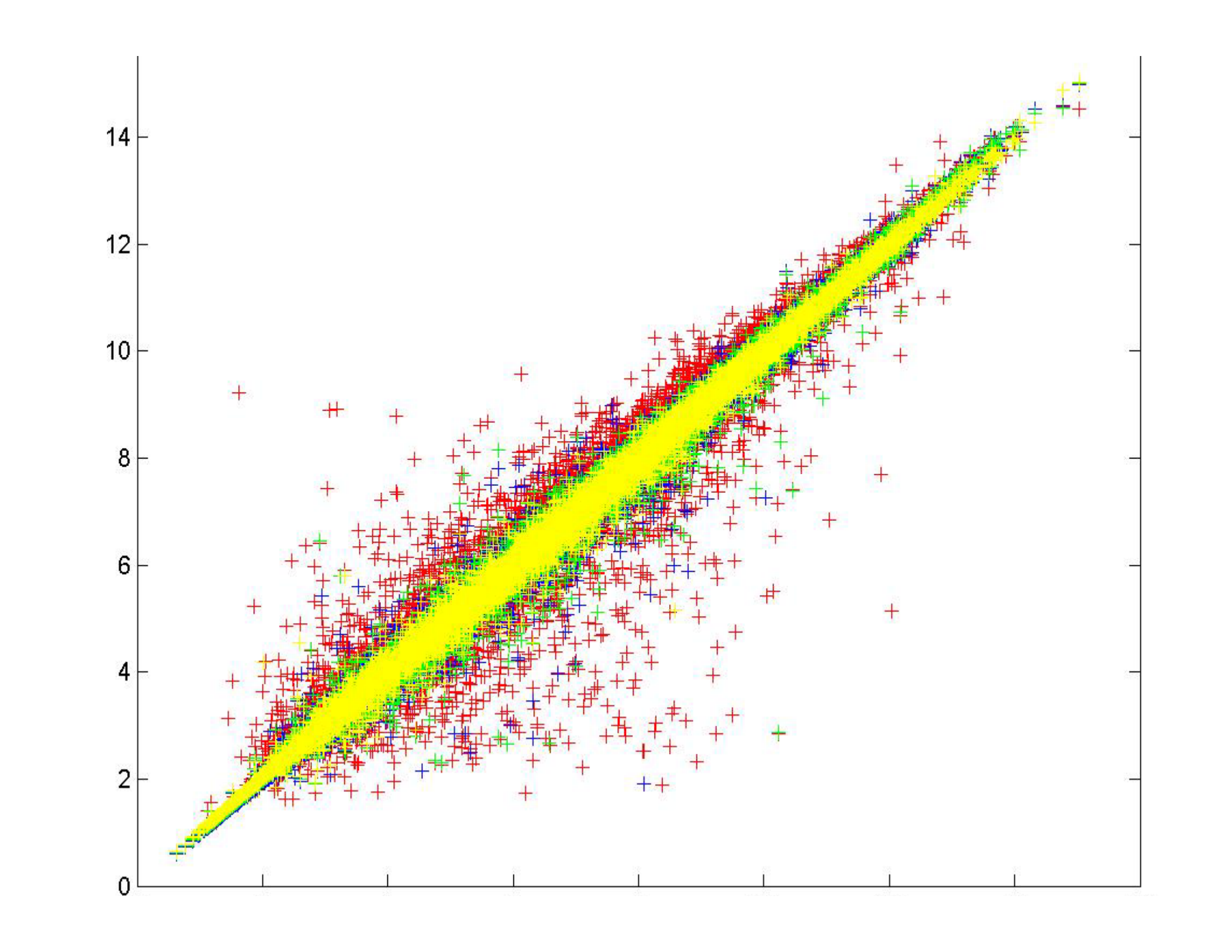
2-DE analysis of brain proteins from distantly related mouse strains (Joachim Klose)



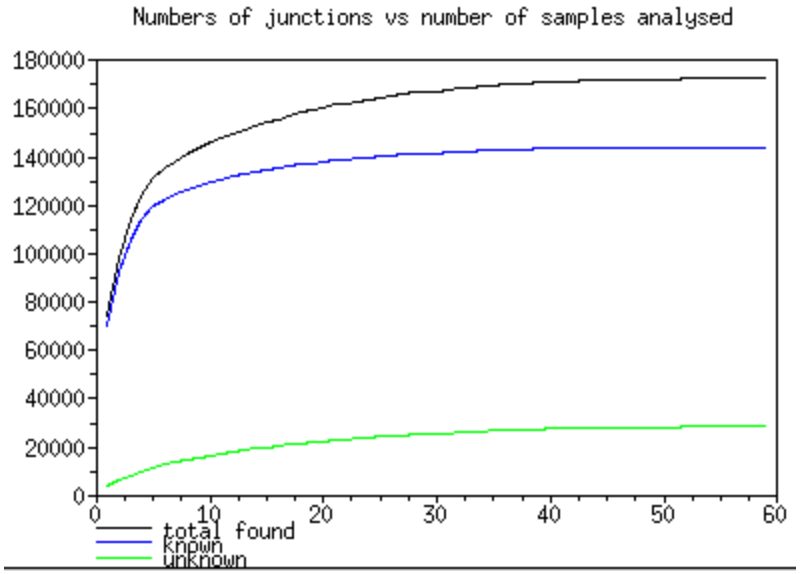


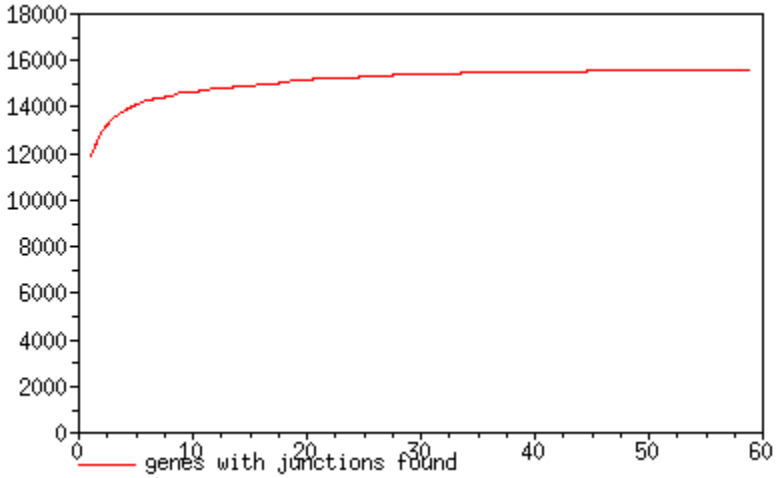


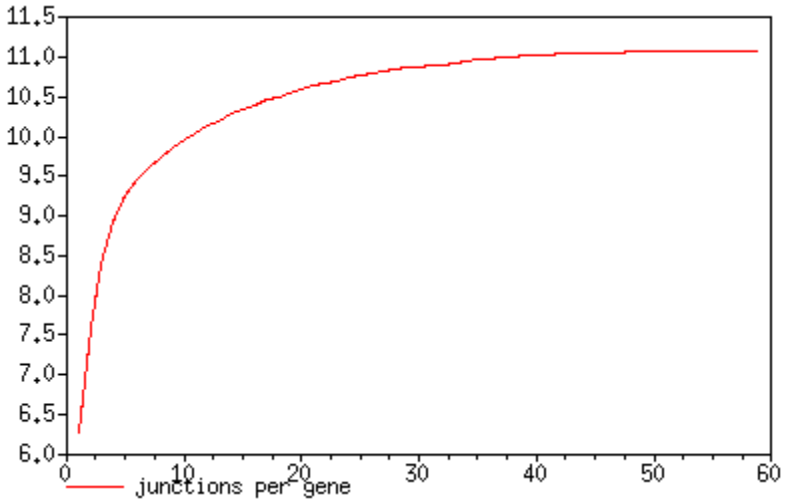

DBA/1J
DBA/2J
CBA/J
C3H/HeJ
SM/J
LLnJ
CE/J
PERA/Ei
WSB/Ei
ZALENDE/Ei
SPRET/Ei
SEC/Pas
CAST/Ei
MOLF/Ei
MSM/Ms
JFI/Ms
CZECHII/Ei
MAI/Pas
PWD/Ph
AKR/J
PL/J
LG/J
A/J
BALB/cByJ
SEA/GnJ
ST/bJ
BUB/BnJ
NOD/LtJ
NON/LtJ
FVB/NJ
SWR/J
SJL/J
DDK/Pas
MA/MyJ
RIIIS/J
KK/HlJ
NZB/BINJ
NZW/LacJ
129S1/SvImJ
129X1/SvJ
LP/J
BTBR
C58/J
C57BR/cdJ
C57L/J
C57BLKS/J
C57BL/10J
C57BL/6J


14
12
10
8
6
4
2
0

Junctions with 3 or more hits





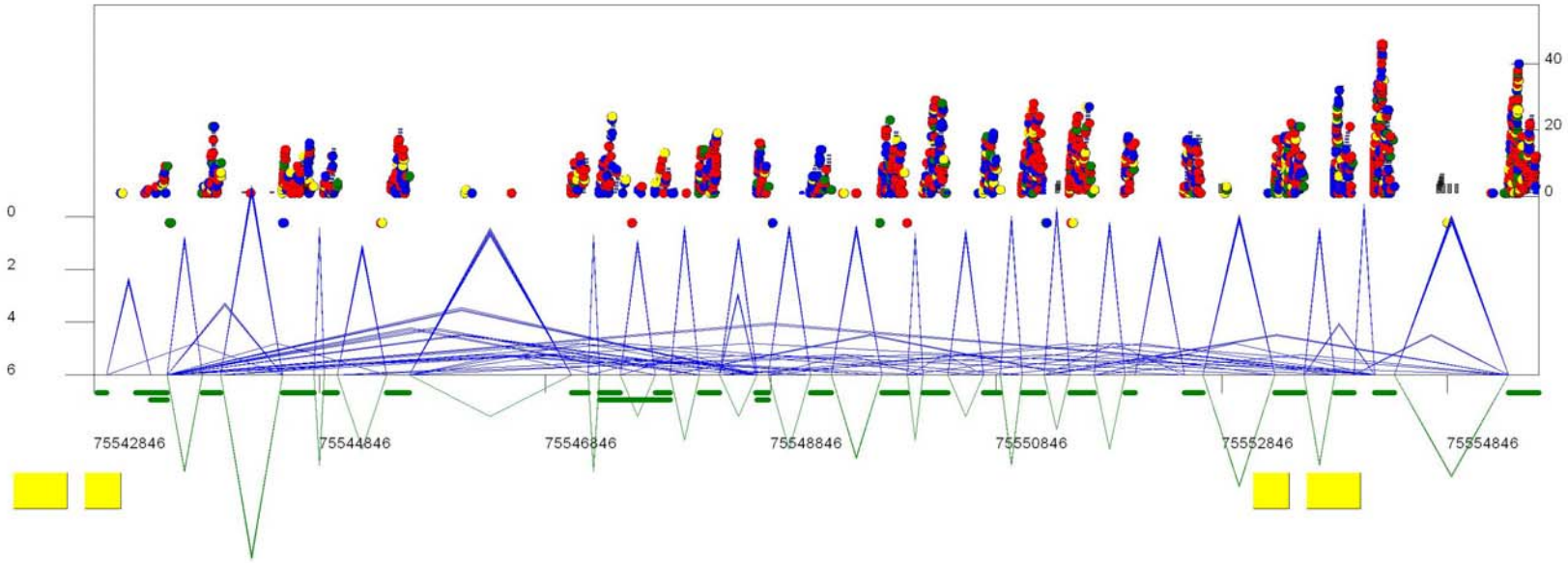


click somewhere on plot to zoom or Unzoom

sum

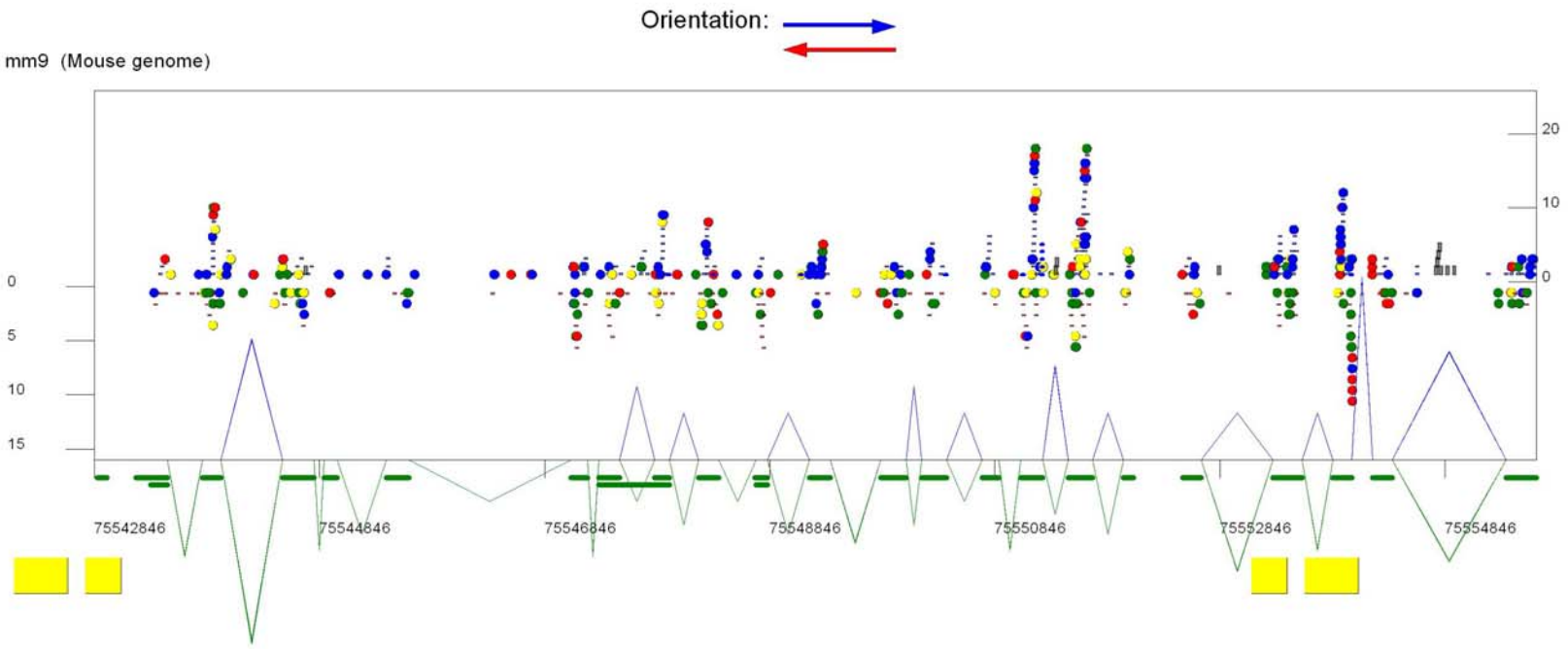
Orientation:

