SNPs and molecular profiles of breast tumors

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Sigurd K. Thoresen Foundation Seminar HUMAN GENOMIC VARIATION AND DISEASE

What proportion of the observed deregulation of gene expression is inheritable

- I. SNP association to mRNA expression in
  - Blood, before and after HRT use
  - Fibroblasts, before and after radiation
  - Tumor, before and after chemotherapy (DOXO, FUMI)
- II. SNP association to
  - DNA methylation associated deregulation
  - Chromosomal aberrations
  - miRNA associated deregulation

What SNPs

4 SNP panels

- 700 SNPs in the ROS pathay
- 500 htSNPs in the estradiol pathway
- 10K linkage panel Illumina (WGA)
- 109 Illumina

Expression

The experiments

- A panel of 1036 SNPs in 208 genes from the Reactive Oxigen Species metabolism and cell signalling genotyped in:

- 193 breast cancer patient cases (718 SNPs)
- 109 healthy controls (830SNPs)
- 44 fibroblast cell lines (830SNPs)
- 96 cervical cancers (930SNPs)

Functional pathway association analysis

Hege Edvardsen

Metabolism of oxygen radicals
e.g. ALOX12, CAT, PTGS1, PTGS2, GPX1, GSR, NOX1, HMOX1,2

Signalling molecules regulated by the redox levels in the cell
e.g. AKT1, FOS, JUN, EGFR, IER3, CDK2, CCND1

Metabolism of Xenobiotics
e.g. CYP1A1, 1A2, 2E1, 2C7,8,9, GST, NQO1

5000 SNPS in 233 CANDIDATE GENES

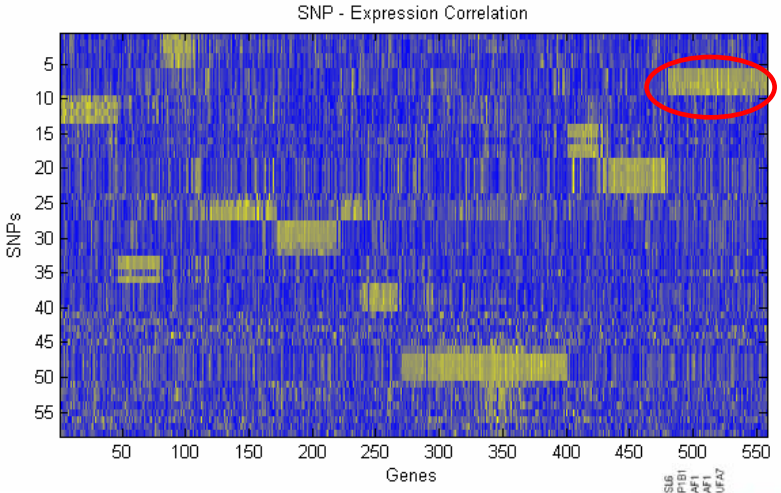
ROS as second messenger
e.g. FGF2, RAF1, ICAM1, FIGF, LTA, LTB, TANK

Apoptosis
e.g. BCL2, BAX, BAK1, UQCRC1

Membrane transporters
e.g. MDR1, MRP1, ATP binding cassette fam A, B, C

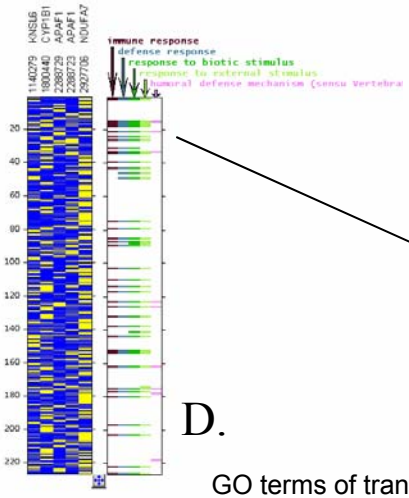
DNA repair
e.g. LigIII, XRCC1, APEX, PolB, PolD, PolE, MGMT

A.



B.

C.



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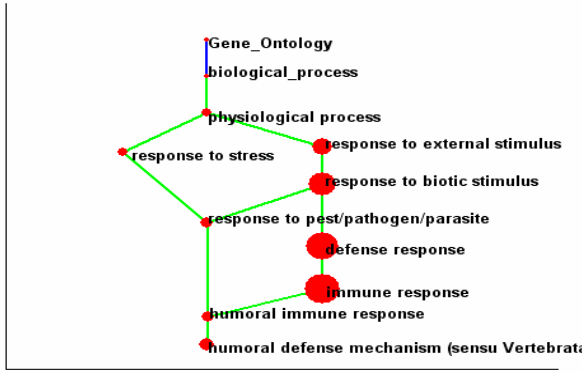
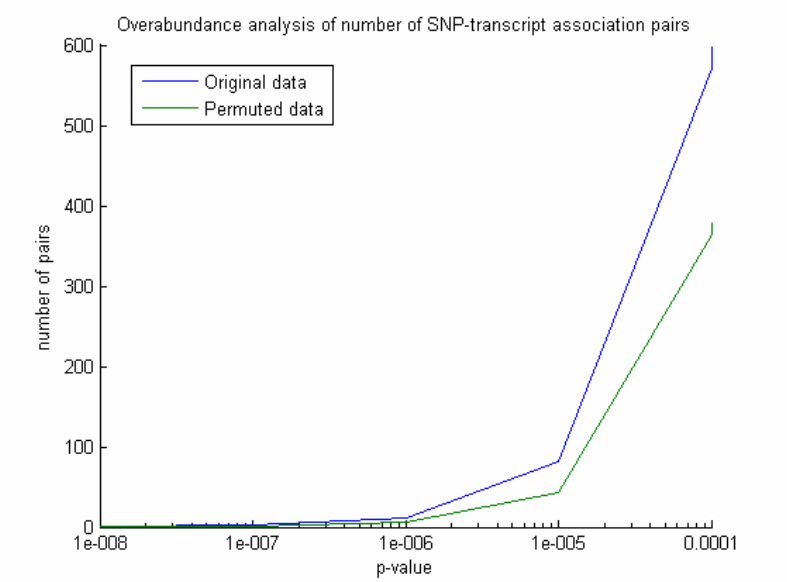


E.

GO terms of transcripts associated to SNPs in *APAF1*, *CYP1B1*, *KMNSL6* and *NDUFA7*

Overabundance analysis results



Comparison of numbers of ANOVA-based association pairs in original and permuted data.

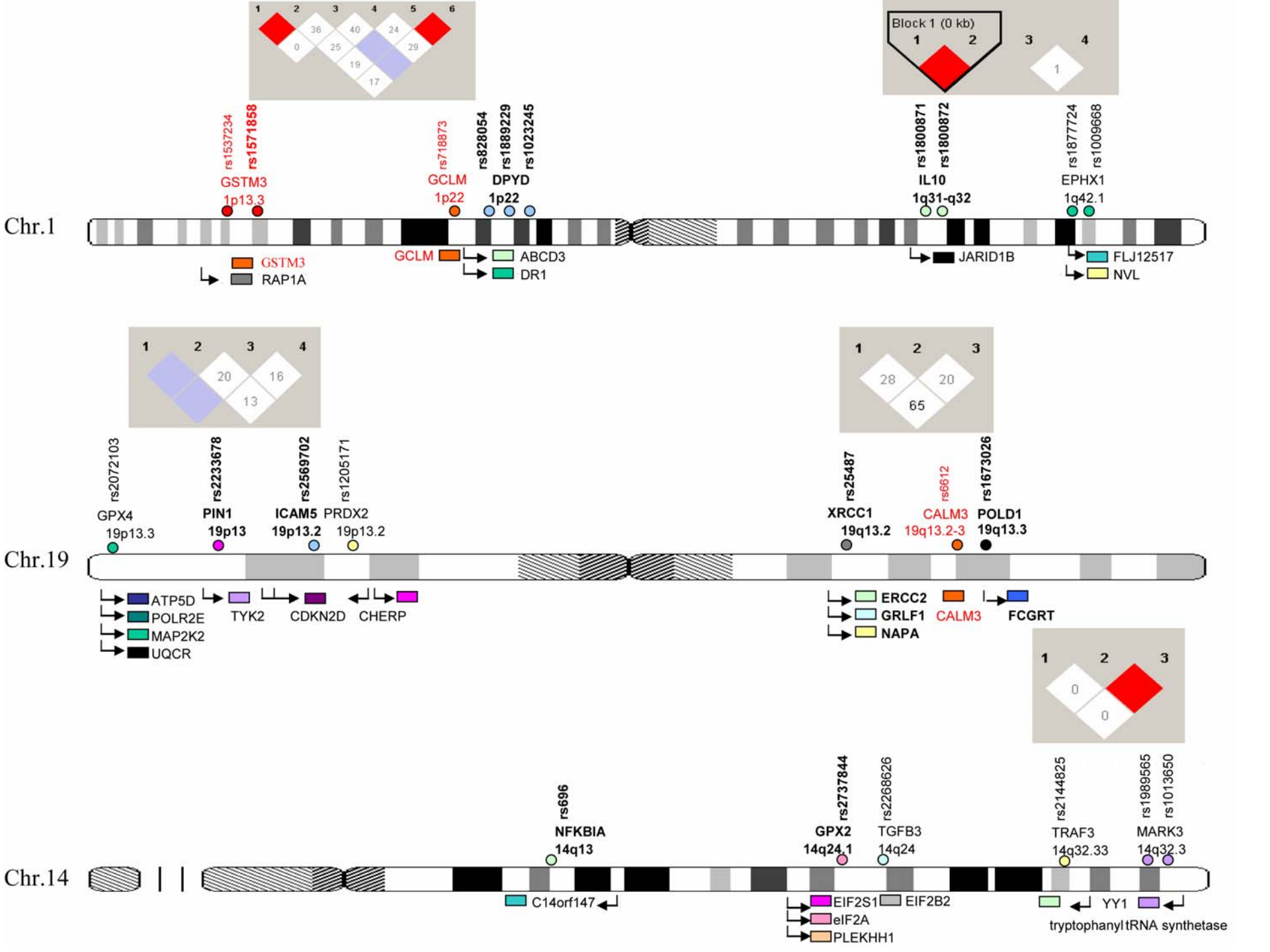
Permuted data represents averages over 50 permuted data sets.

EGF, *IL1A*, *MAPK8*, *XPC*, *SOD2* and *ALOX12*
with regulatory SNPs, p-values<0.0001 by all 3 methods.

Epidermal growth factor
Interleukin 1A
c-jun N-terminal kinase 1 (MAPK8)
Gene mutated in XP group C
Superoxide dismutase 2

- SNPs regulating *in cis*
- *grouped according to position (on chromosomes)*
- *grouped according to function (cliques in gene ontology)*

Kristensen VN, Edvardsen H, Tsalenko A, Nordgard SH, Sorlie T, Sharan R, Vailaya A, Ben-Dor A, Lonning PE, Lien S, Omholt S, Syvanen AC, Yakhini Z, Borresen-Dale AL.
Genetic variation in putative regulatory loci controlling gene expression in breast cancer.
Proc Natl Acad Sci U S A. 2006 May 16;103(20):7735-40. Epub 2006


Chr.1
rs1537234
rs1571858
GSTM3
1p13.3
rs718873
GCLM
1p22
rs828054
rs1889229
rs1023245
DPYD
1p22
rs1800871
rs1800872
IL10
1q31-q32
rs1877724
rs1009668
EPHX1
1q42.1
GSTM3
RAP1A
GCLM
ABCD3
DR1
JARID1B
FLJ12517
NVL
Block 1 (0 kb)
Chr.19
rs2072103
GPX4
19p13.3
rs2233678
PIN1
19p13
rs2569702
ICAM5
19p13.2
rs1205171
PRDX2
19p13.2
rs25487
XRCC1
19q13.2
rs6612
CALM3
19q13.2-3
rs1673026
POLD1
19q13.3
ATP5D
POLR2E
MAP2K2
UQCR
TYK2
CDKN2D
CHERP
ERCC2
GRLF1
NAPA
CALM3
FCGRT
Chr.14
rs696
NFKBIA
14q13
rs2737844
GPX2
14q24.1
rs2268626
TGFB3
14q24
rs2144825
TRAF3
14q32.33
rs1989565
rs1013650
MARK3
14q32.3
C14orf147
EIF2S1
EIF2B2
eIF2A
PLEKHH1
YY1
tryptophanyl tRNA synthetase

Comparisons in 2 measurements with 16 weeks interval before and after a mono-drug treatment with doxorubicin

Associations before and after/delta at $p<0.001$:

- A/T SNP rs2062011 in BCL2 (18q21.3) MYB before, after
- C/T SNP rs1126510 in CALM3 (19q13.2-q13.3) - DGKG before and in
- A/T SNP rs284190 in TGFBR3(1p33-p32) - IL8 after and in the delta,
- C/T SNP rs2073098 in aldo-keto reductase family 7, member A2 (1p35.1-p36.23) - MYD88 after treatment and in the delta,
- A/T SNP rs2227547 in IL8 on 4q13-q21 - PTPRD before and in the delta
- G/T rs827500 in DPYD - translocation associated membrane protein 1 Hs.4147 AA452556 before and in the delta.