mm9 (Mouse genome)



click somewhere on plot to zoom or Unzoom

D4



LOG (base 2) of number+1 of fragments per 476333 bp for all consomics (name and value are popuping)

click somewhere on plot to zoom or Unzoom

Expression

UCSC

Click on p_val track

Replicas

Ensembl

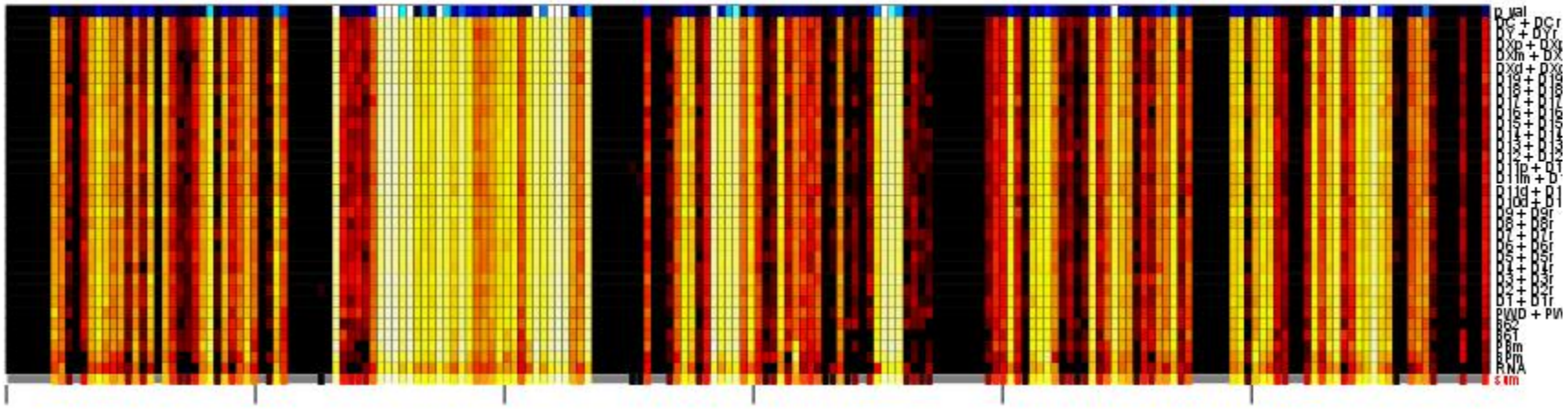
Click on p_val track

mm9 (Mouse genome)

Hits per bin:

0

sum



0 16000000 32000000 4.8E+7 64000000 80000000

<< < > >>

[<< back to index]

LOG (base 2) of number+1 of fragments per 100 bp for all consomics (name and value are popuping)

click somewhere on plot to zoom or Unzoom

Expression

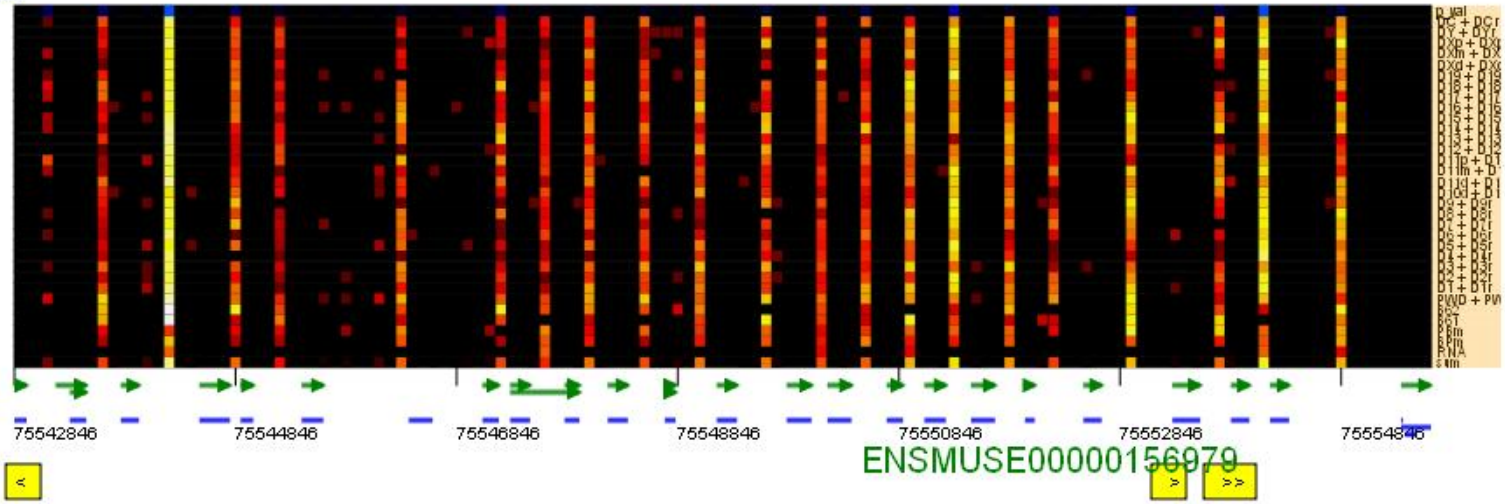
UCSC Click on p_val track

Replicas

Ensembl Click on p_val track

mm9 (Mouse genome)

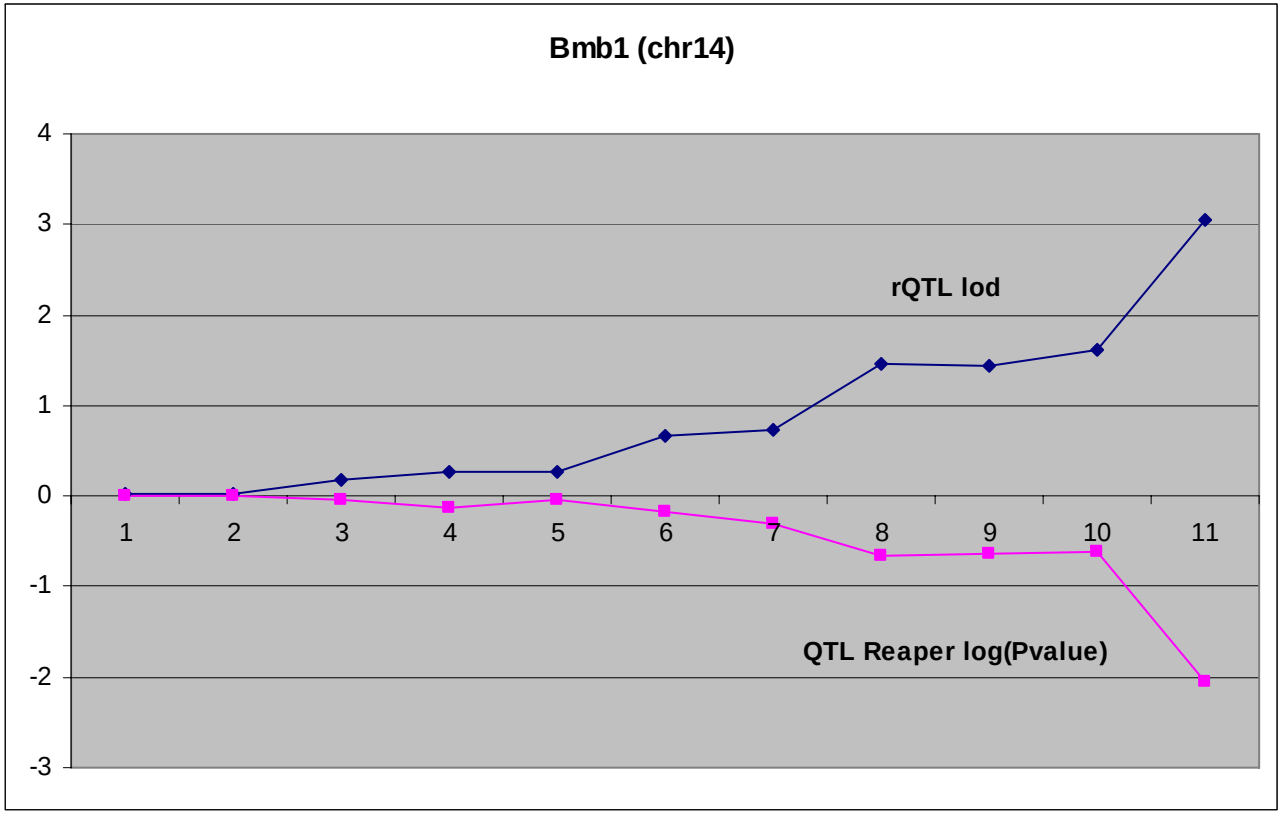
Hits per bin:



Chr. position: 1 | 75542846 | 75555658 | Apply | or ENSMUS_ID

Find any mouse gene (and more) with Ensembl

No	Marker	Start	End	Length	
1	D12Mit37	5394448	5394587	139	1cM
2	D12Mit215	7638581	7638705	124	2cM
3	D12Mit136	30759790	30759936	146	13cM
4	D12Mit147	36308553	36308701	148	16cM
5	D12Mit285	55570751	55570875	124	25cM
6	D12Mit210	66343486	66343631	145	28cM
7	D12Mit201	73210299	73210513	214	29cM
8	D12Mit159	84770461	84770571	110	38cM
9	D12Mit118	91917751	91917878	127	45cM
10	D12Mit7*	103396370	103396470	100	50cM
11	D12Mit20	113809374	113809570	196	58cM

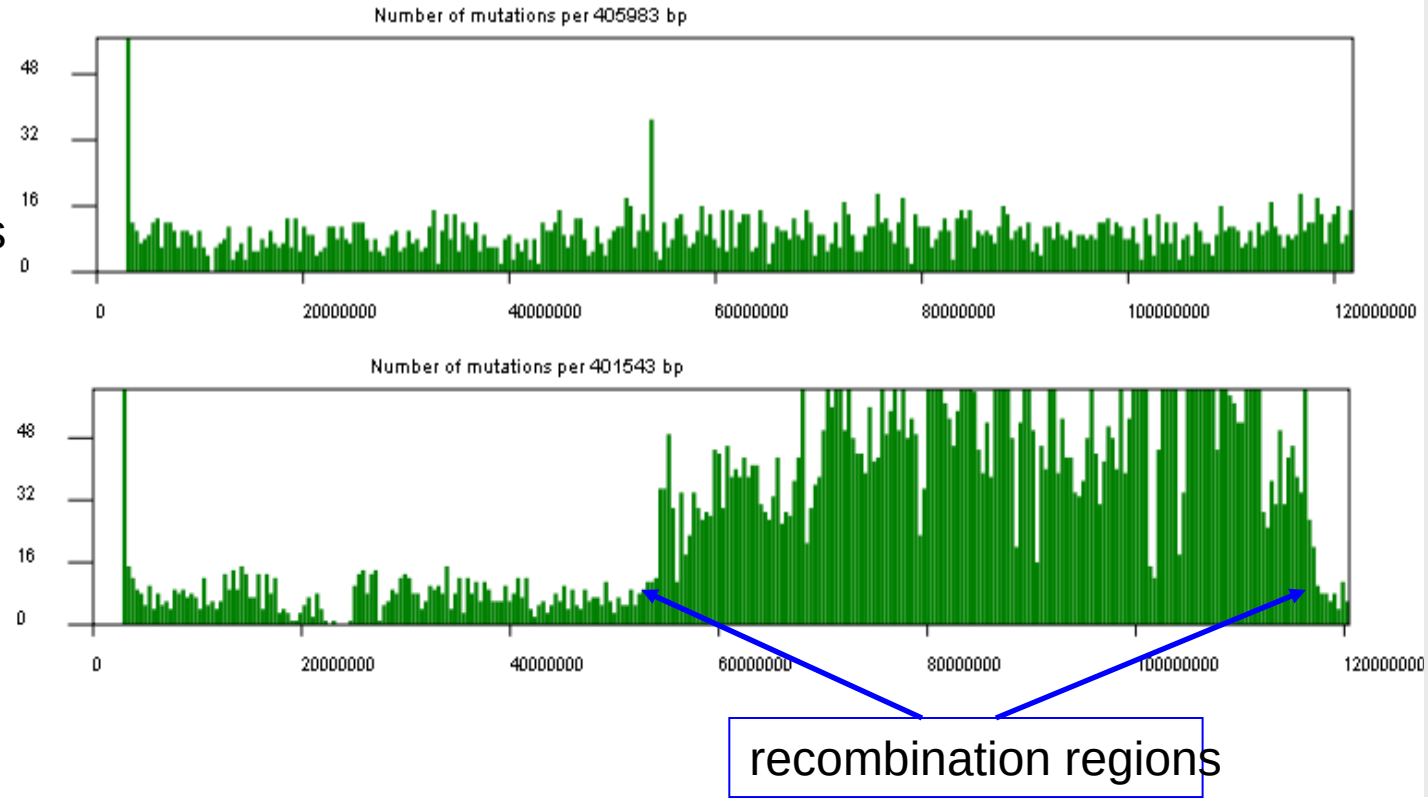


Genotyping of C12 F2 intercross mouse

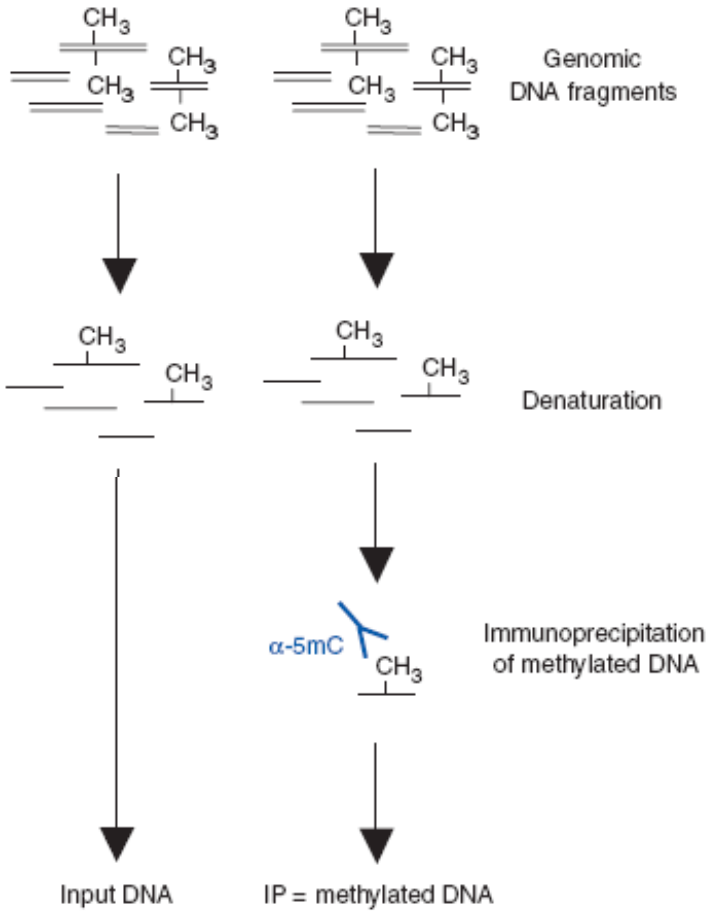
Random sequencing of C12 F2 mouse: 1.8 mln. aligned reads.
Diagram of differences between C12 F2 and C57BL6/6J reference genome.

Chr. 11
100,542 reads

Chr. 12
74,476 reads



Methylated DNA immunoprecipitation (MeDIP)



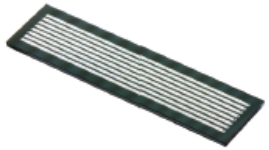
Weber et al. 2005, Nature Genetics 37: 853-862
Keshet et al. 2006, Nature Genetics 38: 149-153

MeDIP-Seq workflow

DNA shearing and

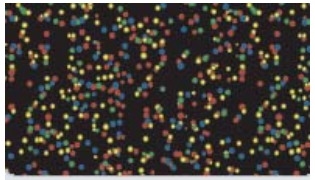
library preparation (2 days)

MeDIP and library amplification (2-3 days)



Cluster generation (1 day)

Sequencing by synthesis (2 days)

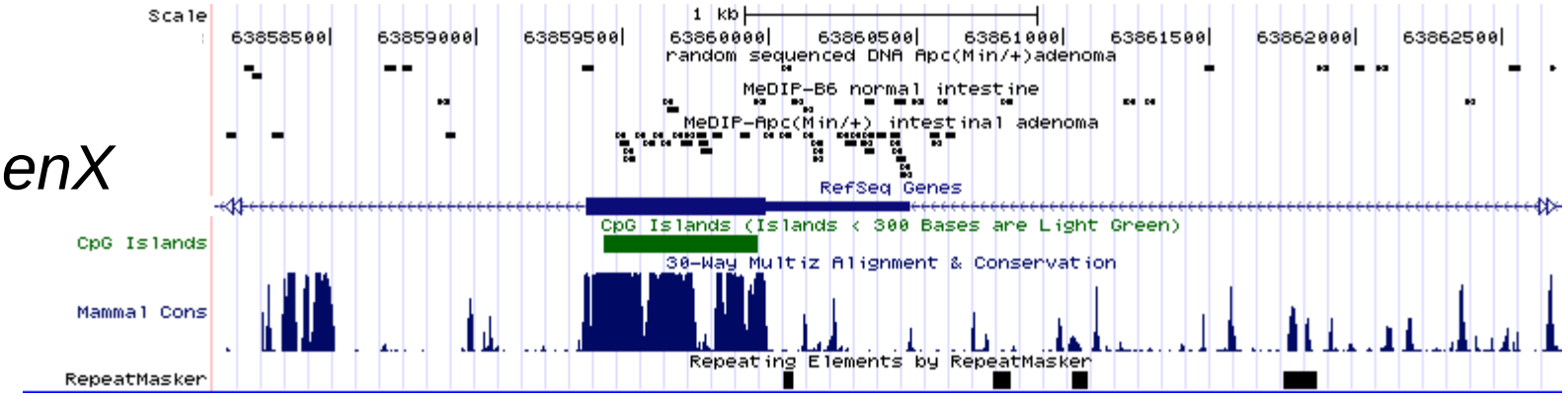


Data processing (1 day)

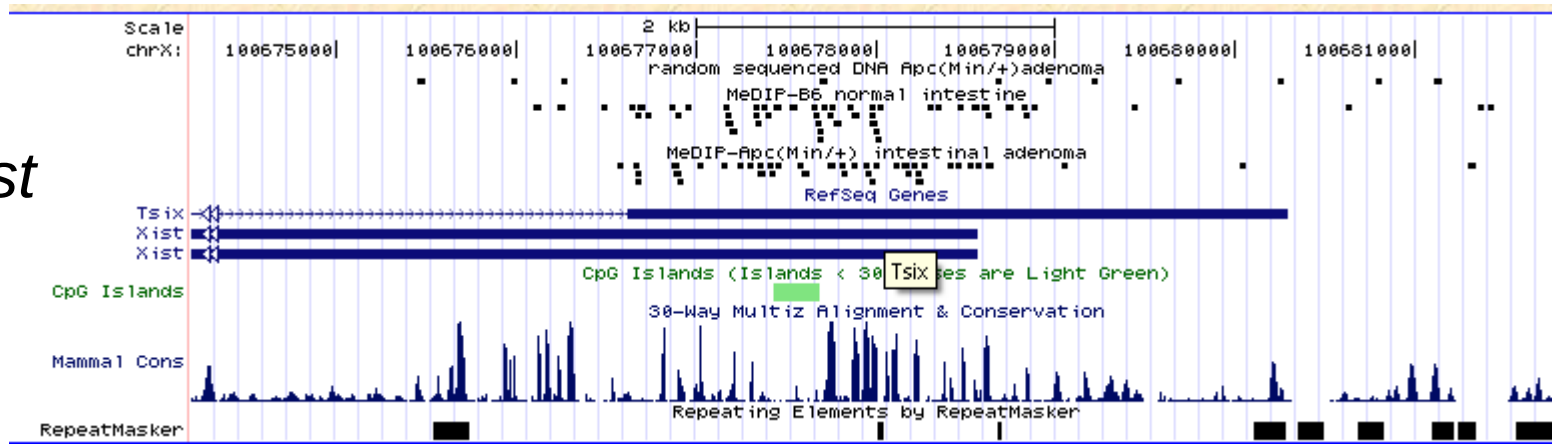
GenX is methylated in adenoma of Apc$^{(min/+)}$, a mouse model of human colon cancer

GenX methylation is known to occur in human colon cancer

GenX



Xist

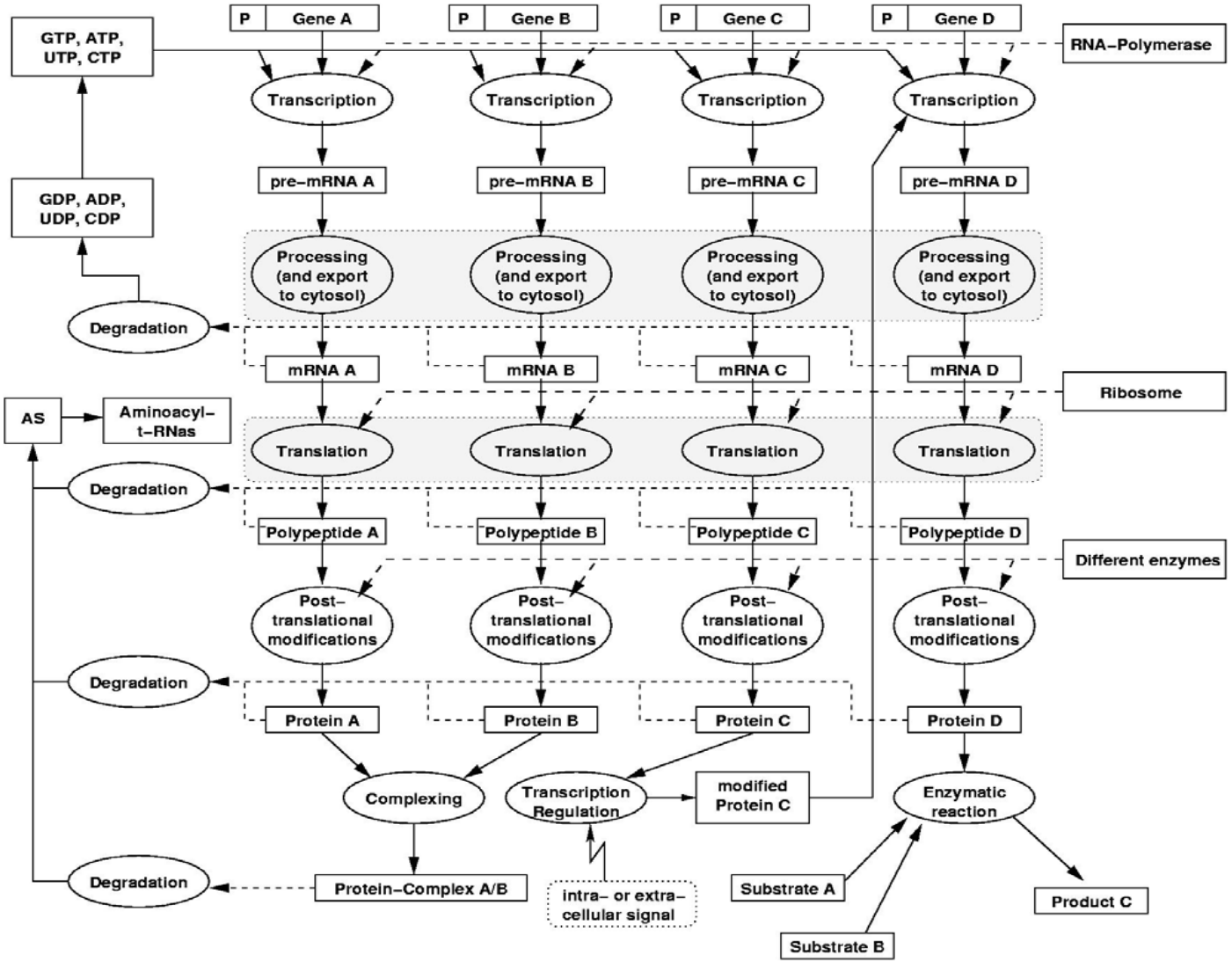


positive control: DNA-methylation of *Xist*

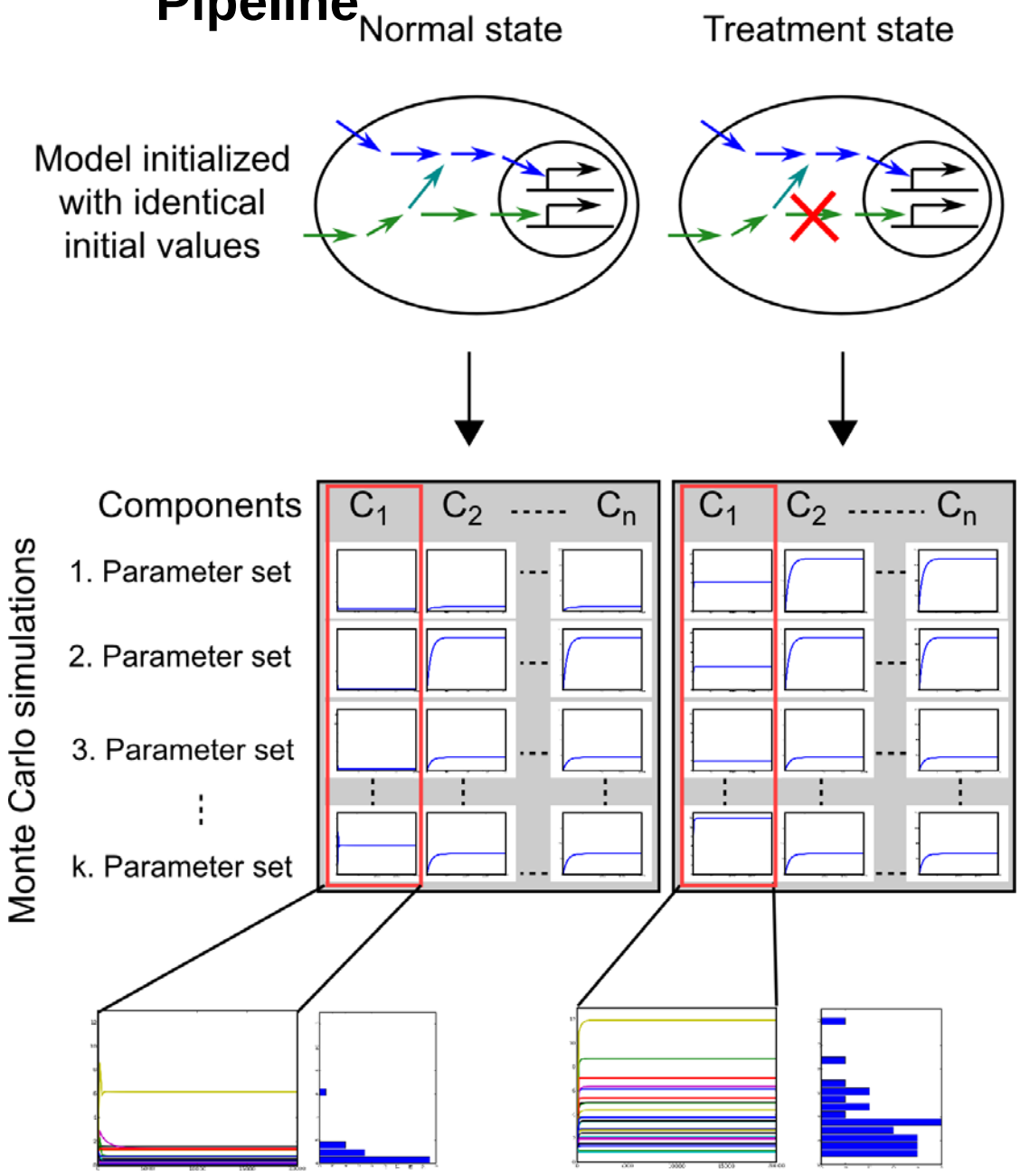
Systems Biology

Systems biology – modelling platform

MAX-PLANCK-GESELLSCHAFT



Monte Carlo Approach – Simulation Pipeline



Implementation of an automatic pipeline for the simulation of individual studies (e.g. mutation, drug treatment, etc.).