Comparison of SNP expression associations between breast Carcinomas and patient fibroblasts in culture

PRDX4
GPX1
MYB
NFKB1
APEX1
GSTP1
TYMS
NQO1
AP2S1
COX6C
XPC
FOS
PTP4A1
IL8
NDUFA4

Rs699473 SOD3- MB myoglobin

rs_fibroblasts	901917	212083	212083	1982673	699473
rs_BCstudy	1192529	215094	215067	2551402	699473
rs_gene_fibroblasts	TGFBR3	ABCC1	ABCC1	BCL2	SOD3
rs_gene_BCstudy	TGFBR3	ABCC1	ABCC1	BCL2	SOD3
expression_gene_fibroblasts	TCF8	TAF6	TAF6	RAB3-GAP150	MB
expression_gene_BCstudy	TCF8	TAF6	TAF6	RAB3-GAP150	MB
SNP_position	chr1:92004428	chr16:16135444	chr16:16135444	chr18:58948995	chr4:24473072
snp_band	1p22.1	16p13.11	16p13.11	18q21.33	4p15.2
gene_chr	chr10	chr7	chr7	chr1	chr22
gene_start	31648169	99349519	99349519	216712987	34327843
gene_end	31856198	99356483	99356483	216834074	34337804

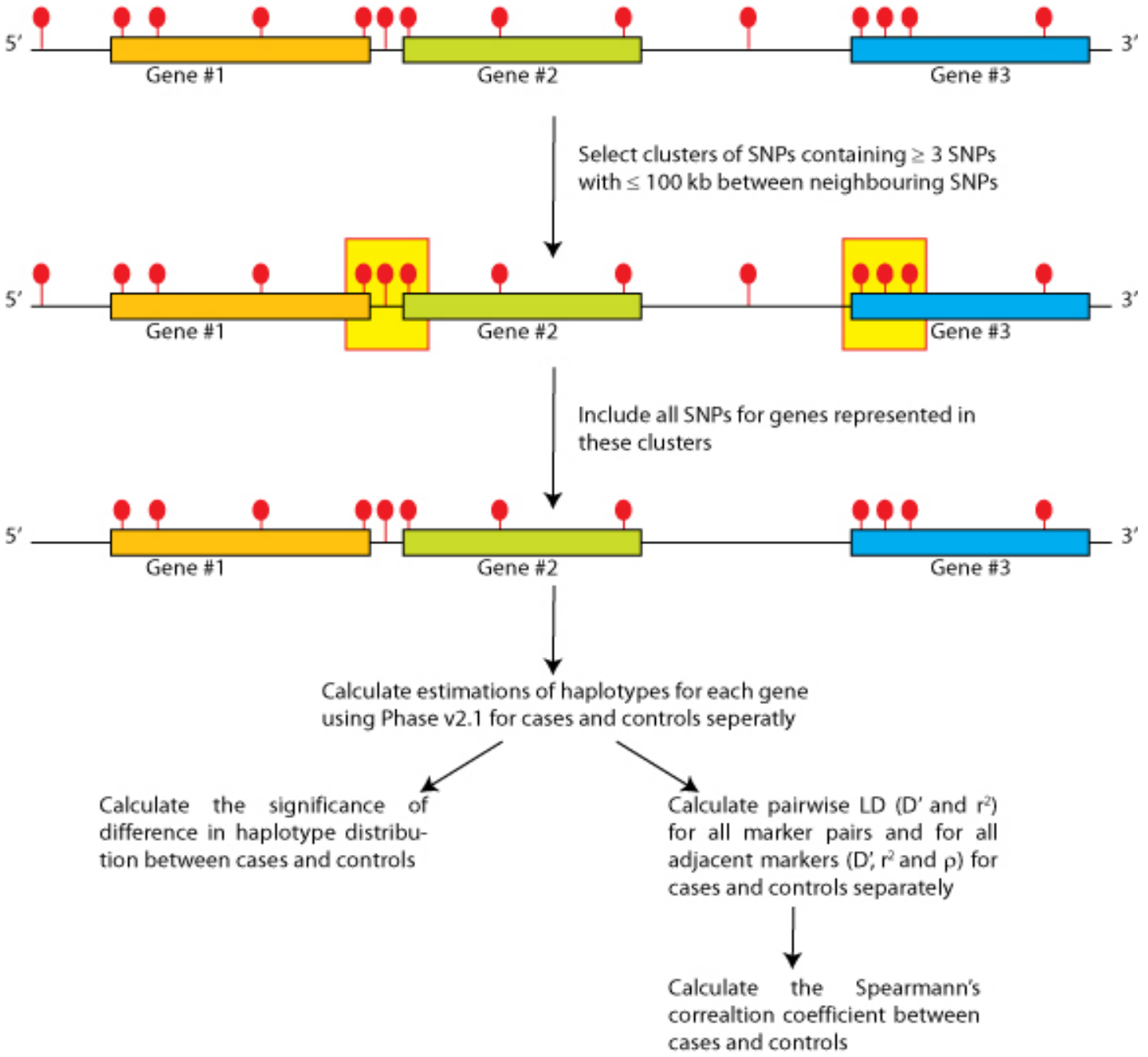
Espen Enerly

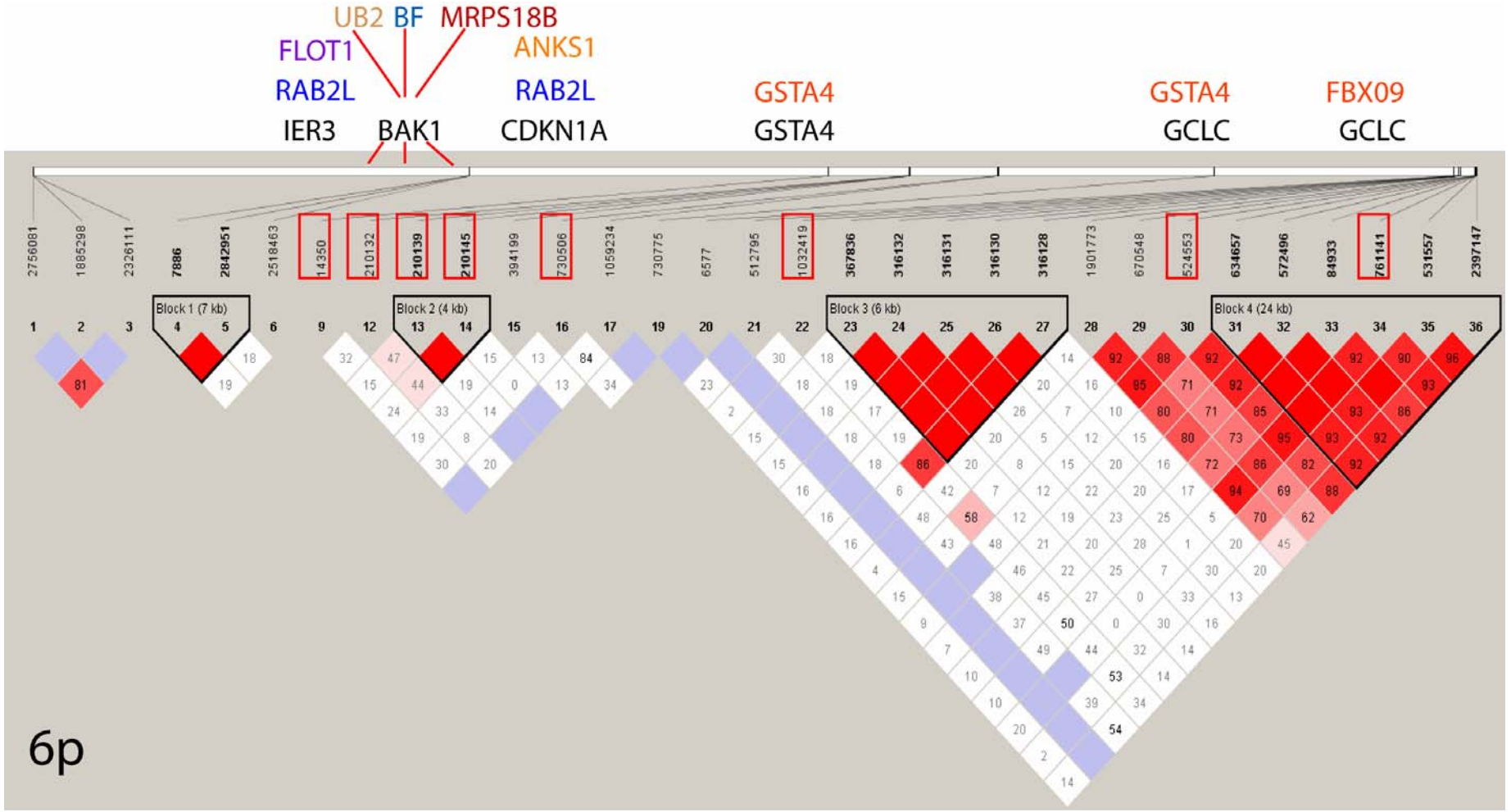
Unique Gene name	SNPs used in the AI assays	Significantly AI association after correcting for multiple testing	Emperical valuated by Pastinen et al.	SNPs genotyped by us	Association our dataset
AHR		Y	Y	2282883	-
				2282885	trans
CAT	511895	Y	Y	511895	-
	2300181			554576	-
				564250	trans
				2073058	trans
EPHX2	747276	Y	Y	747276	trans
	729609			721619	cis
	1042064				
FVT1	6810	Y	Y	2551402	trans
	2236719				
UGT1A1		Y	Y	887829	-
				1018124	-
CDK2	2069398	N	N	1045431	-
	2069408			1045435	-
				2069397	-
				2069400	-
				2069415	-
				3087335	-
IGF1	6214	N	N	6215	-
	6220			6219	-
				6222	-
				972936	-
				1520220	-
TRAF3	1131877	N	N	2403102	-
	8023164				

Hege Edvardsen

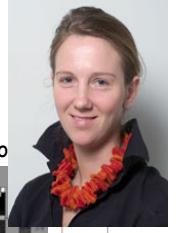
Pastinen T, Ge B, Gurd S, Gaudin T, Dore C, Lemire M *et al.* Mapping common regulatory variants to human haplotypes. *Hum Mol Genet* 2005; **14:**3963-3971.

Hege Edvardsen



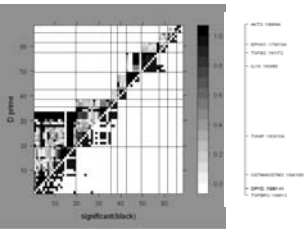

UB2
BF
MRPS18B
FLOT1
ANKS1
RAB2L
RAB2L
GSTA4
GSTA4
FBX09
IER3
BAK1
CDKN1A
GSTA4
GCLC
GCLC
Block 1 (7 kb)
Block 2 (4 kb)
Block 3 (6 kb)
Block 4 (24 kb)
6p

”Chromosome-wise” pharmacogenetics

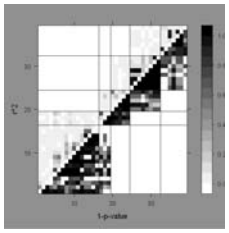


Bettina Kulle

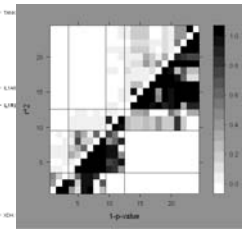
Chromosome 1



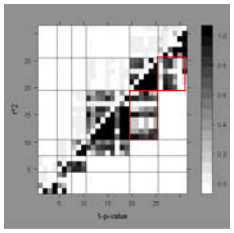
Chromosome 2



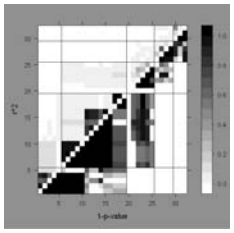
Chromosome 3



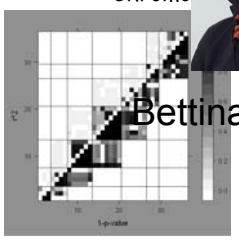
Chromosome 4



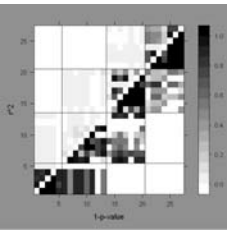
Chromosome 5



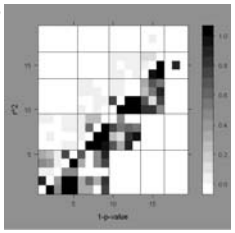
Chromo



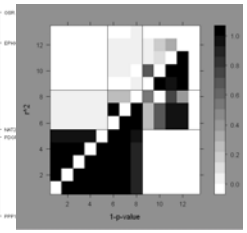
Chromosome 7



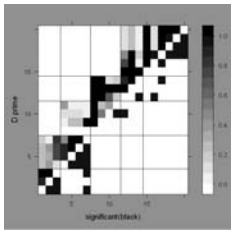
Chromosome 8



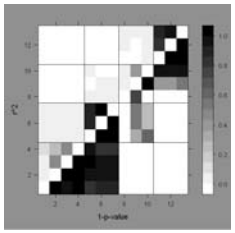
Chromosome 9



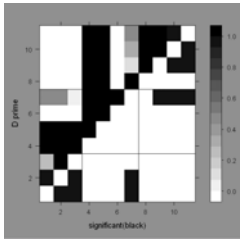
Chromosome 10



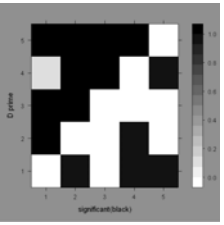
Chromosome 11



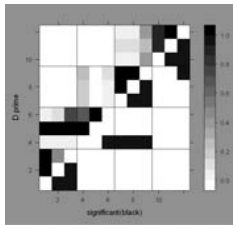
Chromosome 12



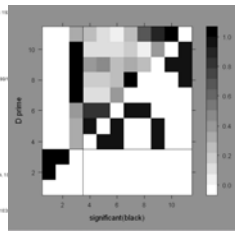
Chromosome 13



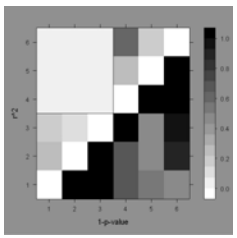
Chromosome 14



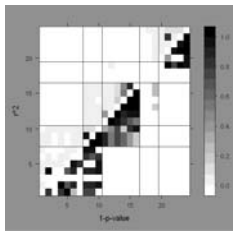
Chromosome 15



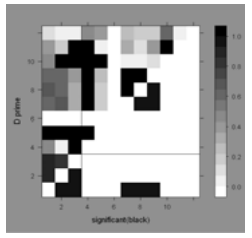
Chromosome 16



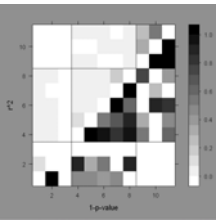
Chromosome 17



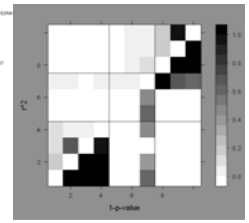
Chromosome 18



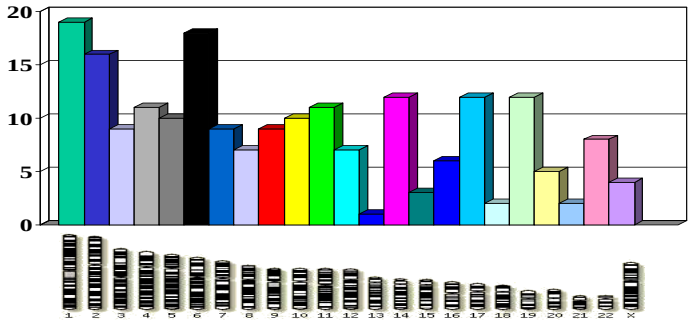
Chromosome 19



Chromosome 22



Nr. of genes



Edvardsen et al, manus

Statistical analysis and Tool development
Bettina Kulle and Arnoldo Frigessi

Fatemeh Kaveh

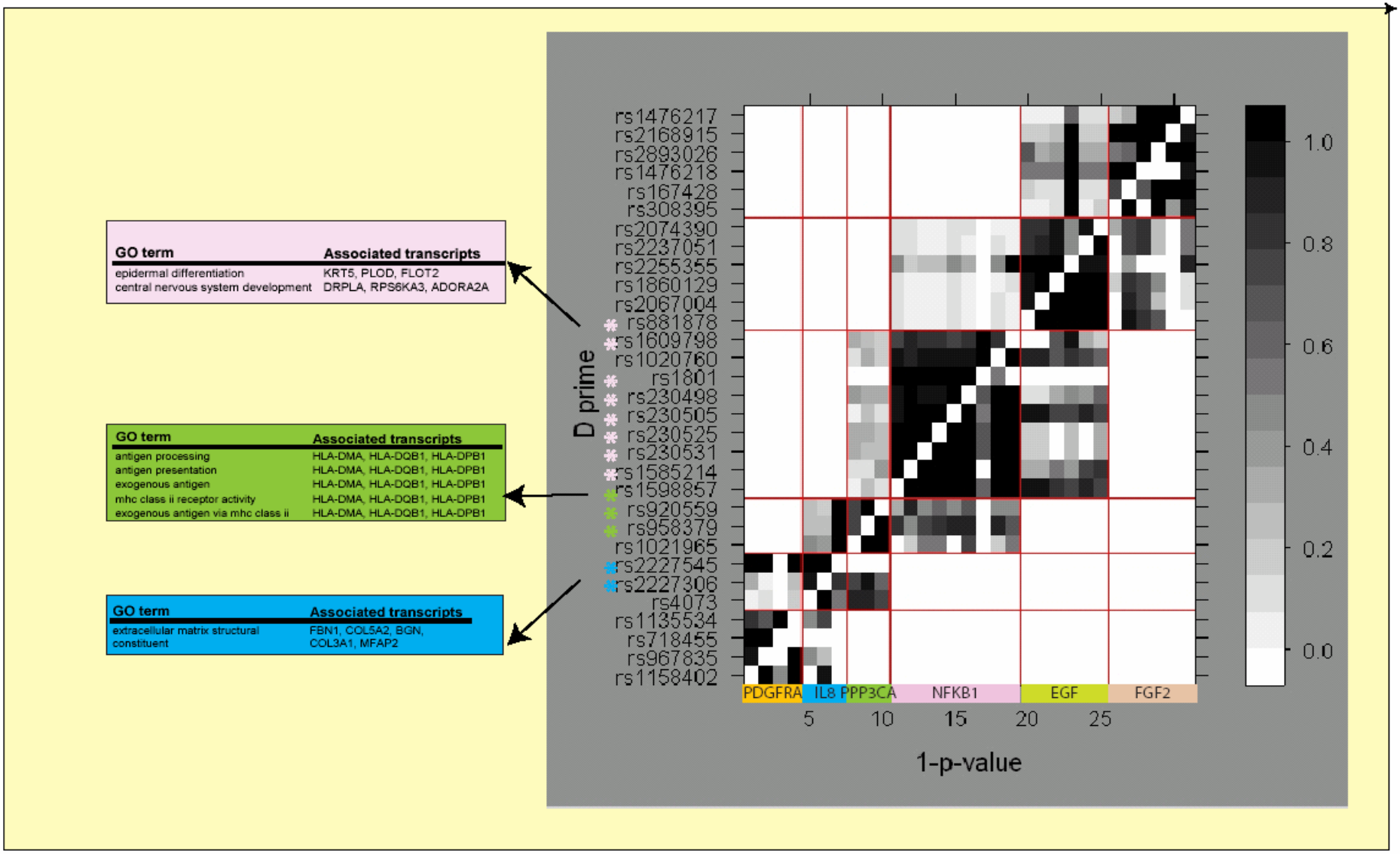
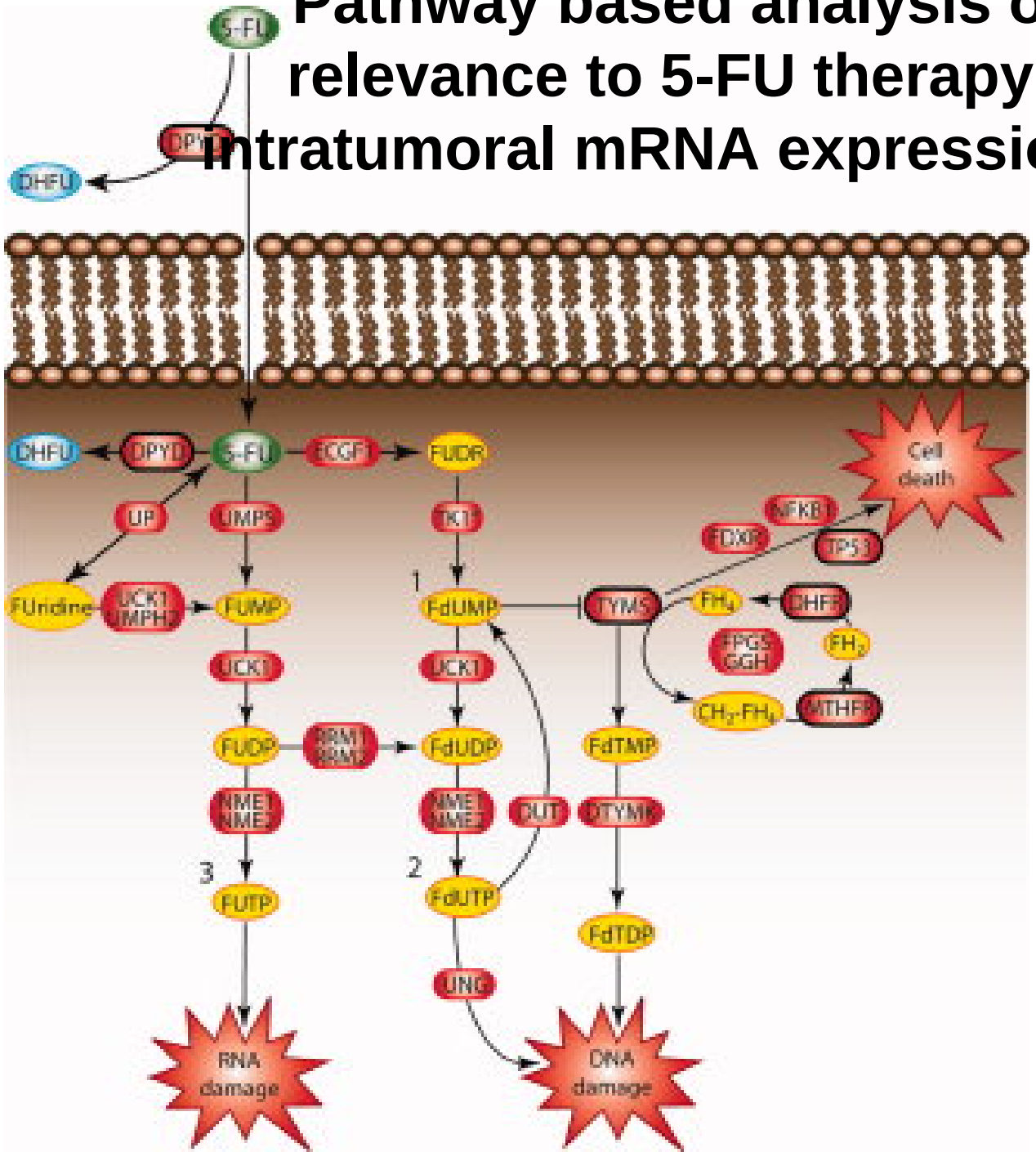


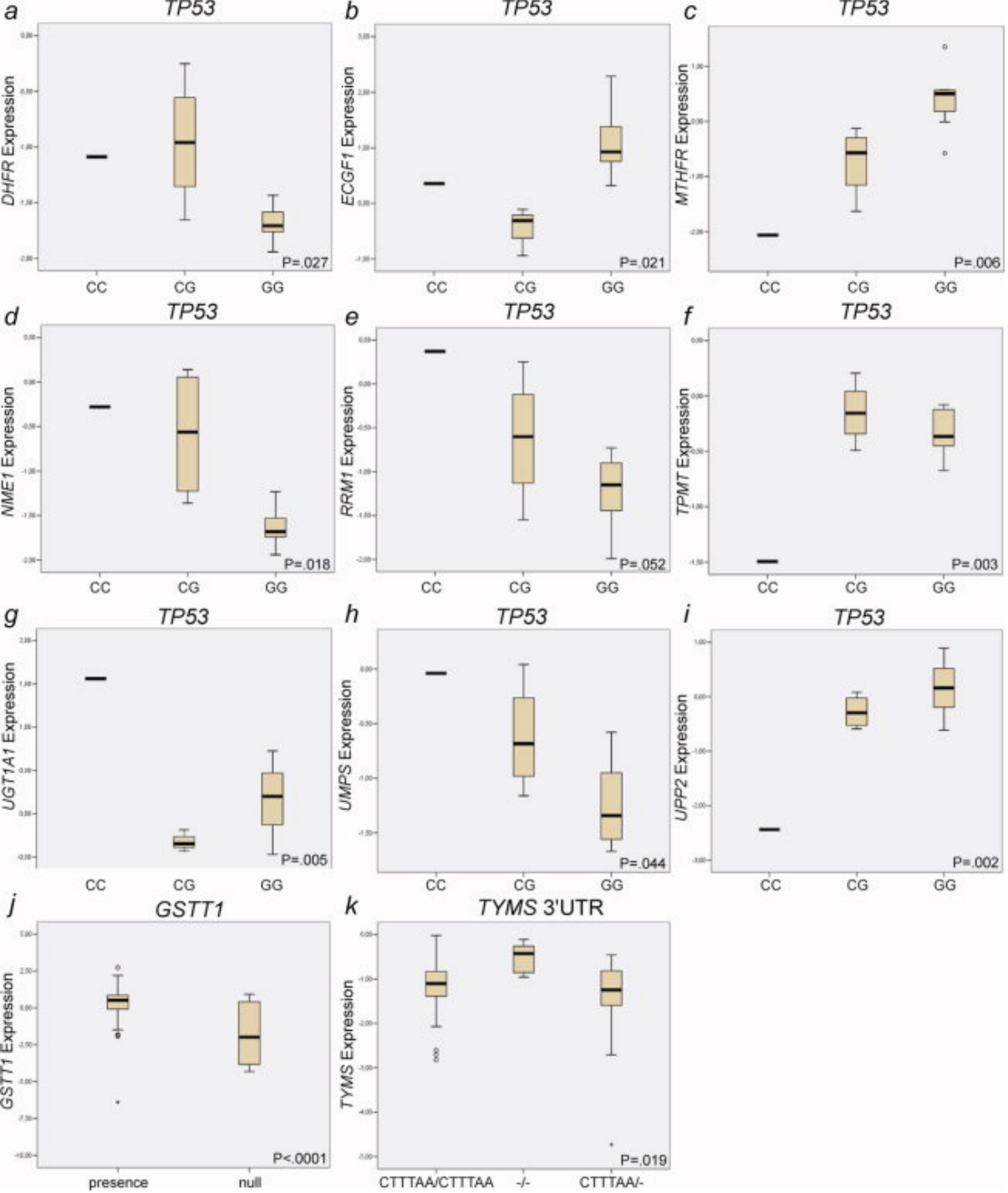
Figure 1. Level of LD in and between genes analyzed on chromosome 4. Star (*) indicate groups SNPs found associated with groups of transcripts. The boxes with corresponding color gives the significantly overrepresented GO terms in this group of transcripts with the transcripts belonging to the GO term. The correlation between neighbouring genes is given in the cells adjacent to the diagonal cells.