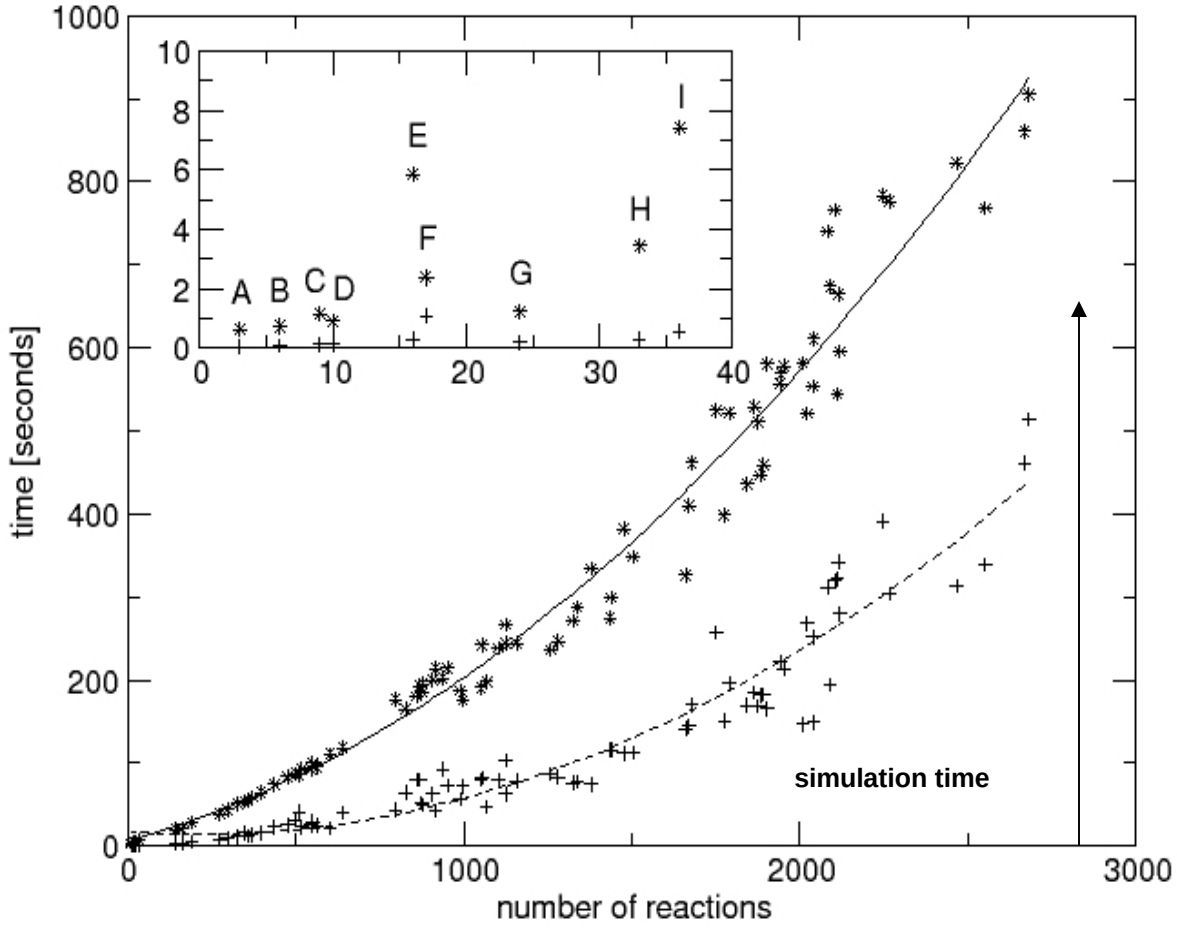
This includes:

1. state definition
2. simulation
3. evaluation

Systems biology – modelling platform

MAX-PLANCK-GESELLSCHAFT

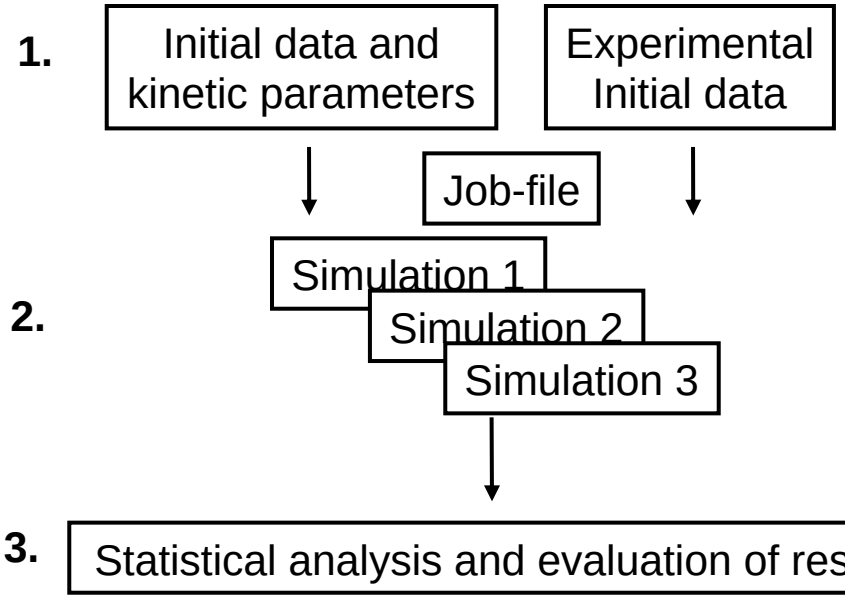
System performance and scaling



- **quadratic scaling behaviour**
- **simulations can handle systems with thousands of components and reactions**

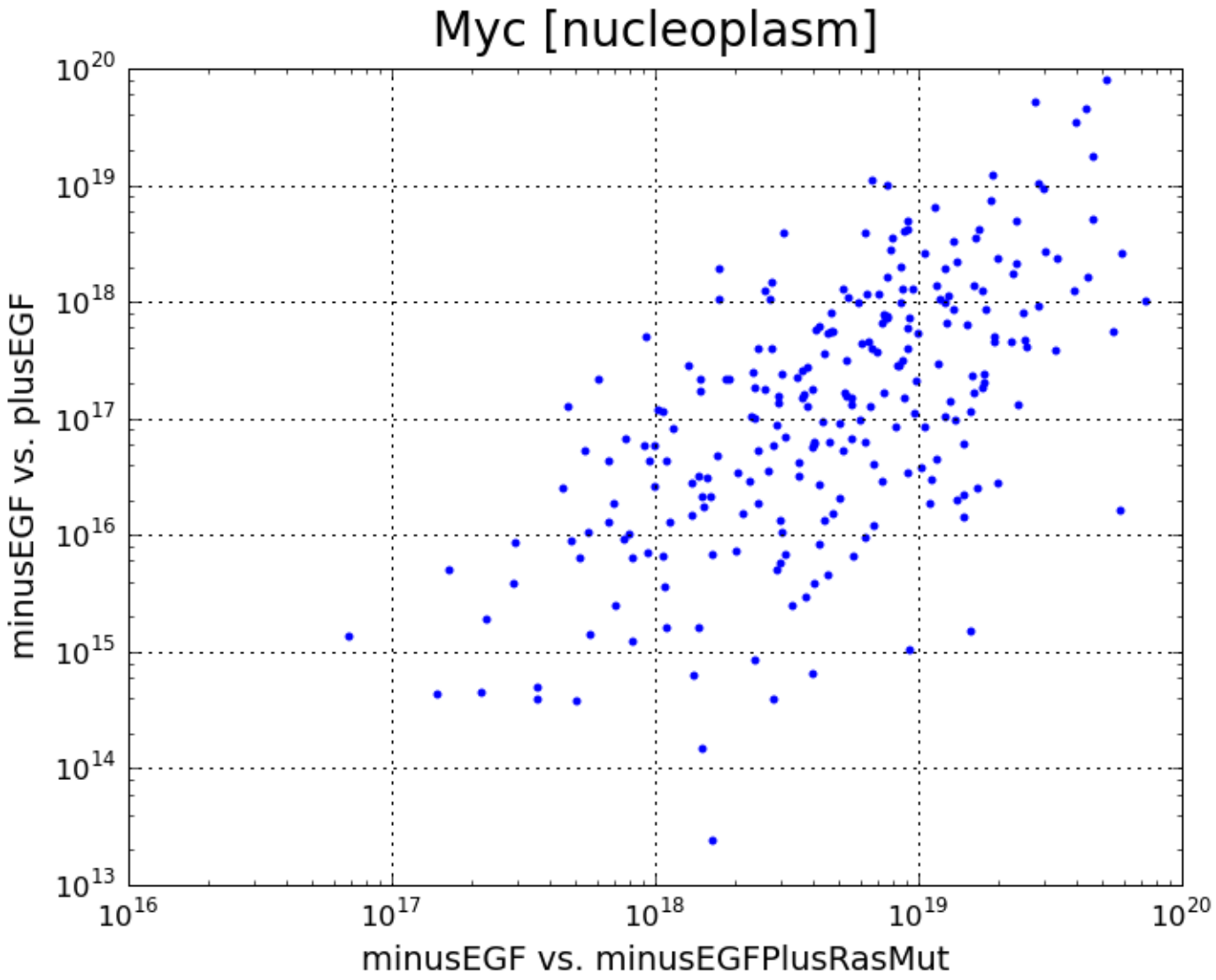
- **numeric ODE solver is stable**

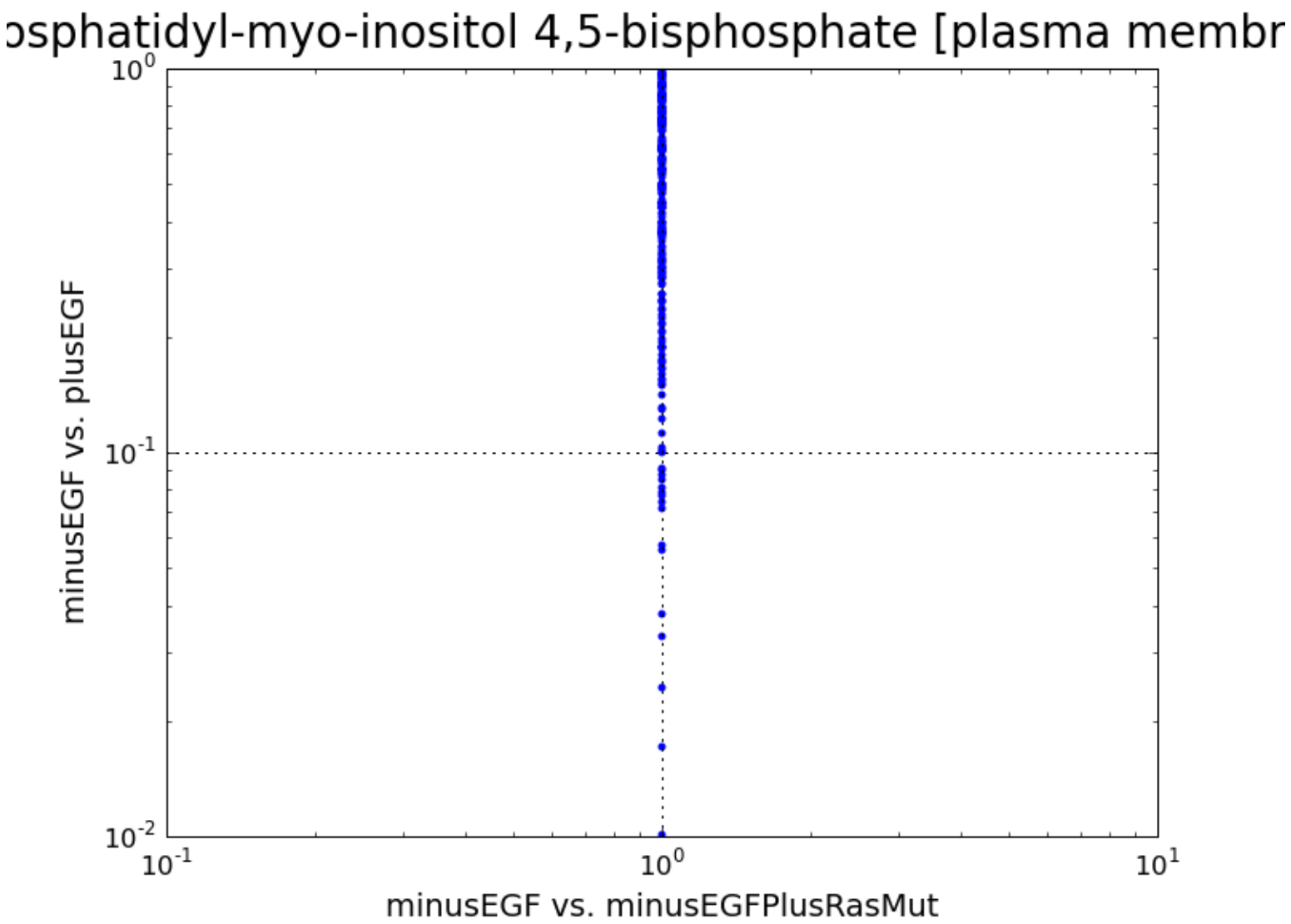
Large scale modelling – EGEE grid

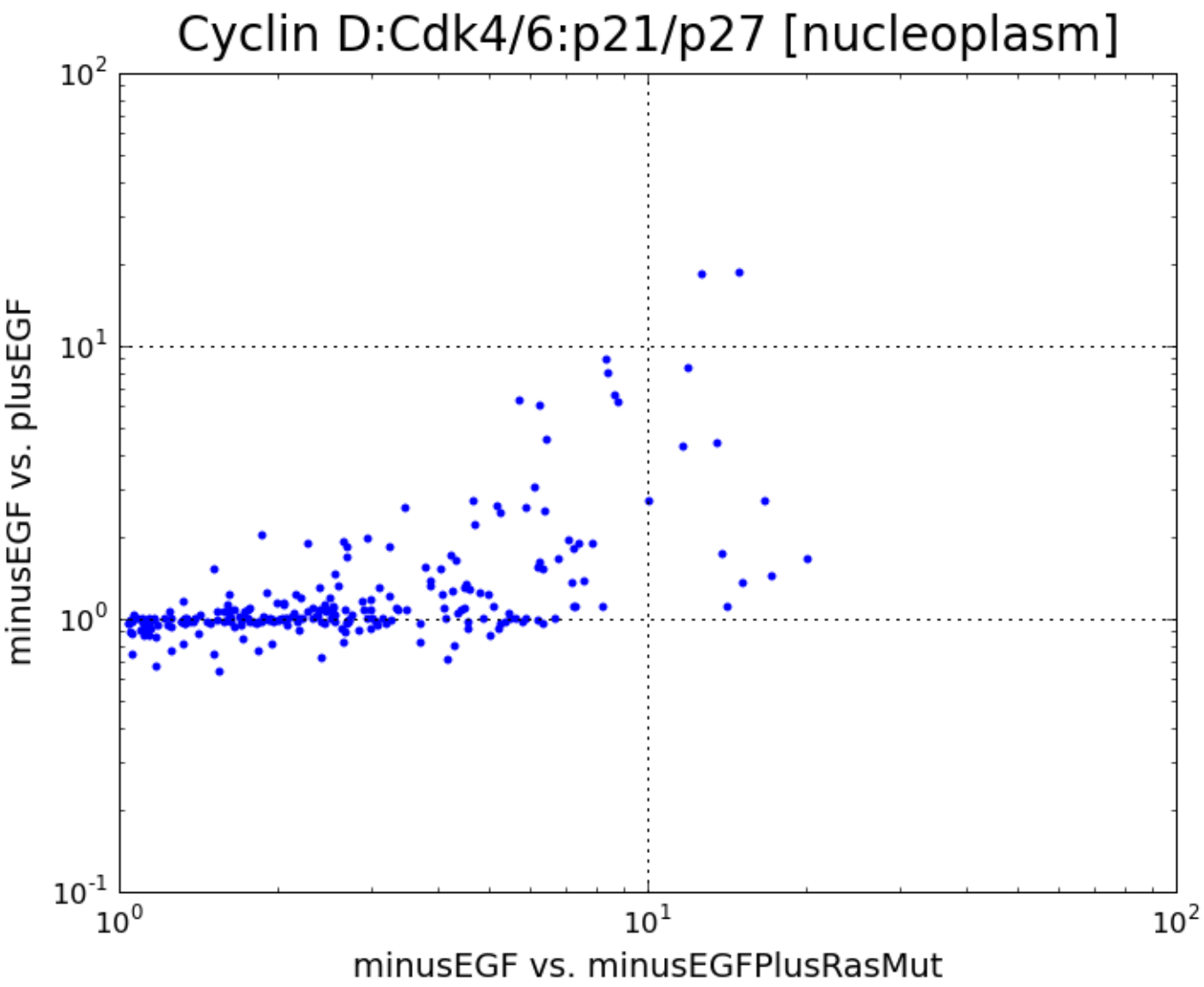


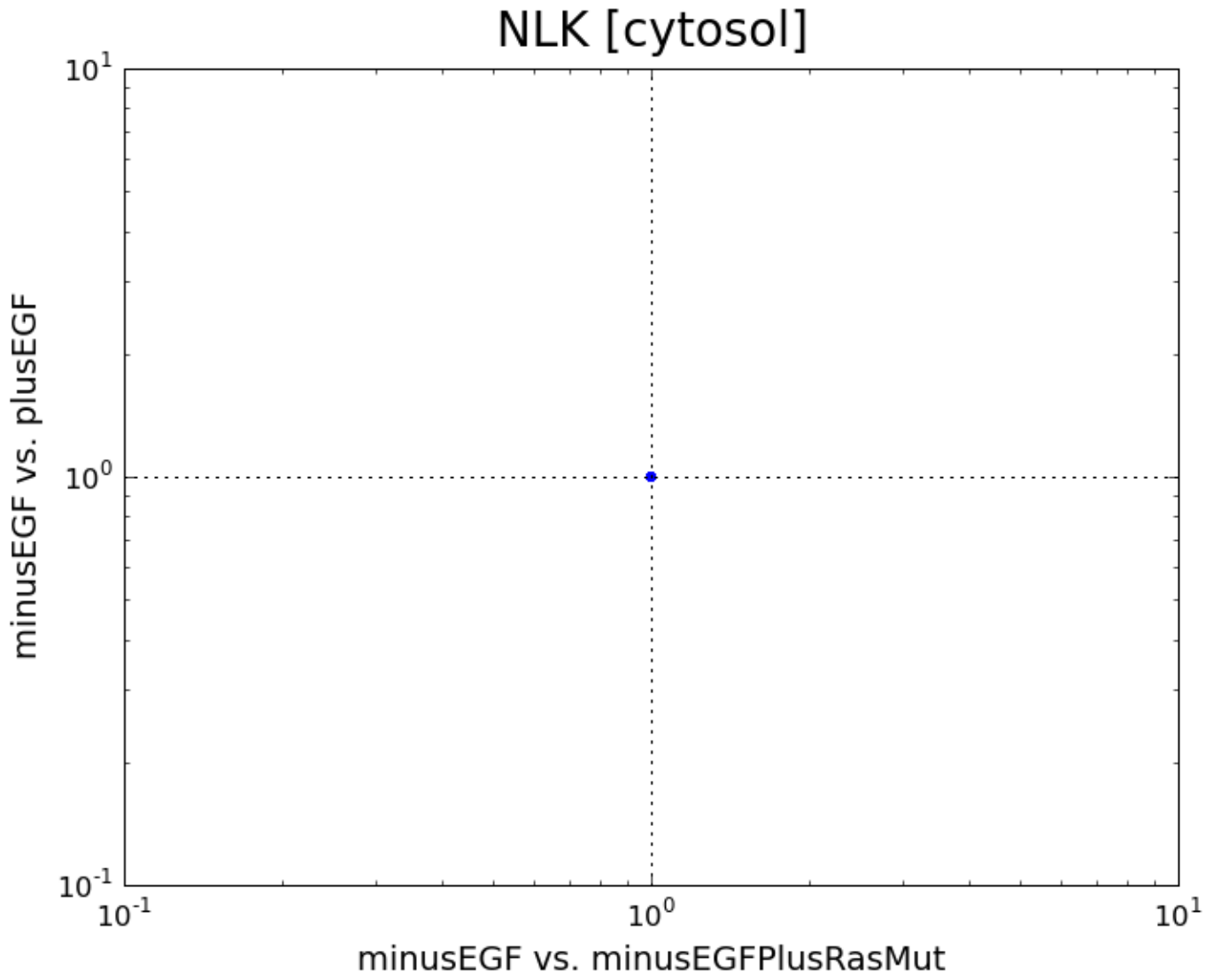
Christophe Blanchet
Centre National de la Recherche Scientifique, Lyon, France

Metabolite	Enzyme 0 knockdown				Enzyme 1 knockdown				Enyzme 2 knockdown			
	Mean(Ratio)	CV(Ratio)	Mean(Conc)	SD(Conc)	Mean(Ratio)	CV(Ratio)	Mean(Conc)	SD(Conc)	Mean(Ratio)	CV(Ratio)	Mean(Conc)	SD(Conc)
M0	0,54	1,37	0,38	2,5	3,48	8,77	0,08	0,58	1,1	0,46	0,07	0,37
M1	3,18	2,34	0,13	0,98	2,09	6,98	0,22	1,36	1,04	0,29	0,29	2,07
M10	2,71	7,47	0,04	0,26	1,06	0,56	0,04	0,2	1,02	0,21	0,05	0,28
M11	1,34	0,87	0,91	2,25	1,65	5,69	1,07	2,54	313,28	14,06	1,05	2,49
M12	0,96	0,25	0,2	0,3	1,47	4,57	0,18	0,19	1	0,04	0,18	0,19
M13	3,16	2,77	0,08	0,5	2,92	8,73	0,06	0,52	1,03	0,28	0,05	0,43
M14	7,68	6,26	269,89	2517,75	38,92	13,77	50	256,4	1,18	2,1	101,58	850,4
M15	1,7	1,79	0,14	0,98	2,74	5,81	0,12	0,94	1,3	0,83	0,17	1,27
M16	8,6	7,42	1,97	24,47	23,69	10,87	0,36	1,75	1,21	0,91	0,4	1,93
M17	0,96	0,42	1,85	14,8	1,01	0,14	1,01	12,91	1,03	0,18	0,73	9
M18	0,97	0,21	4,02	40,96	1	0,04	0,6	1,57	1,01	0,16	0,58	1,51
M19	8,95	7,4	0,3	2,67	37,41	11,97	0,07	0,35	1,21	0,9	0,08	0,39
M2	146,58	11,81	0,1	0,39	24,88	12,89	0,08	0,32	1,49	3,54	0,08	0,28
M20	0,79	1,53	1,56	8,12	1,75	4,05	0,61	3,59	1,07	0,39	0,53	3,05

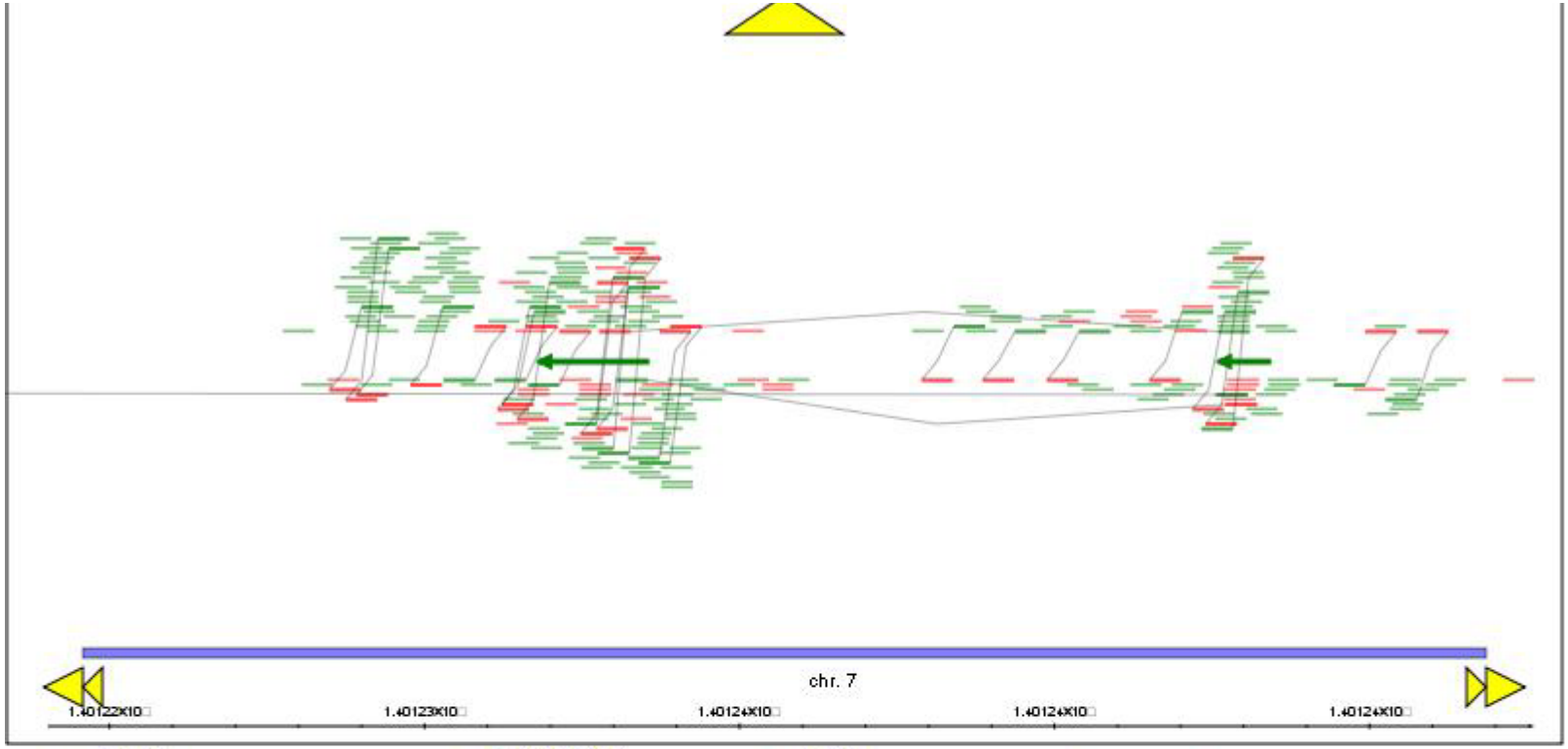

Myc [nucleoplasm]
minusEGF vs. plusEGF
minusEGF vs. minusEGFPlusRasMut
10^{20}
10^{19}
10^{18}
10^{17}
10^{16}
10^{15}
10^{14}
10^{13}
10^{16}
10^{17}
10^{18}
10^{19}
10^{20}


osphatidyl-myo-inositol 4,5-bisphosphate [plasma membr
10^0
10^{-1}
10^{-2}
minusEGF vs. plusEGF
10^{-1}
10^0
10^1
minusEGF vs. minusEGFPlusRasMut


Cyclin D:Cdk4/6:p21/p27 [nucleoplasm]
minusEGF vs. plusEGF
minusEGF vs. minusEGFPlusRasMut
10^2
10^1
10^0
10^{-1}
10^0
10^1
10^2


NLK [cytosol]
10^1
10^0
10^{-1}
minusEGF vs. plusEGF
10^{-1}
10^0
10^1
minusEGF vs. minusEGFPlusRasMut

- 0.5 x genome coverage tumor, tumor stem cells, patient genomes
- 30 x coverage exome, regulome
- 10 million reads tumor/tumor stem cell transcriptome
- Tumor/tumor stem cell epigenome?
- ~10 Gb/patient



Exome:
- + 090429_EAS453_1
- + 090429_EAS453_2
- - 090429_EAS453_3
- - 090429_EAS453_4
- + 090515_EAS453_1
- + 090515_EAS453_2
- + 090515_EAS453_3
- - 090515_EAS453_4
- - 090515_EAS453_5
- - 090515_EAS453_6