Pathway based analysis of SNPs with relevance to 5-FU therapy: Relation to intratumoral mRNA expression and survival



Silje H. Nordgard

Nordgard et al
Intern Journal of Cancer, 2008



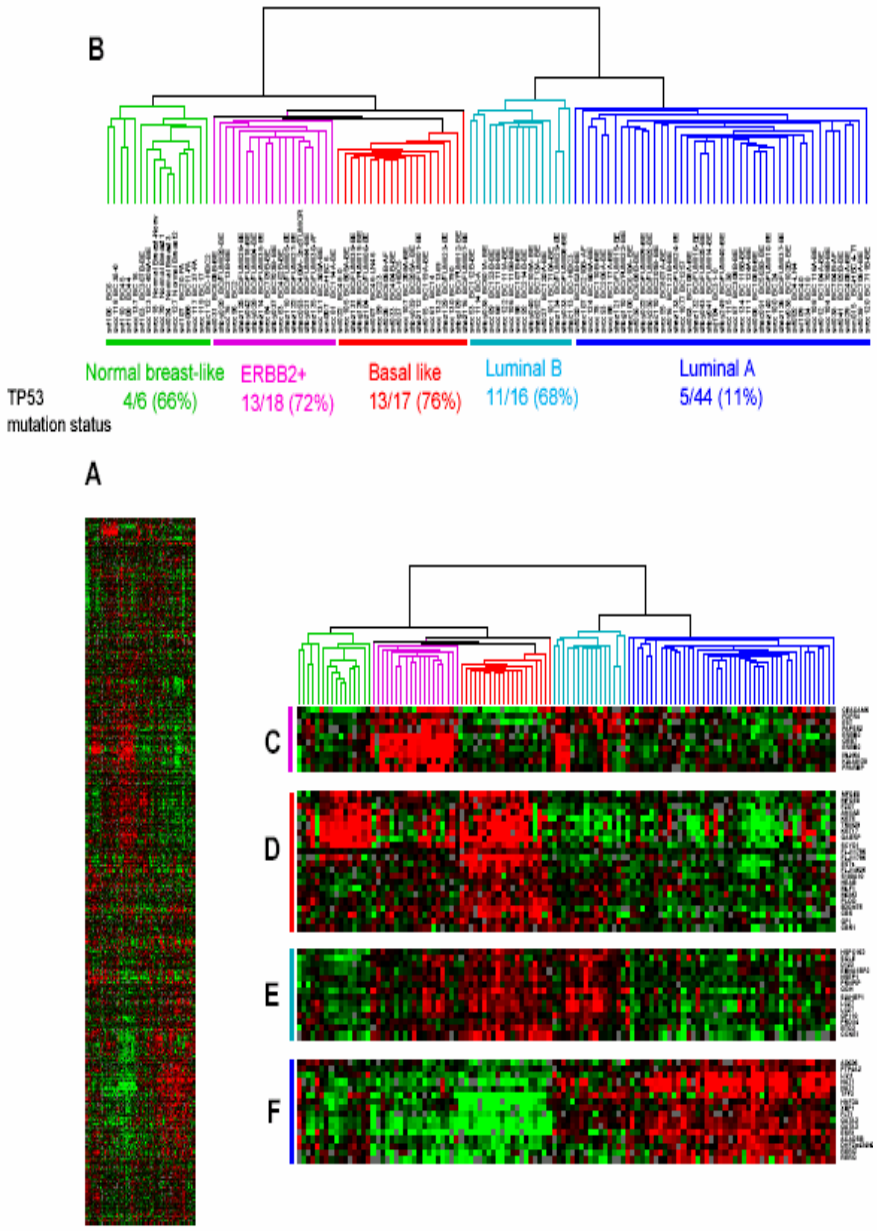
- Promoter analysis of the genes whose expression was significantly associated with the *TP53* codon 72 SNP revealed *in silico* binding sites for TP53 in the promoter of *DHFR*, *ECGF1*, *MTHFR*, *NME1*, *RRM1*, *TPMT* and *UGT1A1*

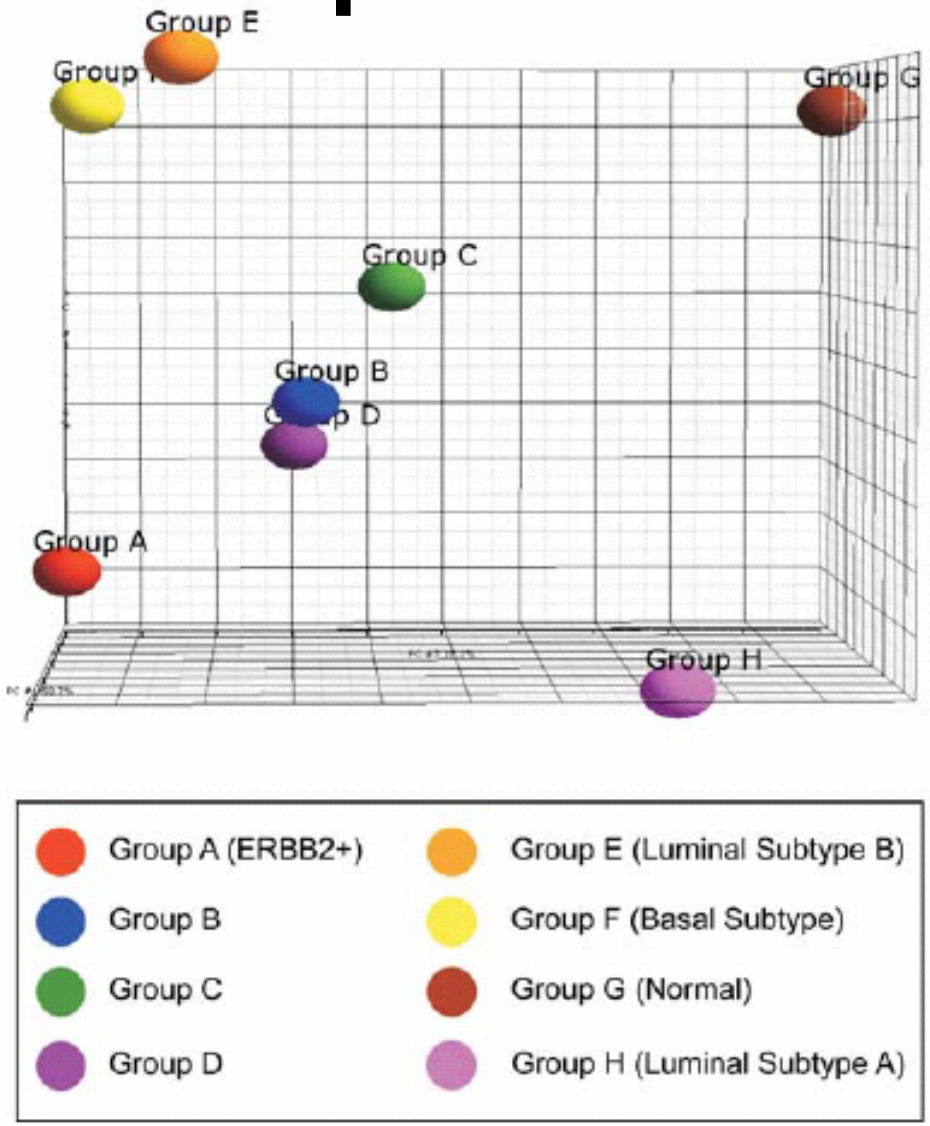
Global association analysis:

10K Results

1. **SNPs associated with the expression of the Intrinsic genes**
2. **SNPs associated to the 5 breast cancer subgroups**
3. **SNPs associated to tumoral *TP53* mutation status**
4. **SNPs associated to Hormone Respetor status**
5. **SNPs associated to two random groups**
6. **Detection of chromosomal aberrations with the 10K SNP set**

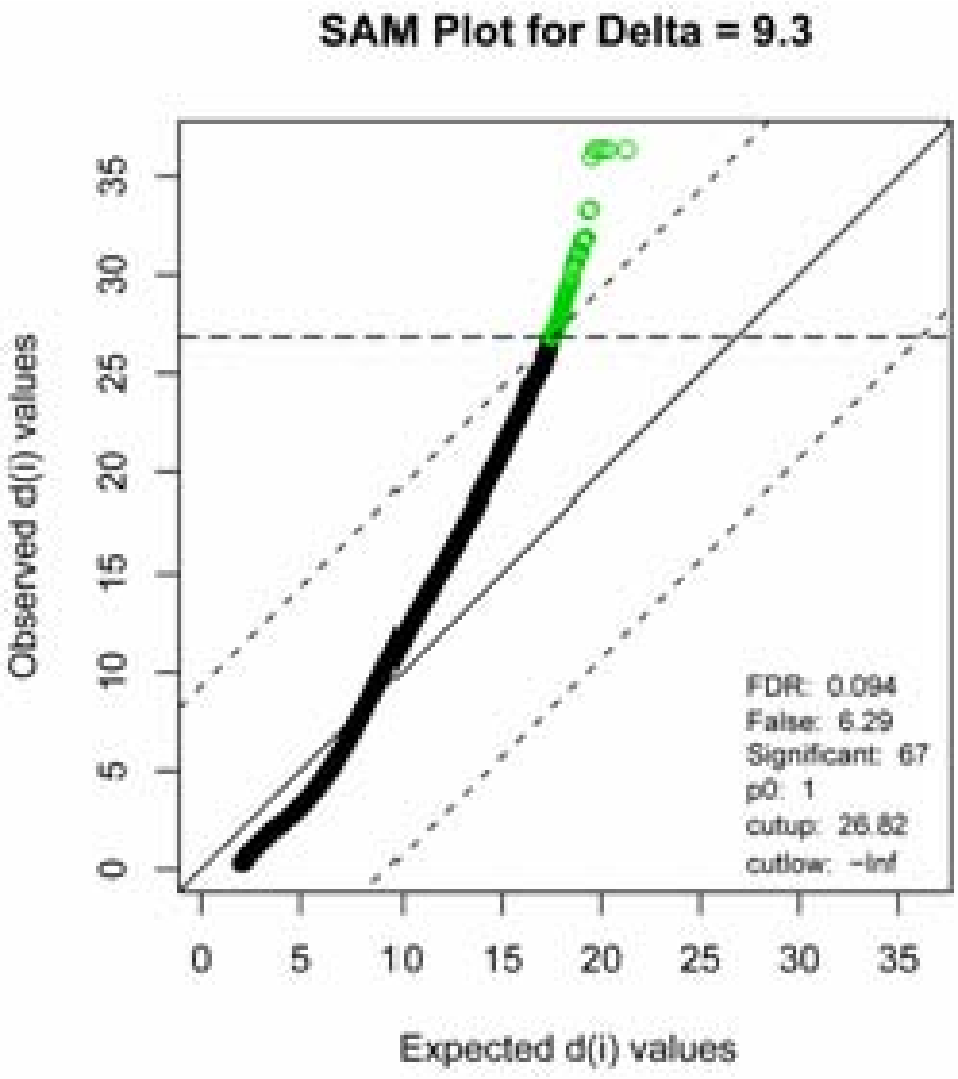
Background mRNA expression





Perou et al 2000, Sørlie et al. 2001, 2003

SNPs associated to tumor subclasses



Bettina Kulle
Marit Holden
Ingunn Tvete
Arnoldo Frigessi

So let us divide our 100K SNPs into different functional pathways

Gene set enrichment analysis for SNPs

Bmstatus	3 sig. pathways
ER	2 -"-
HR	1 -"-
PR	0 -"-
TP53	2 -"-

2 pathways are common for all analysed binære variabler.

- p21 early (13 gener)
- RNA Polymerase (14 gener).

- CENPF, from p21 early, has 12 SNPs very significantly differently distributed in different groups with BM ($p<10^{-5}$), TP53 status and HR.

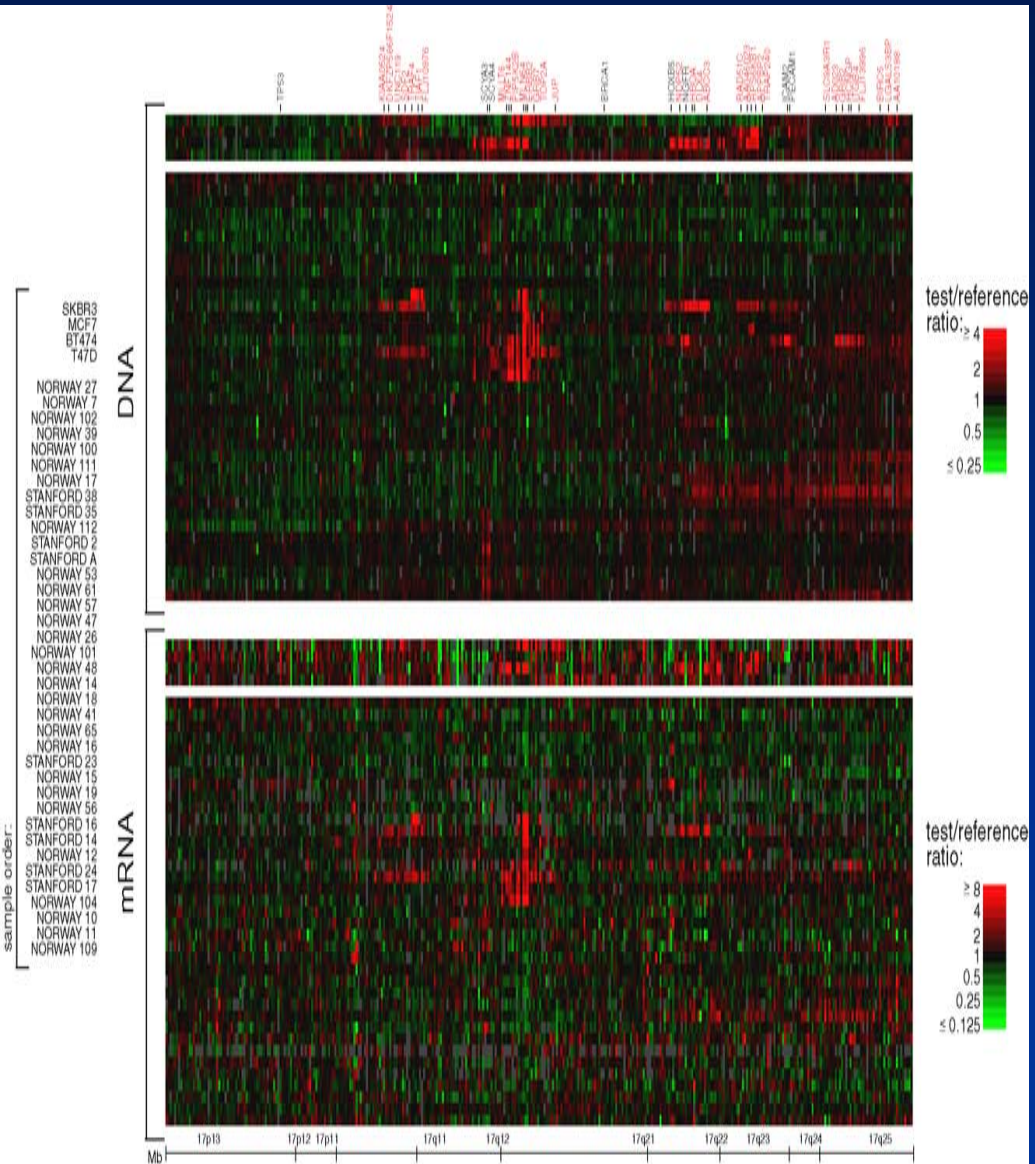
- CENPF (Centromere protein F). Resides on chromosome 1q41 and encodes a protein that associates with the centromere-kinetochore complex. The protein is a component of the nuclear matrix during the G2 phase of interphase. In late G2 the protein associates with the kinetochore and maintains this association through early anaphase. It localizes to the spindle midzone and the intracellular bridge in late anaphase and telophase, respectively, and is thought to be subsequently degraded. The localization of this protein suggests that it may play a role in chromosome segregation during mitotis. It is thought to form either a homodimer or heterodimer. Autoantibodies against this protein have been found in patients with cancer or graft versus host disease.

  CENPF SNPs are in LD, and form 2 blocks. One of these ”disease” haplotypes was associated to BM status with p-value $4{,}4*10^{-5}$

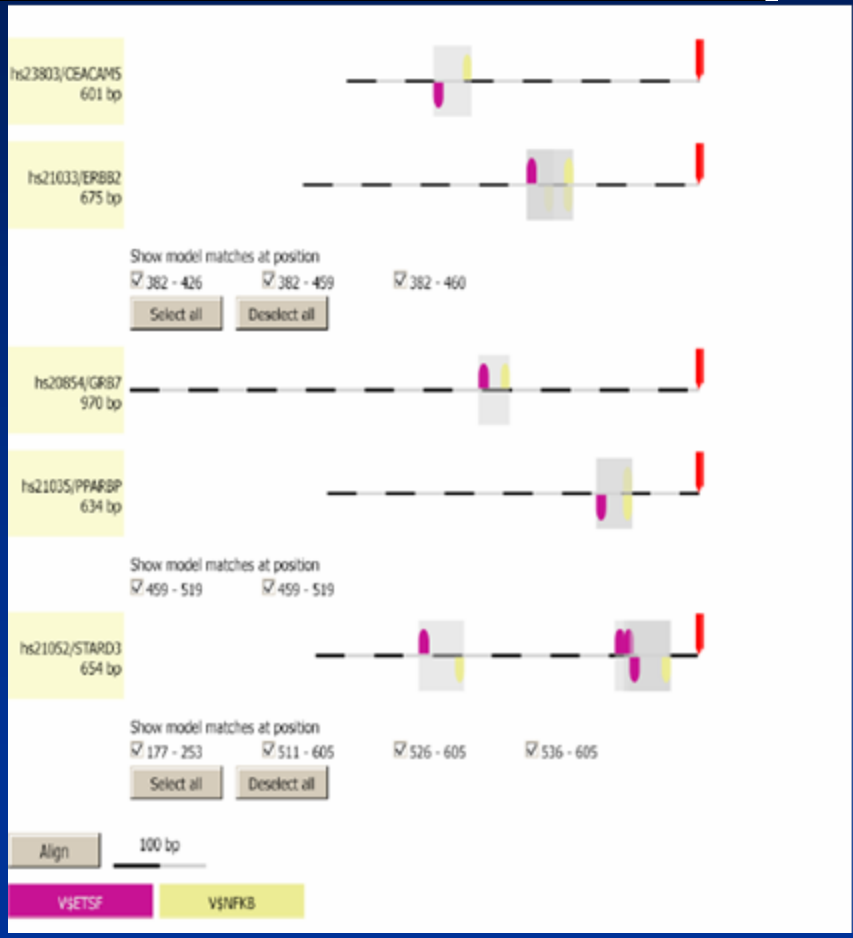
Chromosomal aberrations

Comparison of mRNA levels with DNA Copy Number Changes

Chr 17



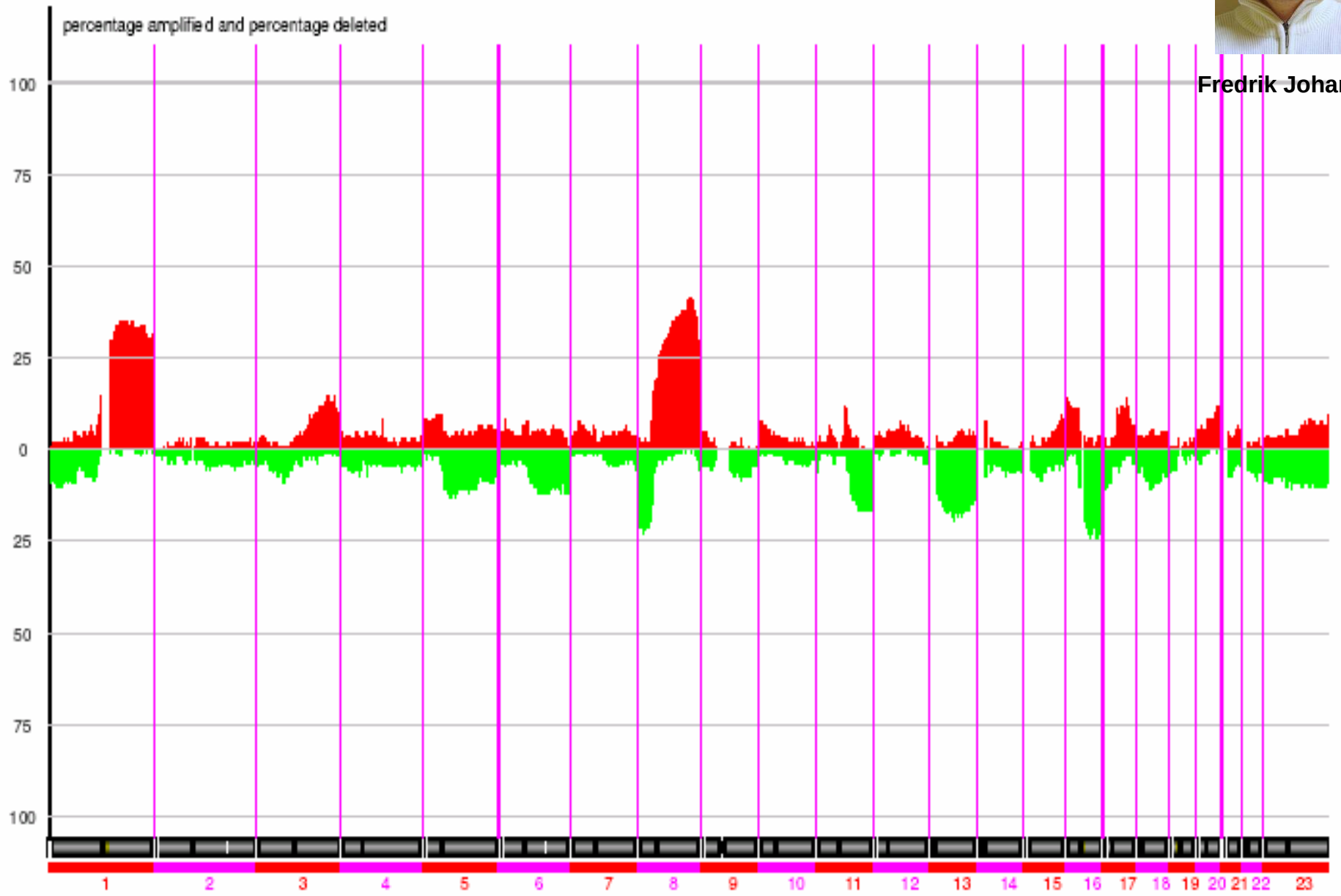
	Element	Strand	Matrix sim.	Distance to next element	Common to	FW-Scores
1	V$ETSF	±	Optimized (min. 0.83)	29 - 79 bp	5 sequences (83 %) 11 matches, 6 non-overlapping	0.45 / 0.83
2	V$NFKB	±	Optimized (min. 0.82)	---		