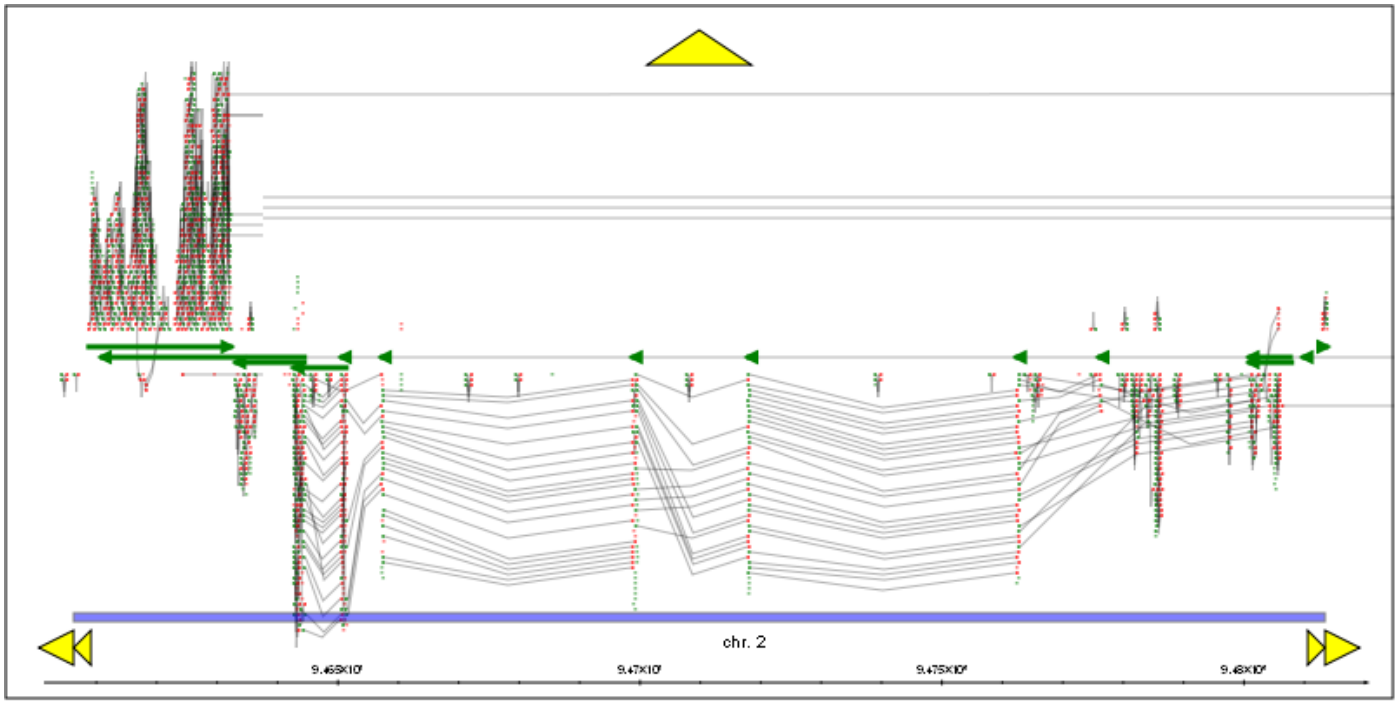
Transcriptome:
- + 090403_4
- + 090403_7
- + 090421_EAS453_6
- + 090421_EAS453_7
- + 090421_EAS453_8
- + 090430_EAS213_8
- + 090508_EAS451_7
- + 090508_EAS451_8
- - 090522_EAS451_7
- + 090522_EAS451_8

Solid:
- + solid0124_20090422_1
- + solid0124_20090422_2
- + solid0124_20090430_1
- + solid0124_20090430_2
- + solid0124_20090511_1
- + solid0124_20090511_2
- + solid0140_20090408_1
- + solid0140_20090408_2
- + solid0140_20090424_1
- + solid0140_20090424_2
- + solid0140_20090506_1
- + solid0140_20090506_2
- + solid0140_20090525_1
- + solid0140_20090525_2

Gene..

SNP..

ssRNA expression profiling and genotyping

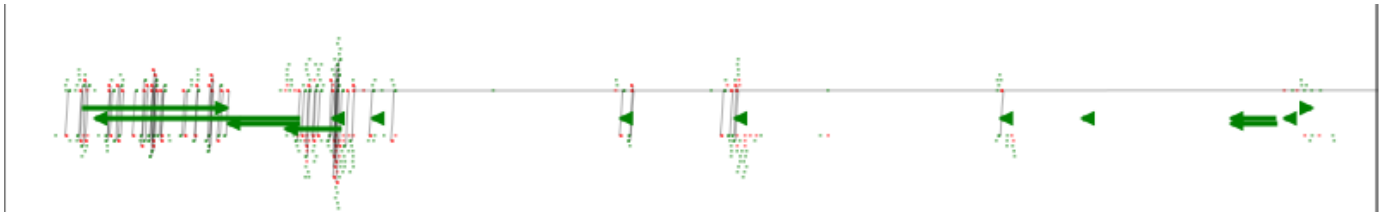


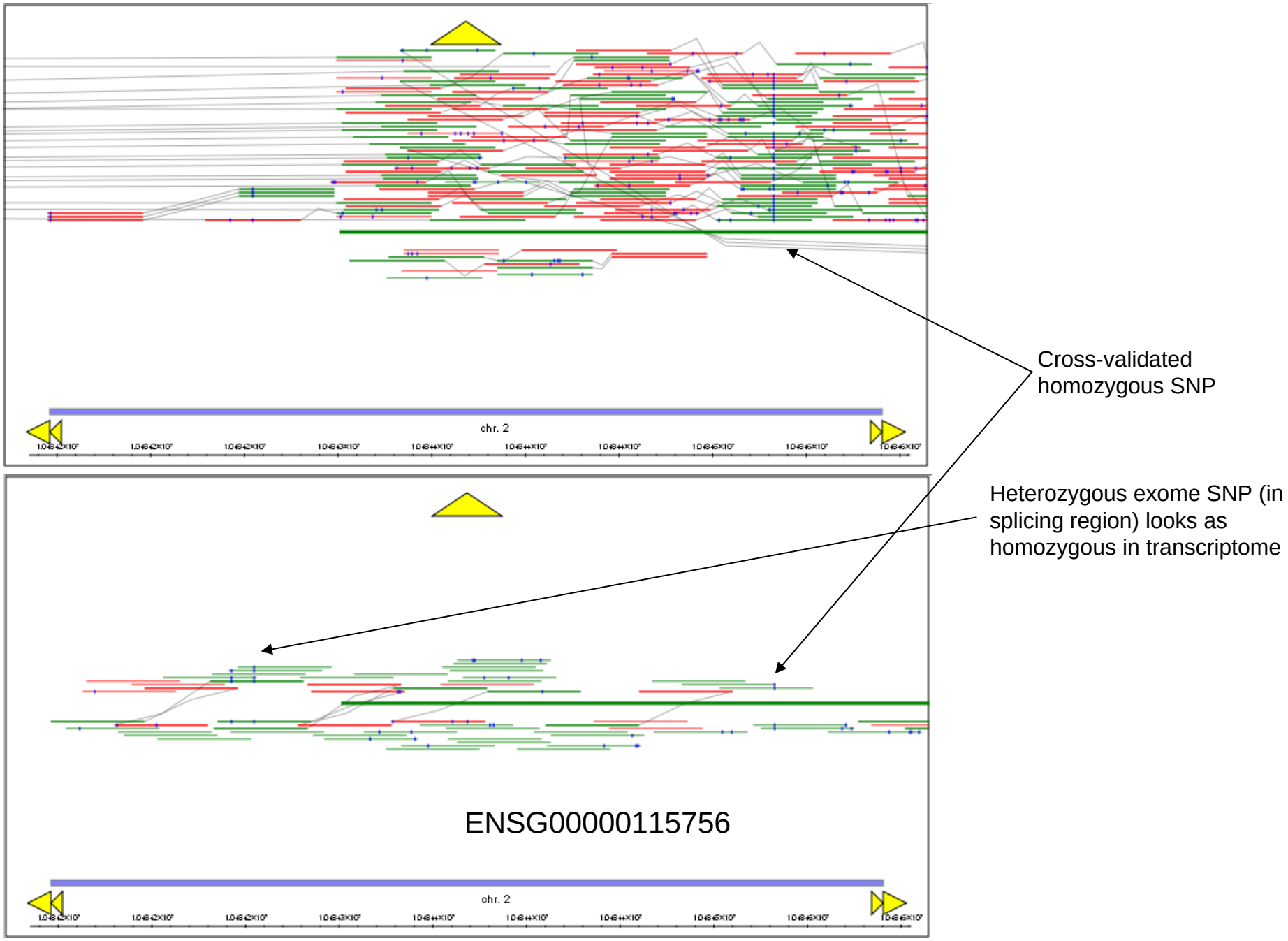
Exome:
090429_EAS453_1
090429_EAS453_2
090429_EAS453_3
090429_EAS453_4
090515_EAS453_1
090515_EAS453_2
090515_EAS453_3
090515_EAS453_4
090515_EAS453_5
090515_EAS453_6

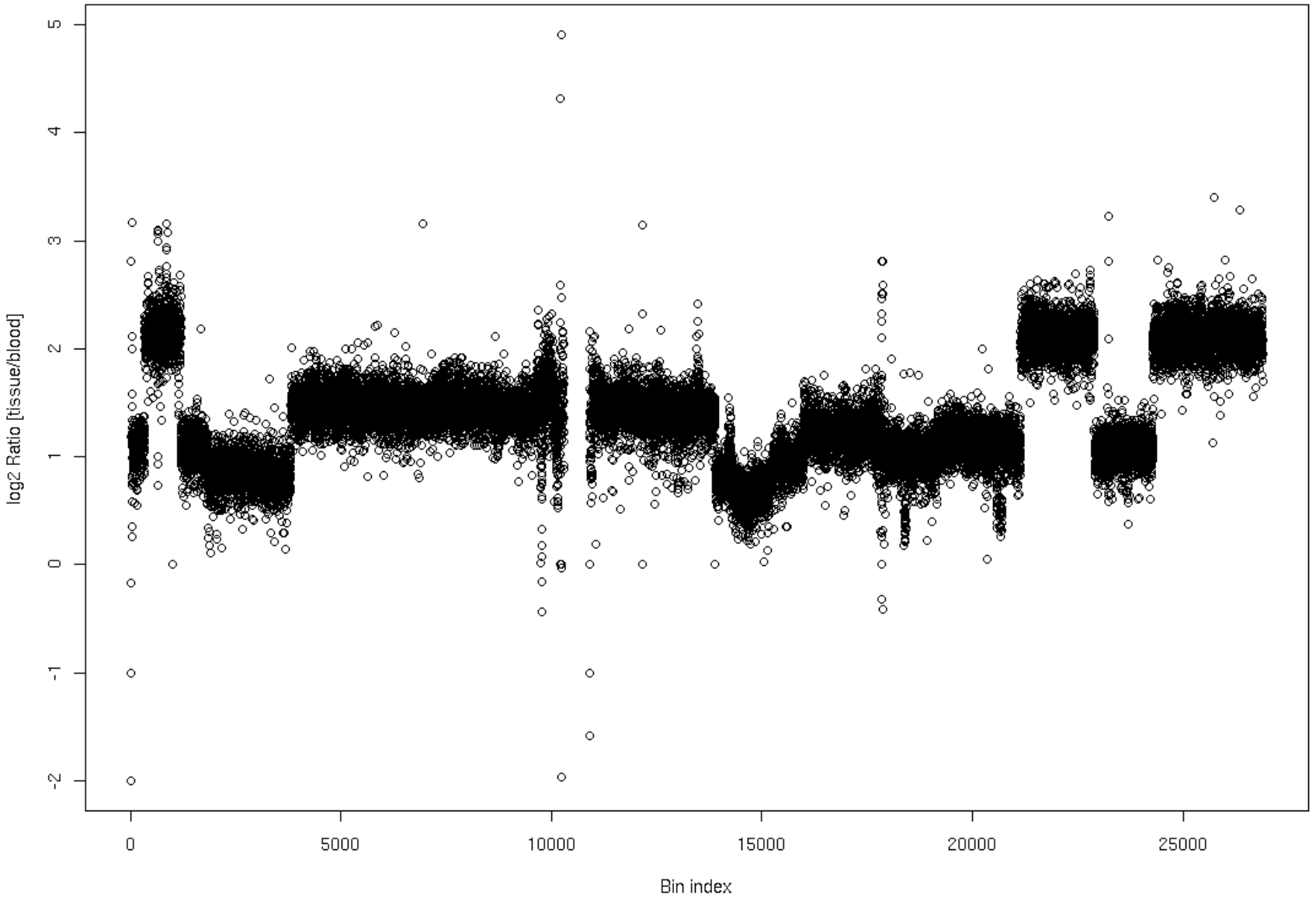
Transcriptome:
090403_4
090403_7
090421_EAS453_6
090421_EAS453_7
090421_EAS453_8
090430_EAS213_8
090508_EAS451_7
090508_EAS451_8
090522_EAS451_7
090522_EAS451_8

Gene..