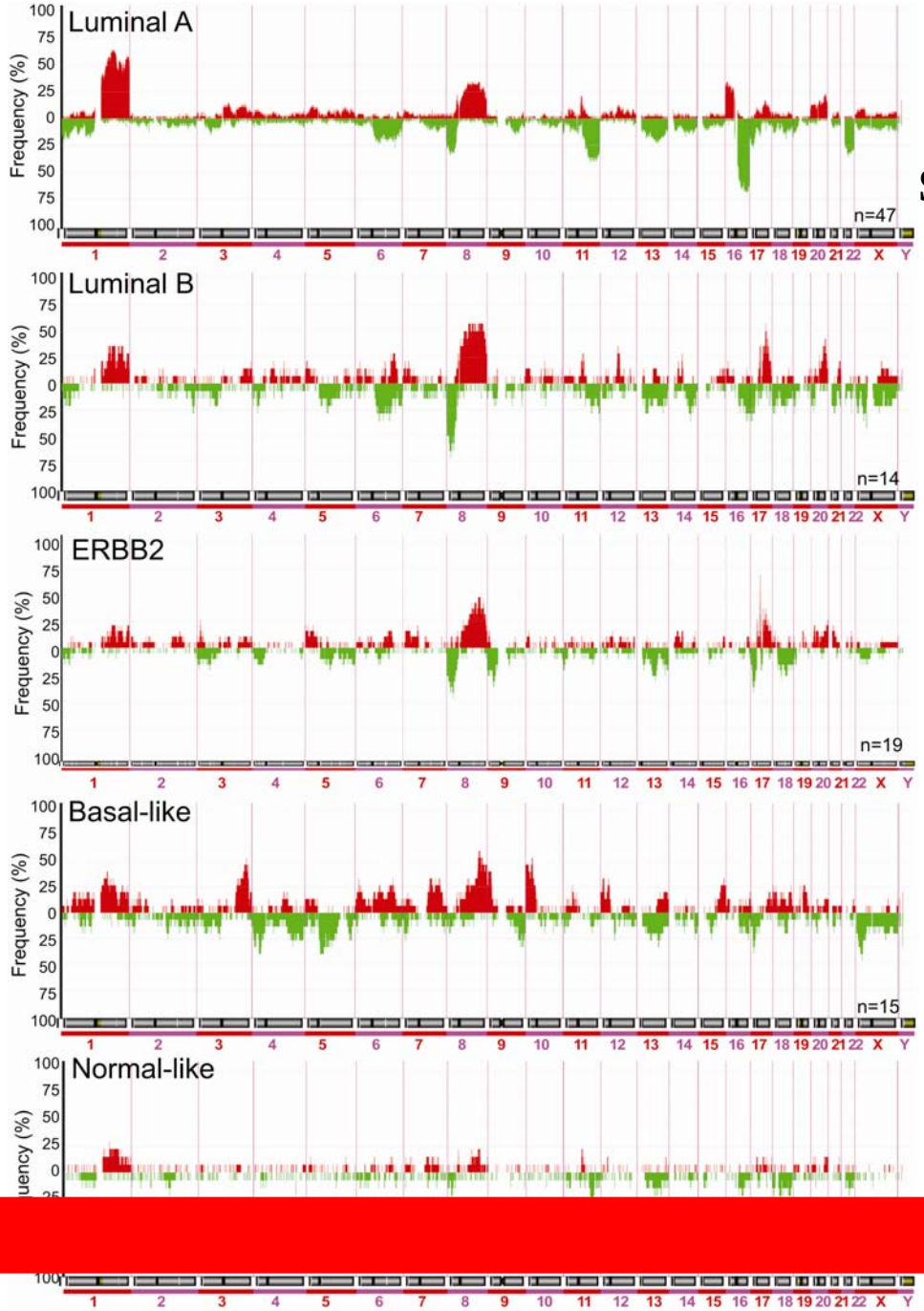
Background CGH

Fredrik Johansen

Summary from CGH-Explorer's ACE algorithm, FDR<0.001



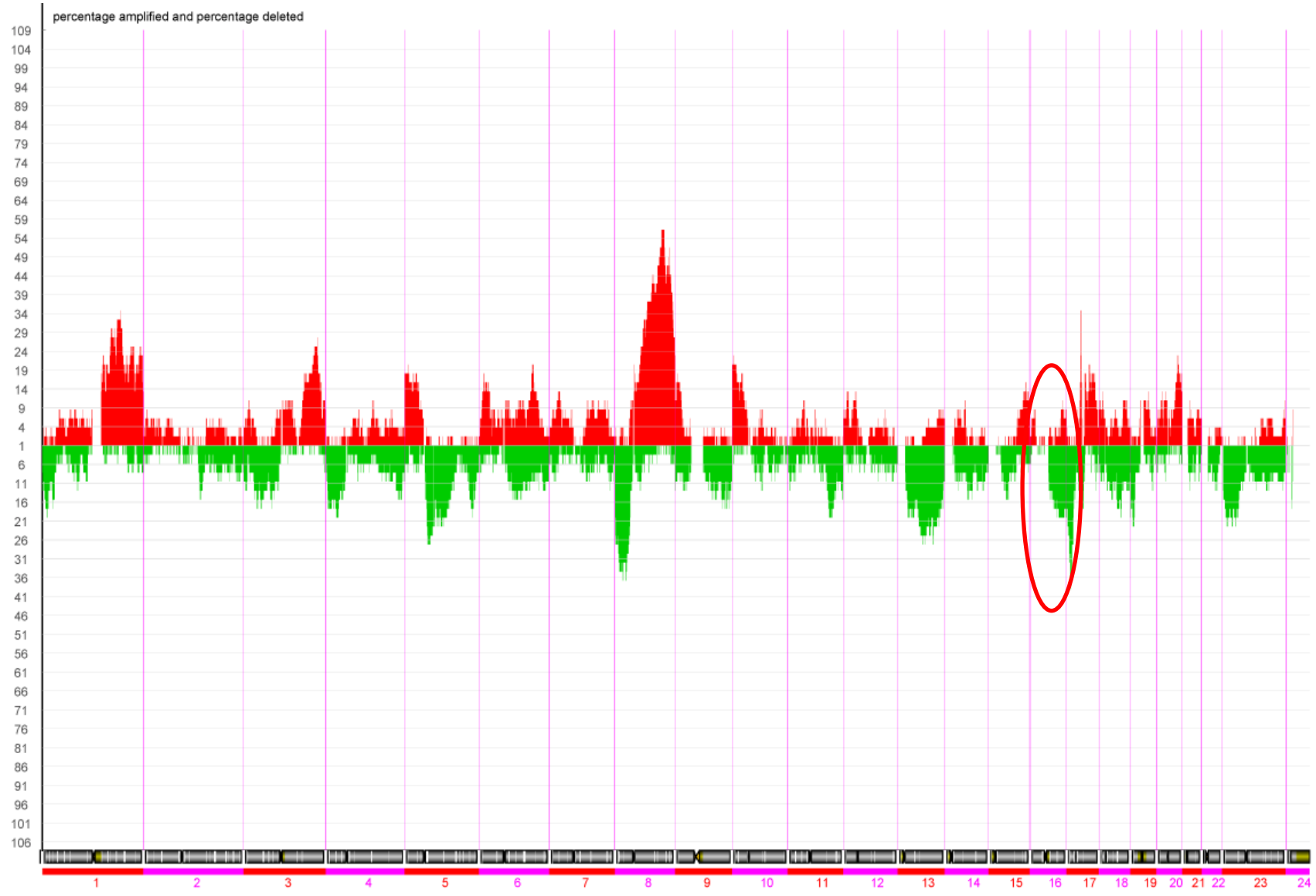
•Aberration frequencies in the 5 TS of early BC

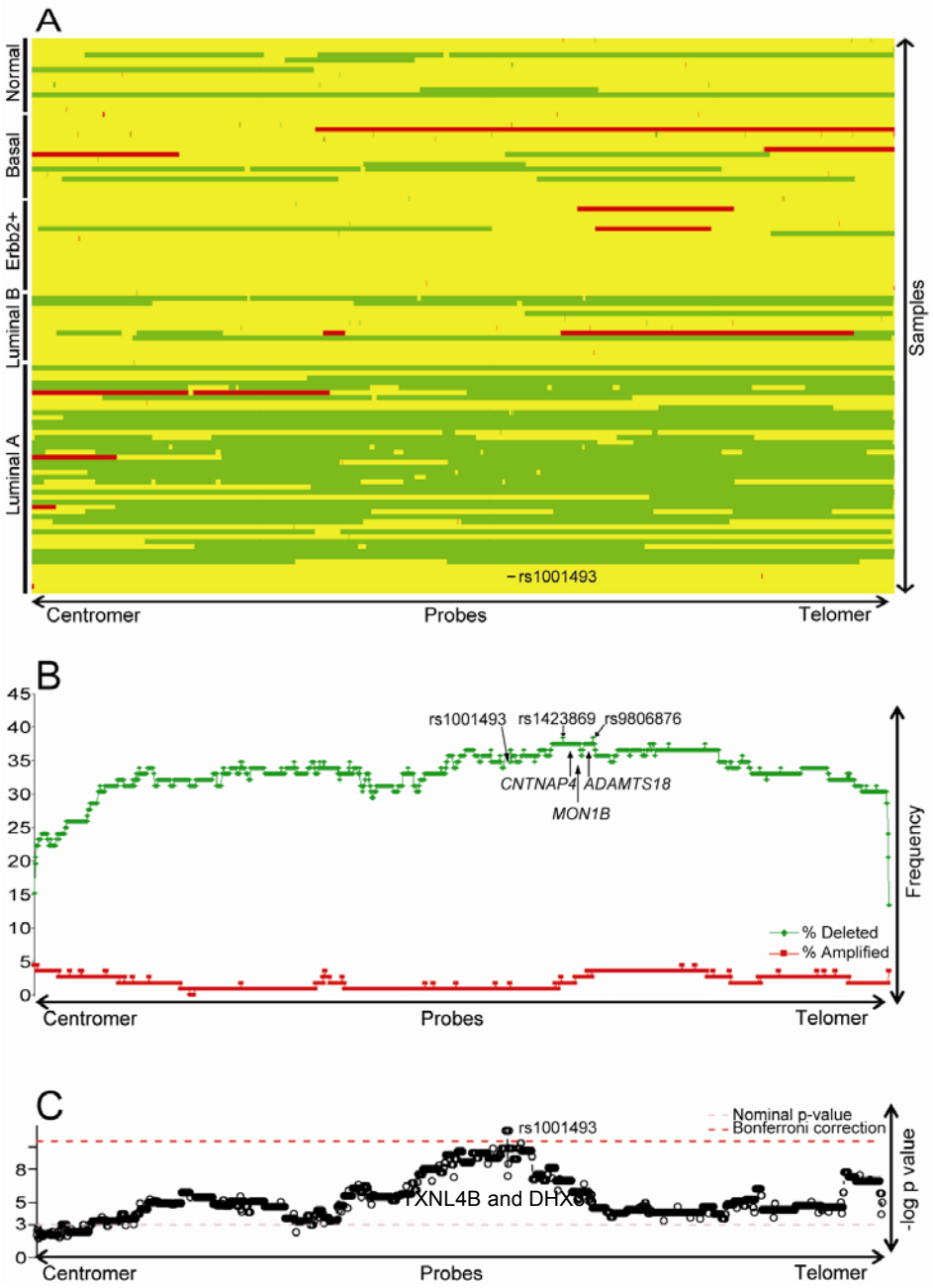


Silje H. Nordgard

n=112 MicMa

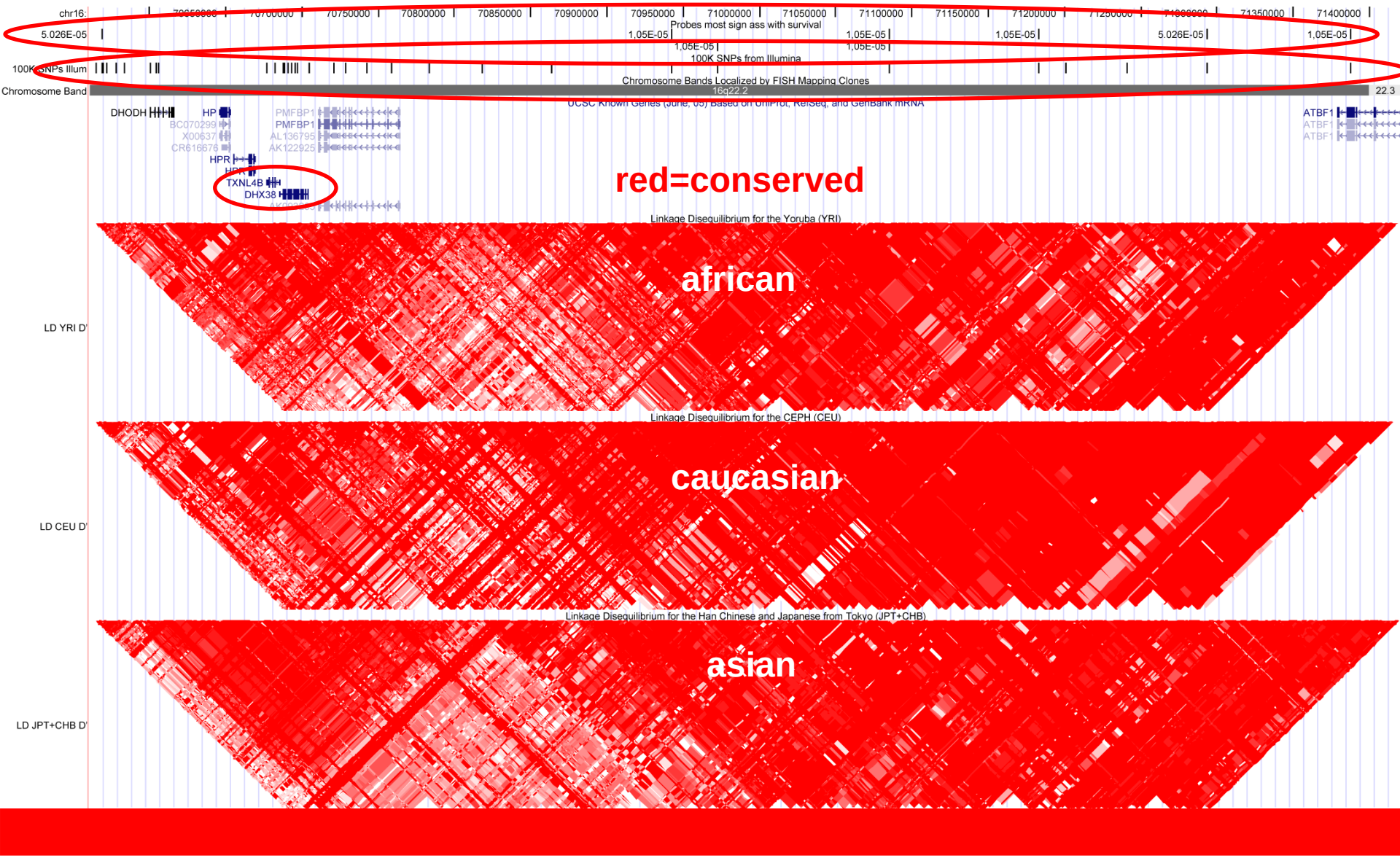
Deletion on 16q




A
Normal
Basal
Erbb2+
Luminal B
Luminal A
rs1001493
Samples
Centromer
Probes
Telomer
B
45
40
35
30
25
20
15
10
5
0
rs1001493
rs1423869
rs9806876
CNTNAP4
ADAMTS18
MON1B
% Deleted
% Amplified
Frequency
Centromer
Probes
Telomer
C
rs1001493
Nominal p-value
Bonferroni correction
8
5
3
0
-log p value
TXNL4B and DHX8
Centromer
Probes
Telomer

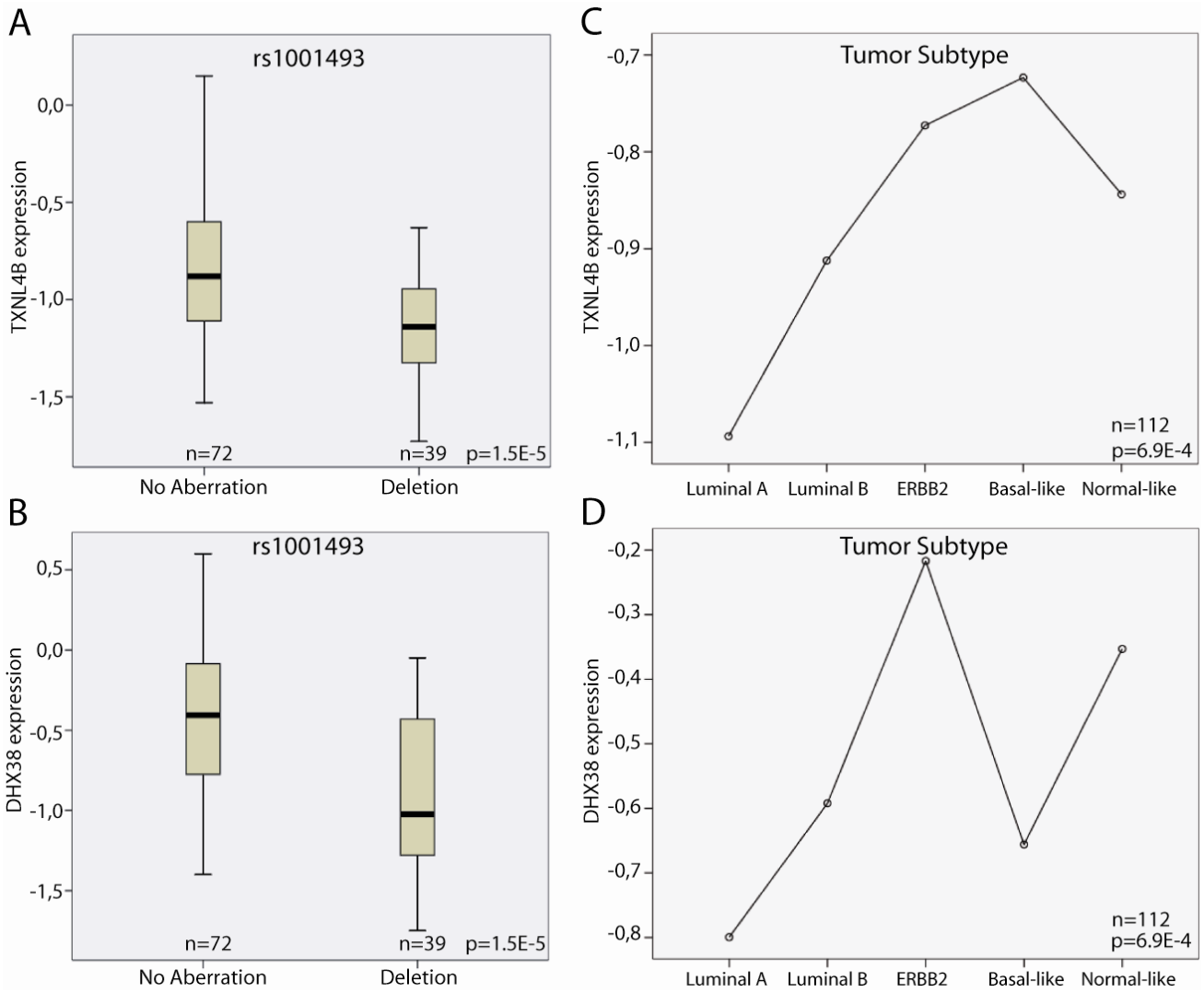
Results

- Significant association to survival is mapped to CNA of 6 probes after BF



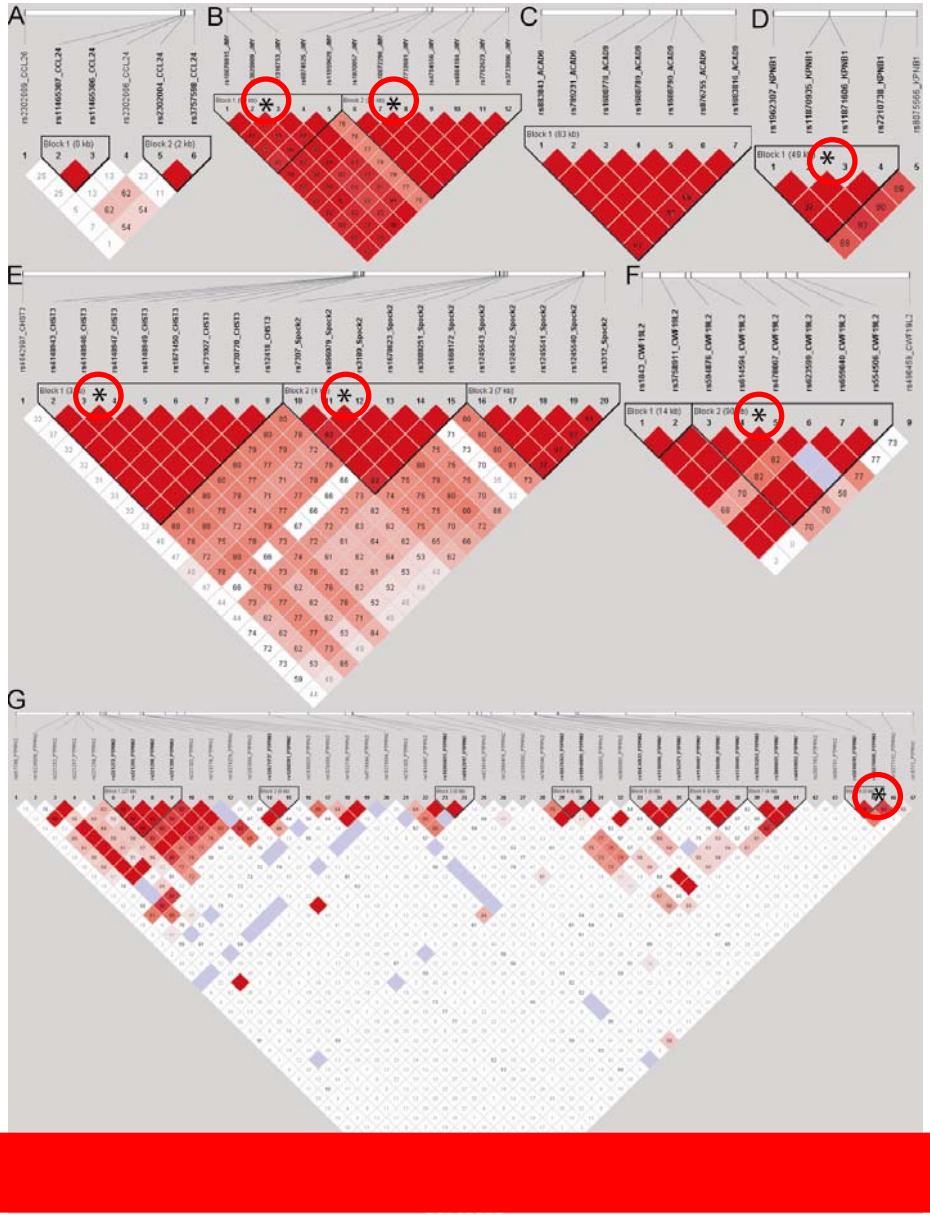
Results

- CNAs associate with the expression of TXNL4B and DHX38



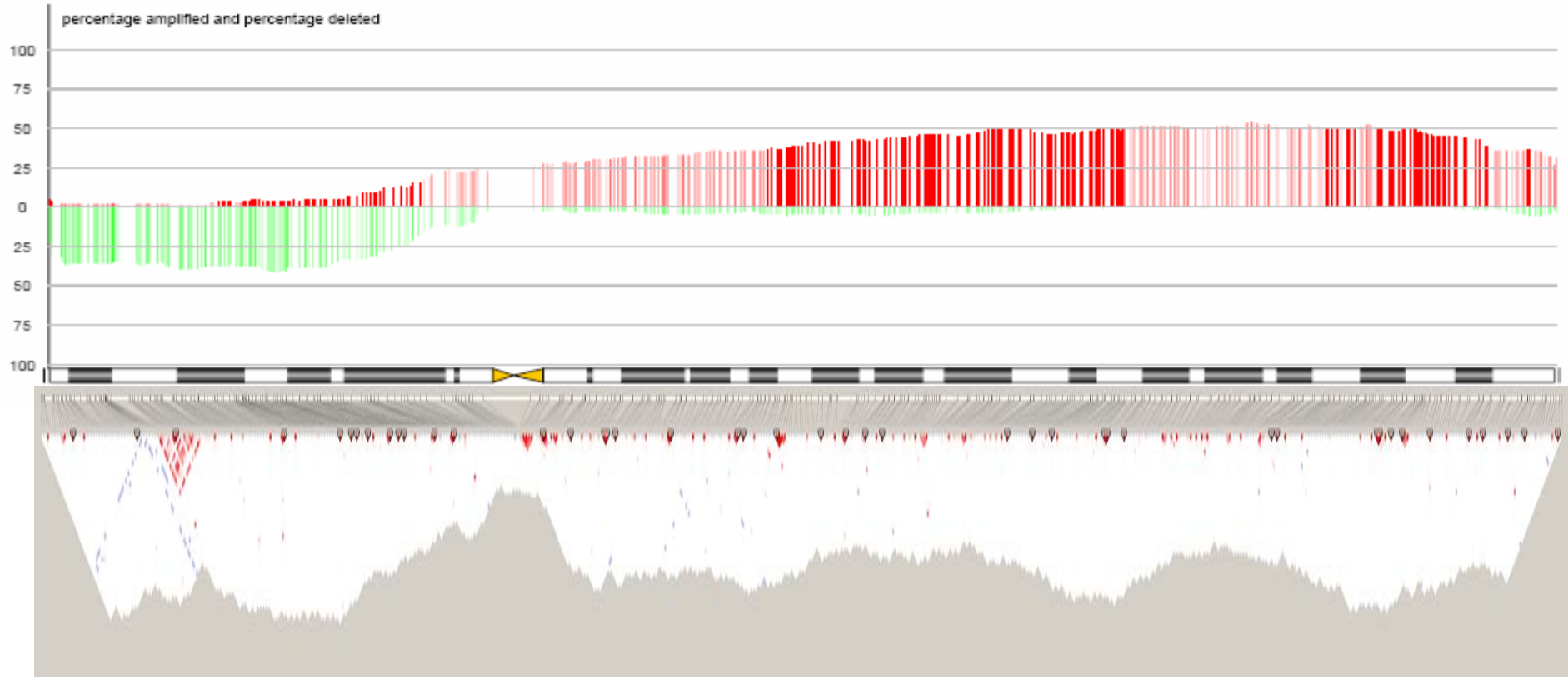
Results

•LD plots of the genes with germline SNPs most significantly associated with 16q deletion status