Exome (exons DNA enriched) profiling (CNV) and genotyping




chr. 2
Cross-validated
homozygous SNP
Heterozygous exome SNP (in
splicing region) looks as
homozygous in transcriptome
ENSG00000115756
chr. 2


log2 Ratio [tissue/blood] chromosome 11
log2 Ratio [tissue/blood]
5
4
3
2
1
0
-1
-2
0
5000
10000
15000
20000
25000
Bin index

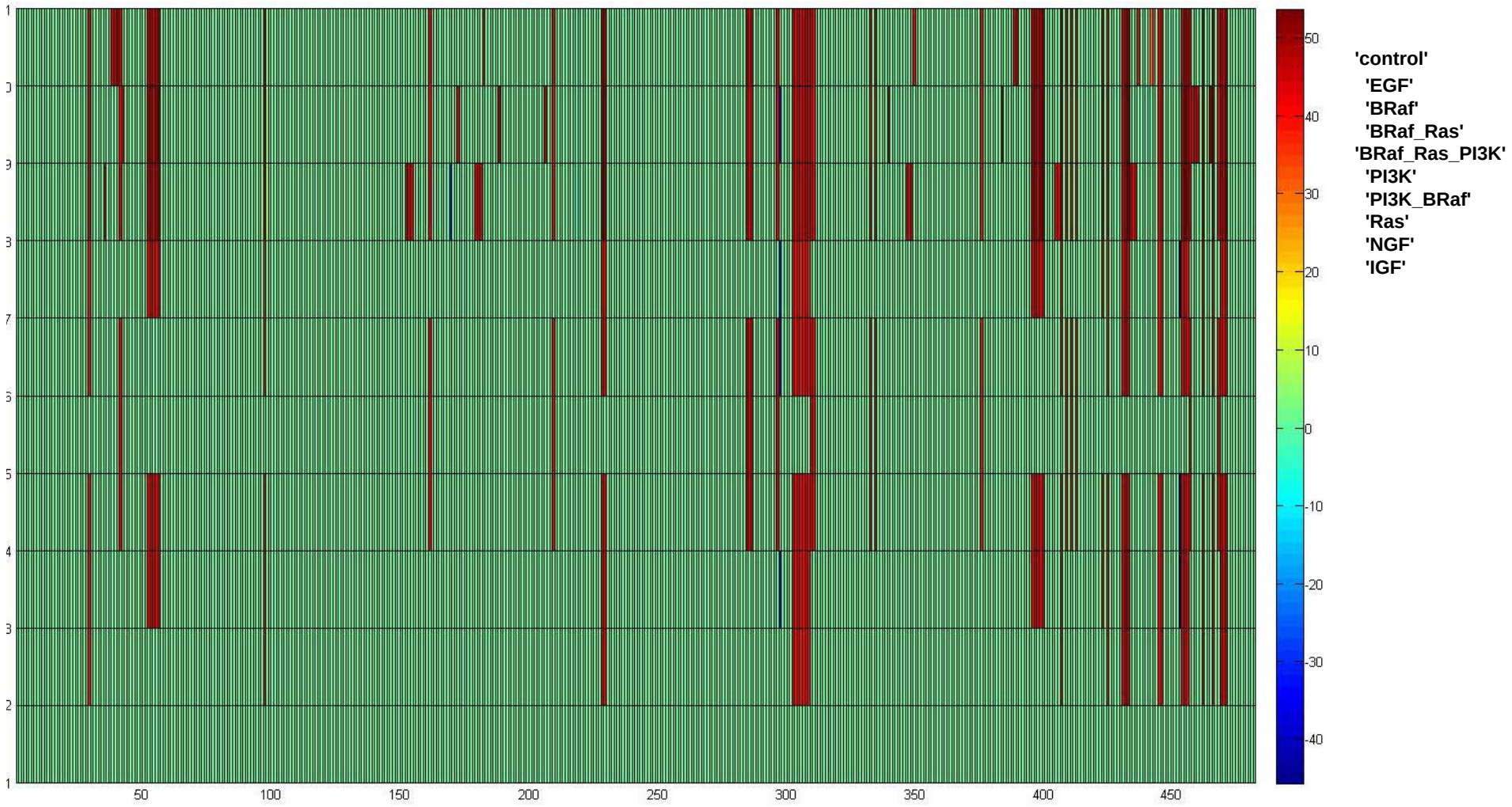
Monte Carlo Simulation Results Based on Tumor- vs. Melanocytes-Expression Data

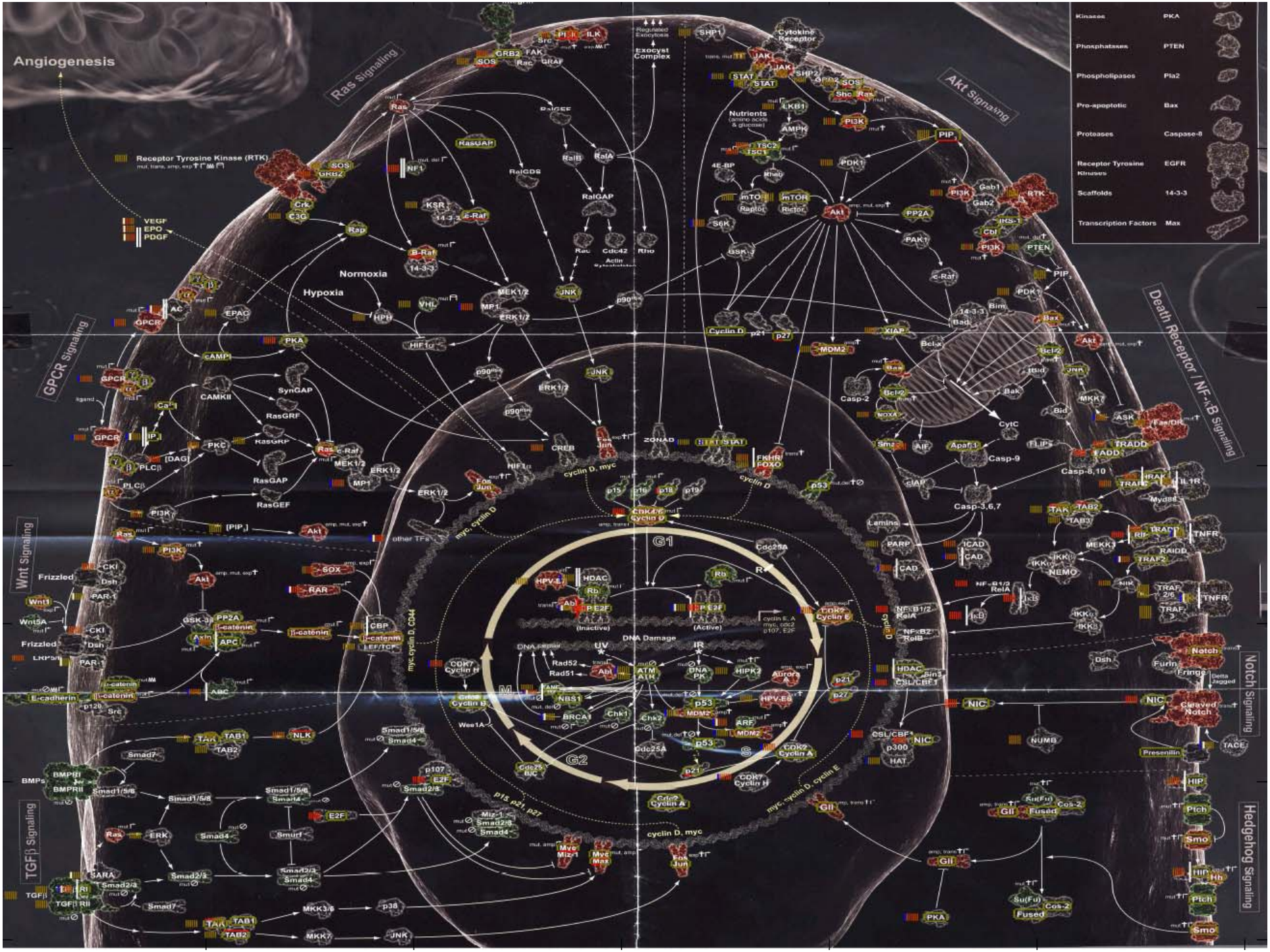
Up-regulated Model components

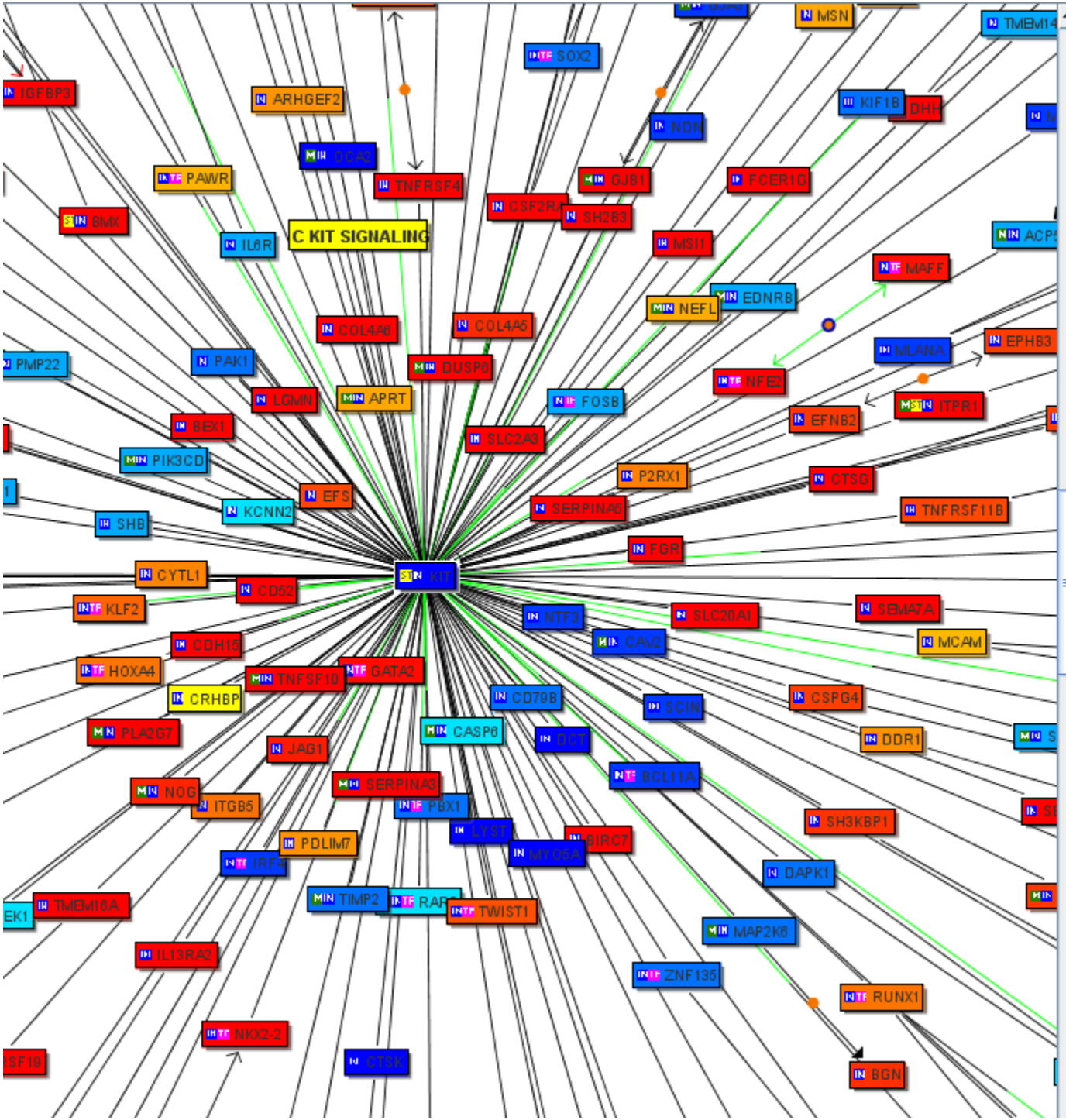
Model component	Rati
Phospho-NF-kappaB Inhibitor [cytosol]	5.1
phospho-SHC:activated IGF-1R [cytosol]	3.42
activated IGF-1R [plasma membrane]	3.37
phospho-SHC [cytosol]	3.36
NF-kappaB inhibitor [cytosol]	3.36
Grb2:SOS:pShc [cytosol]	2.83
Dvl:Notch 1 [plasma membrane]	2.65
Dvl:Notch 4 [plasma membrane]	2.5
IGF:IGF1R dimer [plasma membrane]	2.45
phospho-ERK-1-dimer [nucleoplasm]	2.2
ATF-2-P [cytosol]	2.19
B-Raf:Ras:GTP:pMEK [cytosol]	2.11
Myc/Max heterodimer [nucleoplasm]	2.07
phospho-ERK-1-dimer [cytosol]	2.06
Myc [nucleoplasm]	2.04
B-Raf:Ras:GTP:pMEK:ERK [cytosol]	2.03
Phospho-SMAD1:CO-SMAD [cytosol]	2.01
NFkB2 [cytosol]	2.01

Down-regulated Model components

Model component	Ratio
Cyclin D:phospho-CDK4/6:p21/p27 [nucleoplasm]	0.49
phospho-(Ser45, Thr41, Ser37) beta-catenin:Axin,GSK3:CK1alpha:APC:PP2A complex [cytosol]	0.48
Inhibited TSC2-1-P at Ser 939, 1130 and Thr 1462 [cytosol]	0.43
Phosphorylated PDE3B [cytosol]	0.42
phospho-GSK3beta [cytosol]	0.42
phospho-p21/phospho-p27 [cytosol]	0.42
FOXO4 phosphorylated [cytosol]	0.4
PIP3:Phosphorylated PKB complex [plasma membrane]	0.39
143B:phospo-BAD complex [cytosol]	0.38
Phospho-BAD [cytosol]	0.37
Phosphorylated Mdm2:p53 [nucleoplasm]	0.36
Insulin receptor substrate-1 [cytosol]	0.36
phospho-Retinoblastoma protein [nucleoplasm]	0.33
phospho-(Ser45, Thr41) beta-catenin:Axin:GSK3:CK1alpha:APC:PP2A complex [cytosol]	0.22


50
100
150
200
250
300
350
400
450
50
40
30
20
10
0
-10
-20
-30
-40
'control'
'EGF'
'BRaf'
'BRaf_Ras'
'BRaf_Ras_PI3K'
'PI3K'
'PI3K_BRaf'
'Ras'
'NGF'
'IGF'


Angiogenesis
Ras Signaling
Akt Signaling
GPCR Signaling
Death Receptor / NF-κB Signaling
Wnt Signaling
Notch Signaling
TGFβ Signaling
Hedgehog Signaling
Receptor Tyrosine Kinase (RTK)
VEGF
EPO
PDGF
Normoxia
Hypoxia
Nutrients
(amino acids & glucose)
Exocyst Complex
Cytokine Receptor
DNA Damage
G1
S
G2
M
Kinases PKA
Phosphatases PTEN
Phospholipases Plα2
Pro-apoptotic Bax
Proteases Caspase-8
Receptor Tyrosine Kinases EGFR
Scaffolds 14-3-3
Transcription Factors Max



Relationship between ADRB2 and PTEN

Node Info | Unconnected Nodes

Gene symbol:KIT (id:3815)
Full Name: v-kit Hardy-Zuckerman 4 feline homolog

Analyze Promoter(s) of KIT
Show BiblioSphere for KIT
Get ElDorado annotation for KIT
Show comparative Genomics for KIT
Remove KIT from BiblioSphere

Description:This gene encodes the human h
proto-oncogene c-kit. C-kit was first identi
homolog of the feline sarcoma viral oncoge
a type 3 transmembrane receptor for MGF
factor, also known as stem cell factor). Mu
associated with gastrointestinal stromal tum
acute myelogenous lukemia, and piebaldism
variants encoding different isoforms have b
[provided by RefSeq]

Genetic Subgrouping of Melanoma Reveals New Opportunities for Targeted Therapy

Keiran S.M. Smalley,[1] Katherine L. Nathanson,[2,4] and Keith T. Flaherty[3,4]

[1]Molecular Oncology Program and Department of Cutaneous Oncology, The Moffitt Cancer Center & Research Institute, Tampa, Florida; and Divisions of [2]Medical Genetics and [3]Hematology-Oncology, Department of Medicine, and [4]The Abramson Cancer Center, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

Abstract

The discovery of activating oncogenic *BRAF* V600E mutations in the majority of melanomas has not yet been translated into more effective therapy. The failure of agents may be due to lack of sufficiently targeted therapeutics, but is more likely based on the activation of multiple oncogenic pathways in melanomas in addition to the mitogen-activated protein kinase signaling pathway. In contrast, there are groups of melanomas that instead rely on either c-KIT or CRAF signaling that may be amenable to single-agent targeted therapy. In the current review, we discuss how knowledge about these new melanoma subgroups may lead to improved strategies for treating melanomas harboring *BRAF* V600E mutations. [Cancer Res 2009;69(8):3241–4]

Background

After decades of negative clinical trials, the new hope for melanoma treatment is targeted therapy, using small-molecule inhibitors directed against the oncogenic mutations responsible for driving tumor progression. Although extensive preclinical studies have validated the *BRAF* V600E mutation and the concept for melanoma targeted therapy. We suggest that a greater understanding of these two subgroups, in which one oncogenic event drives both proliferation and survival, can point to novel strategies for treating *BRAF* V600E mutated melanomas.

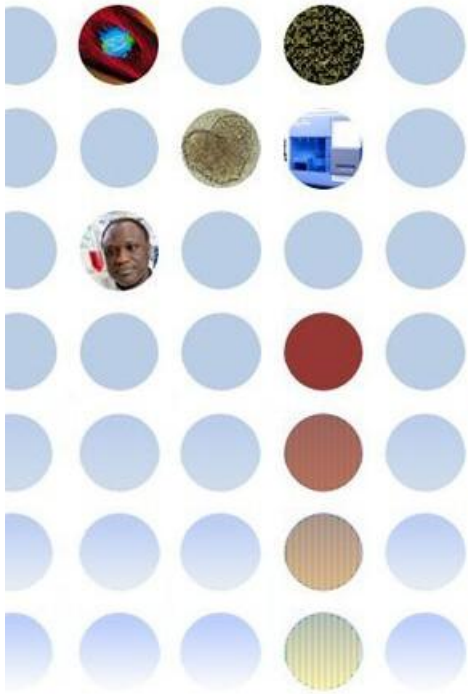
Key Findings

Inhibition of c-KIT modulates both growth and survival. Although a role for c-KIT signaling in melanoma has been long disputed (12, 13), interest in this receptor tyrosine kinase (RTK) was recently rekindled following the identification of subgroups of melanoma harboring activating *KIT* mutations (14). Melanomas that develop on body sites with little UV exposure, such as the soles of the feet or subungual sites (acral melanomas), or on mucous membranes (mucosal melanomas) have a very low incidence of *BRAF* mutations, but often harbor activating mutations in *KIT* (14–16). Within these subgroups of melanoma there also are instances in which c-KIT is amplified in the absence of a mutation, so that the total number of c-KIT aberrations is 39% for mucosal, 36% for acral, and 28% for sun-damaged skin melanomas (14). c-KIT has since been shown to be expressed in 88% of oral mucosal melanomas, with 22% of these lesions harboring *KIT* mutations (16). Other studies showed that 62% of acral and mucosal melanomas exhibited constitutive c-KIT

AApos	AA	mutAA	enst	gene	Tumor
288	Gly	Arg	ENST00000299163	HIF1AN	1
433	Ile	Val	ENST00000354827	BTRC	1
965	Ala	Val	ENST00000406432	PSD	1
483	Pro	Thr	ENST00000355995	TCF7L2	1
181	Asn	Asp	ENST00000369321	CASP7	1
345	Val	Ala	ENST00000355371	KIAA1598	1
164	Thr	Pro	ENST00000368595	INPP5A	1
182	His	Pro	ENST00000368595	INPP5A	1
413	Asn	Ile	ENST00000278060	PAOX	1
225	Phe	Ile	ENST00000396343	PDSS1	1
121	Leu	Phe	ENST00000374694	FZD8	1
273	His	Arg	ENST00000298375	AKR1CL2	1
593	Asn	Asp	ENST00000374056	CTGLF3	1
179	Cys	Arg	ENST00000373109	SPOCK2	1
398	Tyr	Cys	ENST00000372516	ZNF503	1
232	Gln	Arg	ENST00000371809	IFIT1L	1
367	Leu	Pro	ENST00000371795	IFIT5	1
560	Ser	Phe	ENST00000357947	TLL2	1
1711	Thr	Met	ENST00000359061	MUC2	1
438	Lys	Asn	ENST00000404468	CADM1	1
49	Gln	Arg	ENST00000328965	OAF	1
497	Val	Ala	ENST00000319925	ROBO4	1
138	Asp	Asn	ENST00000319925	ROBO4	1

The TREAT 1000 project

Making tomorrow's treatment available today



WELCOME TO THE TREAT 1000 WEBSITE!

TREAT1000 is an innovative project with the aim of bringing the benefits of genomic medicine to the cancer care of 1000 patients now. TREAT1000 was founded by top researchers and doctors from the Max Planck Institute of Molecular Genetics in Berlin, Harvard Medical School, the Charité Universitätsmedizin Berlin, Alacris Pharmaceuticals GmbH and CollabRx Inc. The project aim is to use a hybrid combination of funding sources, including patient and donor funding to fund applied research in patient treatment, research which will lead both to medical advances and to direct benefit for the patients involved in the project.

Every patient and every tumor is unique. Sequencing each patient's genome and their tumor genome will help their oncologists understand the specific mechanisms of tumor resistance and susceptibility for each patient's specific disease.

All data and conclusions generated in the project will be made publicly available through collaborations with the Personal Genome Project and with Health Commons.

More information about TREAT1000:

TREAT1000 workshop at Harvard Medical School, January 21st-22nd

Marc Sultan

Christine Grimm

Marie-Laure Yaspo

Christian Regenbrecht

Michal Schweiger

Aleksey Soldatov

Tatjana Borodina

Dmitri Parkhomchuk

Andreas Dahl

Bernd Timmermann

Ralf Herwig

Christoph Wierling

Bernhard Herrmann

Jiri Forejt (Prag)

Martin Vingron

Genomatix

Peter Schlag (Charite, Berlin)

Reinhold Schäfer (Charite, Berlin)

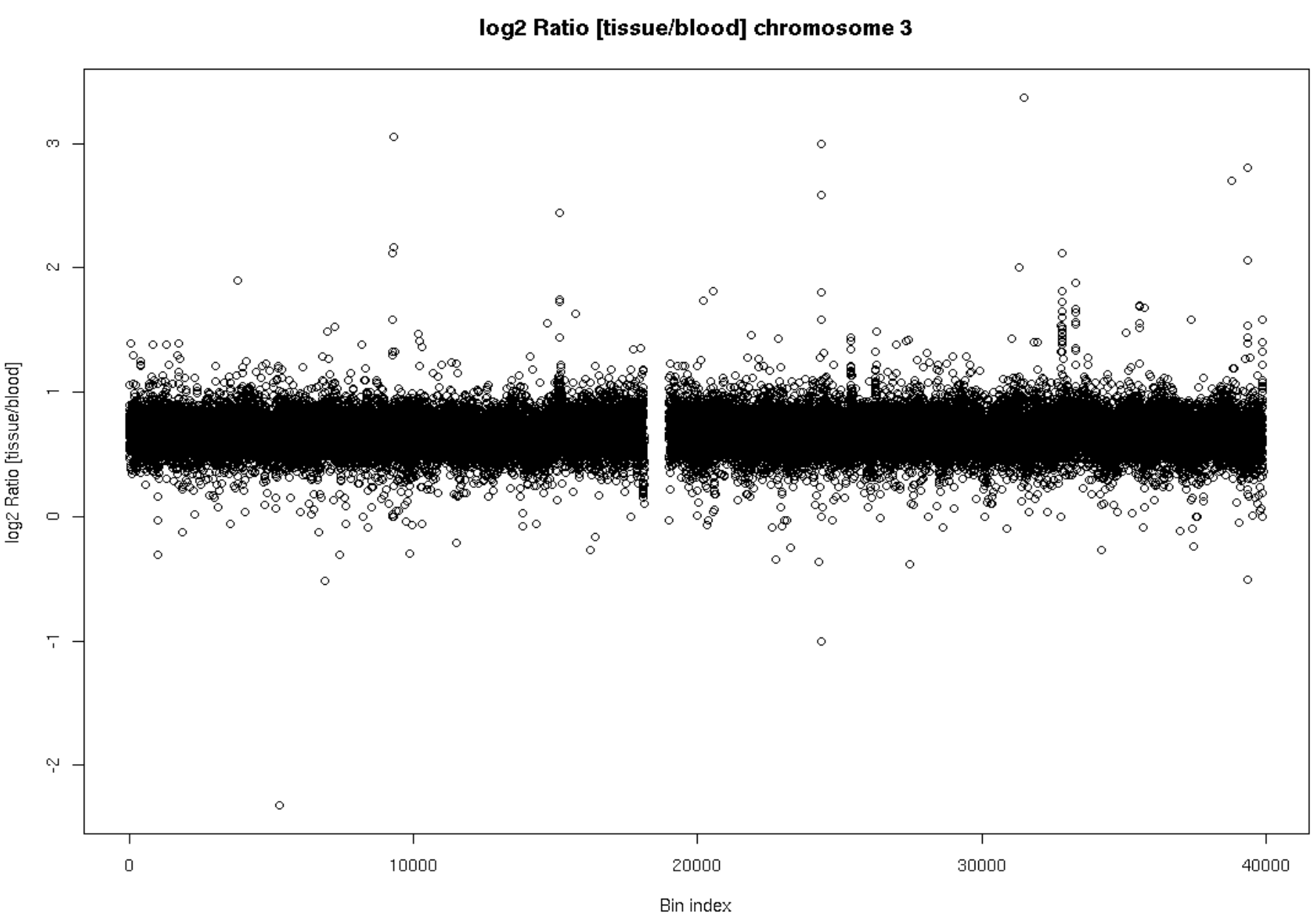
Manfred Dietel (Charite, Berlin)

George Church (Harvard Medical School)

Alacris Pharmaceutical

CollabRx

www.treat1000.org


log2 Ratio [tissue/blood] chromosome 3
log2 Ratio [tissue/blood]
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0
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30000
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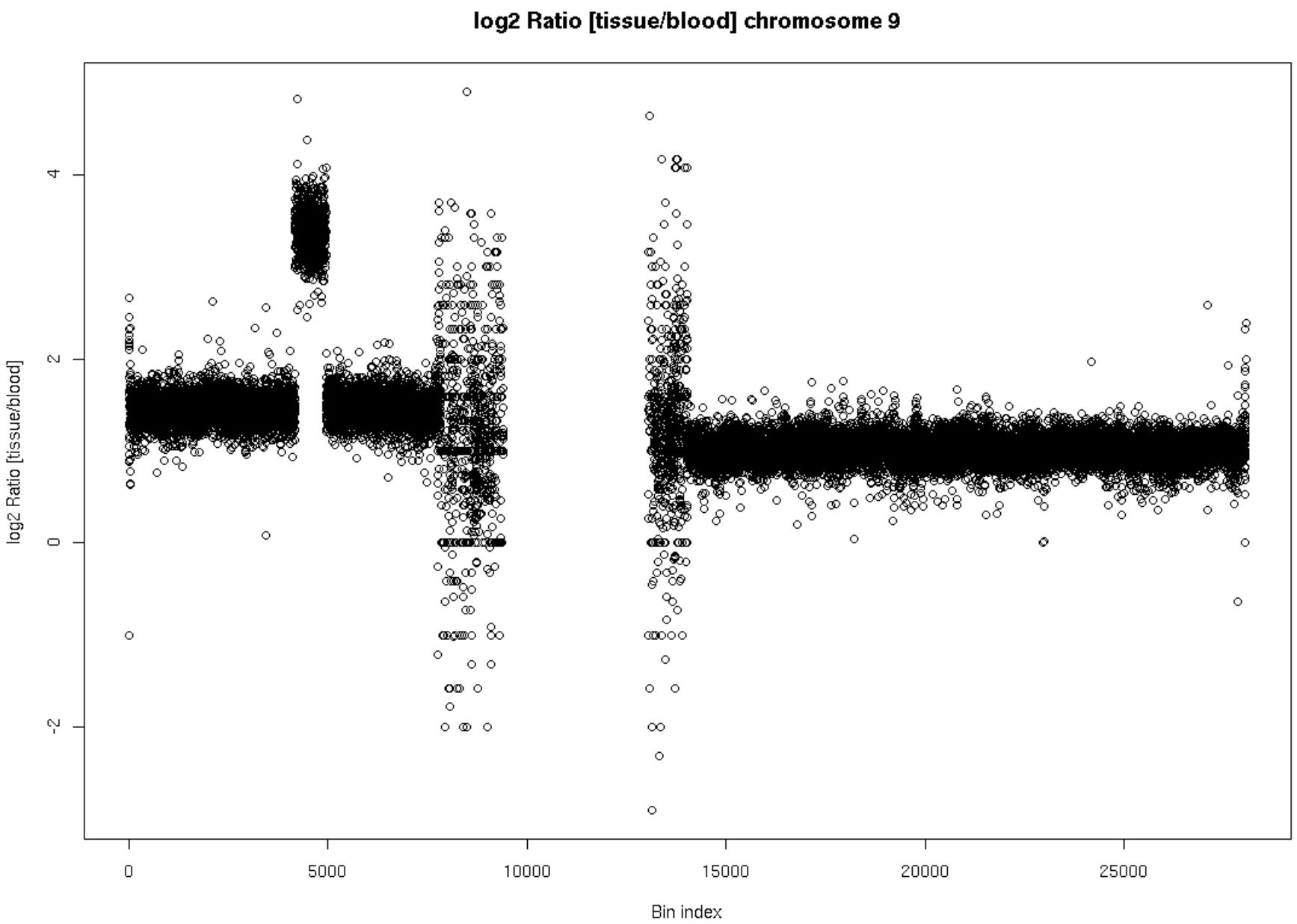
Bin index


log2 Ratio [tissue/blood] chromosome 9
log2 Ratio [tissue/blood]
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-2
0
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20000
25000
Bin index