In cis

Chromosome 8



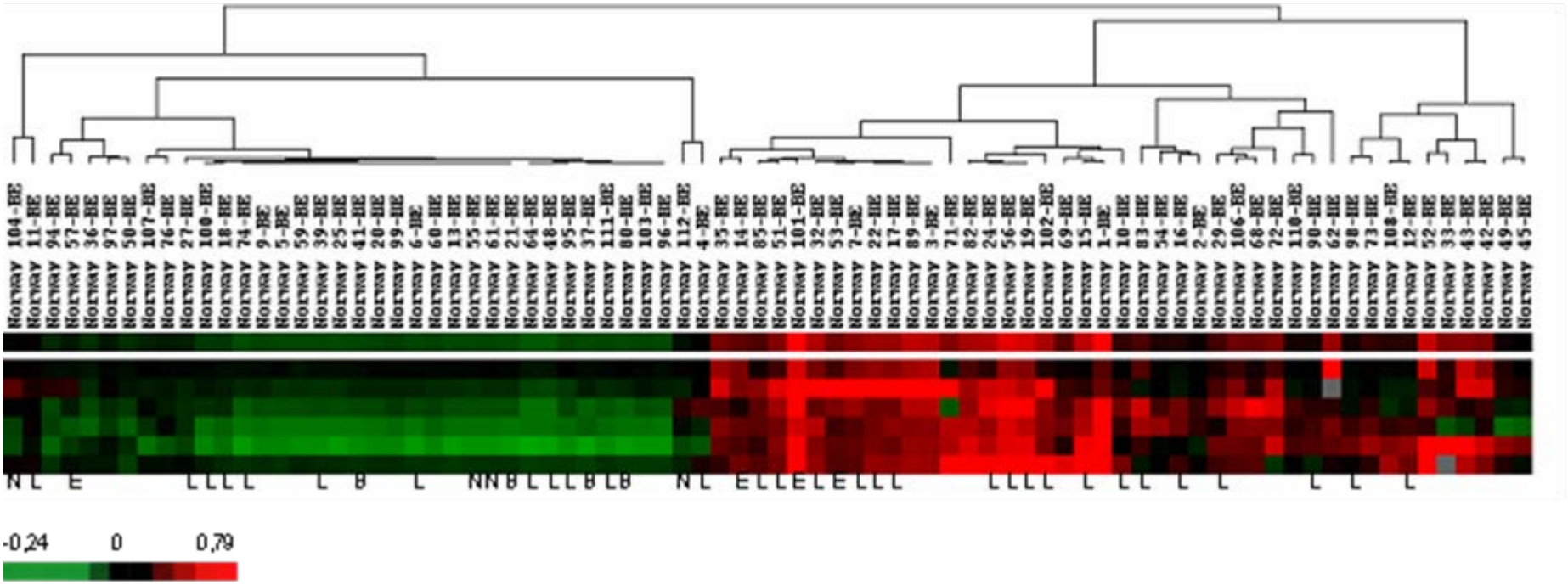
In trans

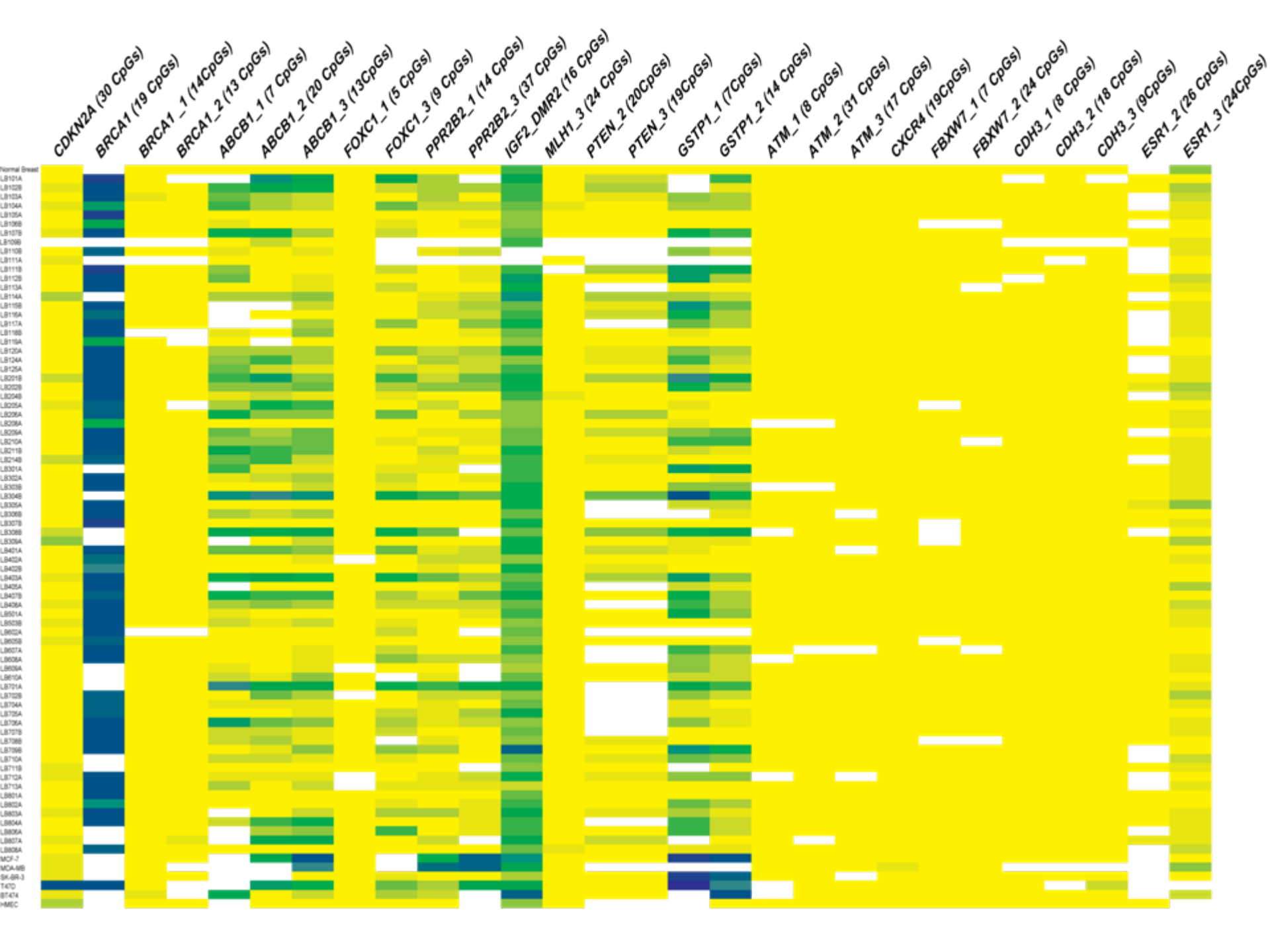
Name	Chromoso	In Gene?	Allele	Chi square	P value
APC and RAD50					
rs1496390	5	KCNN2	G	5.601	0.0179
rs171661	5		T	4.253	0.0392
hLMH1					
rs1403470	3		C	4.821	0.0281
MGMT					
rs196290	10	BAG3	T	6.628	0.01
rs765934	10		C	5.762	0.0164
rs1545693	10	ADAM12	C	5.649	0.0175
rs947582	10	UROS	G	5.217	0.0224
rs1041517	10		T	4.861	0.0275
rs1535461	10	TACC2	G	4.697	0.0302
NBS1					
rs997597	8	FLJ35802	C	7.459	0.0063
rs734546	8		C	4.703	0.0301
STK6					
rs1570160	20		A	2,43	0.0099
rs195022	20		A	4.934	0.0263
TP53					
No Associ	17				

DNA methylation

Non-random distribution of methylated CpGs in subclasses of breast cancer

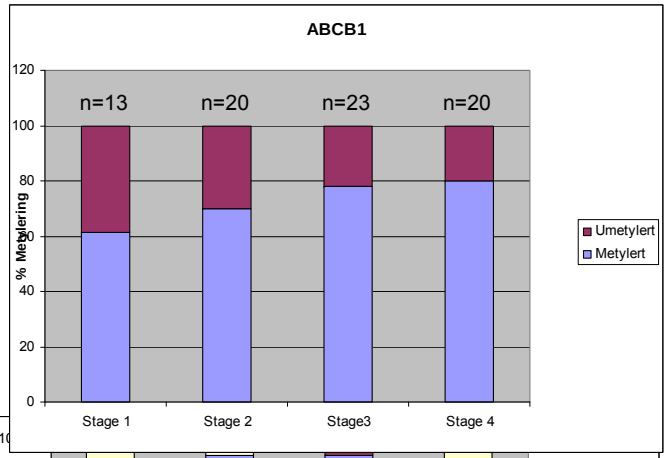
Jo Anders Rønneberg

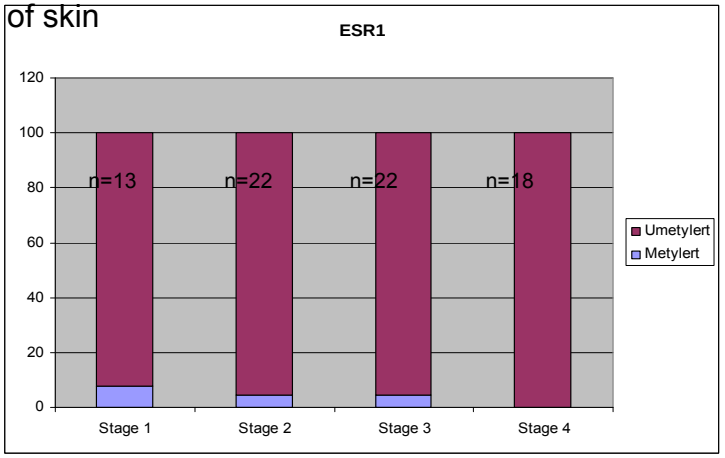


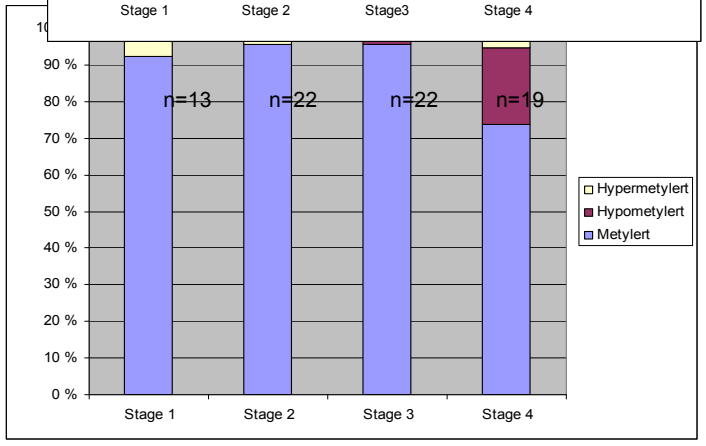

CDKN2A (30 CpGs)
BRCA1 (19 CpGs)
BRCA1_1 (14CpGs)
BRCA1_2 (13 CpGs)
ABCB1_1 (7 CpGs)
ABCB1_2 (20 CpGs)
ABCB1_3 (13CpGs)
FOXC1_1 (5 CpGs)
FOXC1_3 (9 CpGs)
PPR2B2_1 (14 CpGs)
PPR2B2_3 (37 CpGs)
IGF2_DMR2 (16 CpGs)
MLH1_3 (24 CpGs)
PTEN_2 (20CpGs)
PTEN_3 (19CpGs)
GSTP1_1 (7CpGs)
GSTP1_2 (14 CpGs)
ATM_1 (8 CpGs)
ATM_2 (31 CpGs)
ATM_3 (17 CpGs)
CXCR4 (19CpGs)
FBXW7_1 (7 CpGs)
FBXW7_2 (24 CpGs)
CDH3_1 (8 CpGs)
CDH3_2 (18 CpGs)
CDH3_3 (9CpGs)
ESR1_2 (26 CpGs)
ESR1_3 (24CpGs)
Normal Breast
MCF-7
MDA-MB
SK-BR-3
T47D
BT474
HMEC

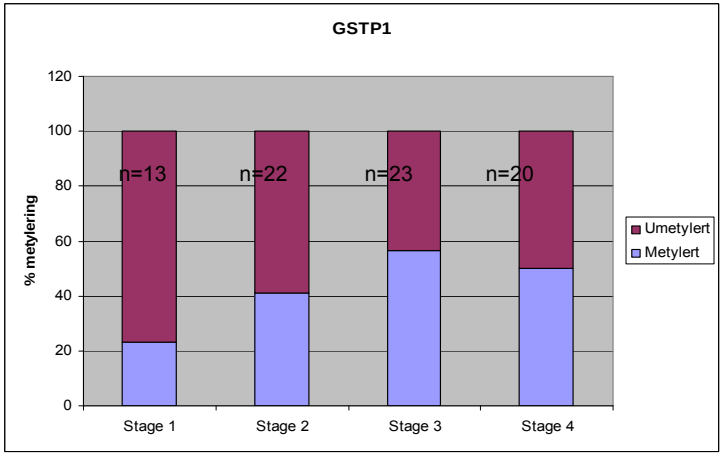
Stage and DNA methylation

Stage 1:Tumors less than 2,0 cm in diameter
Stage 2:Tumors between 2-5 cm
Stage 3:Tumors greater than 5 cm
Stage 4:Fixation to chest wall, peu d'orange, ulceriation of skin



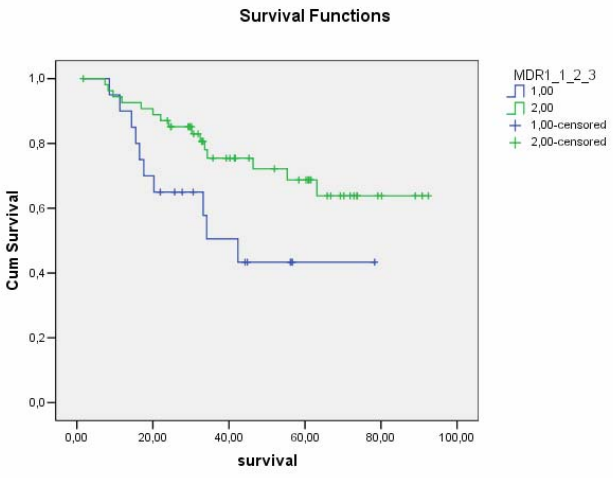






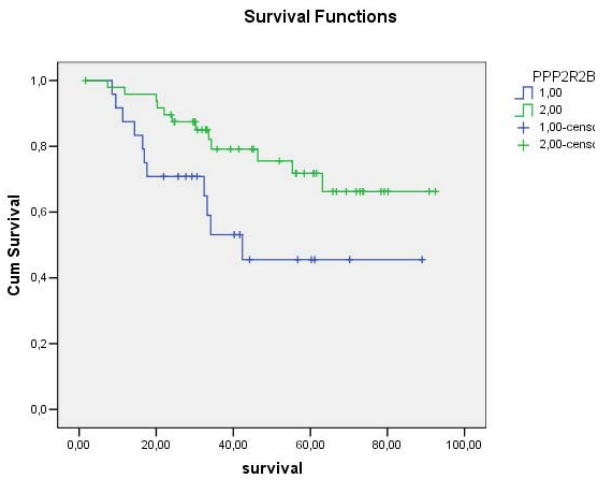
DNA methylation and survival

MDR1_MSP1_2_3



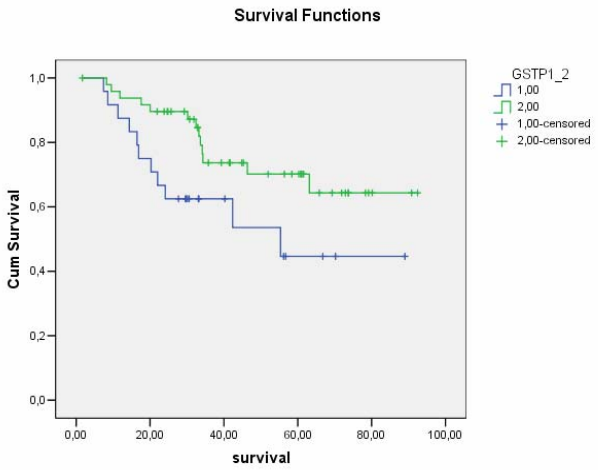
P = 0.030

PPP2R2B_MSP1_3



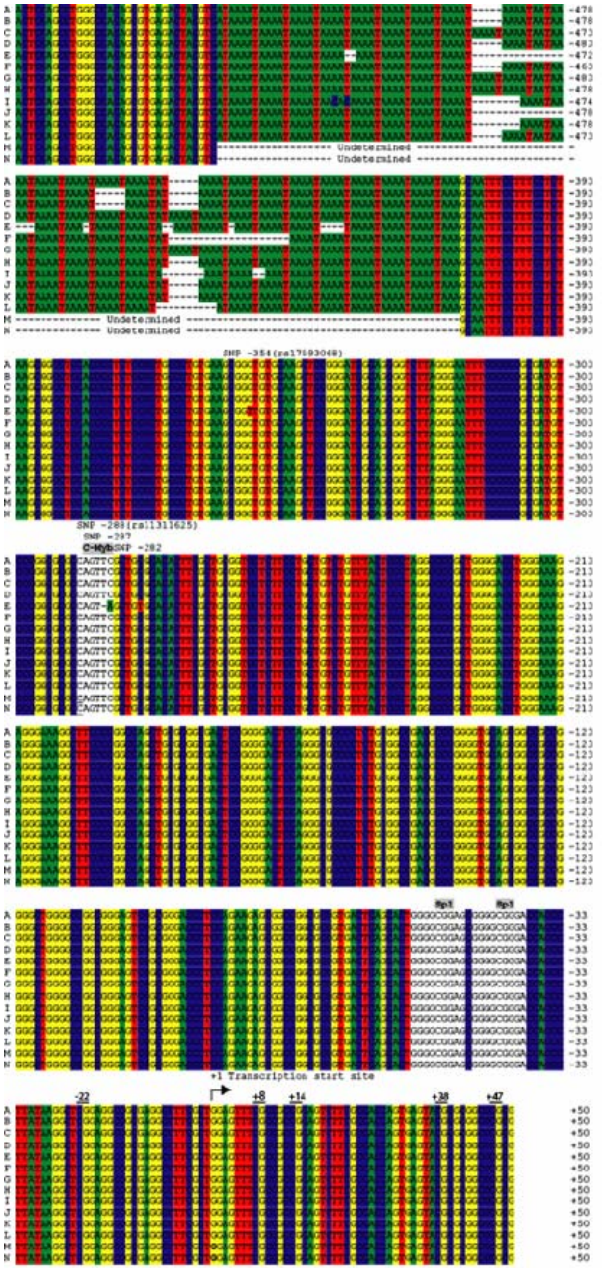
P = 0.024

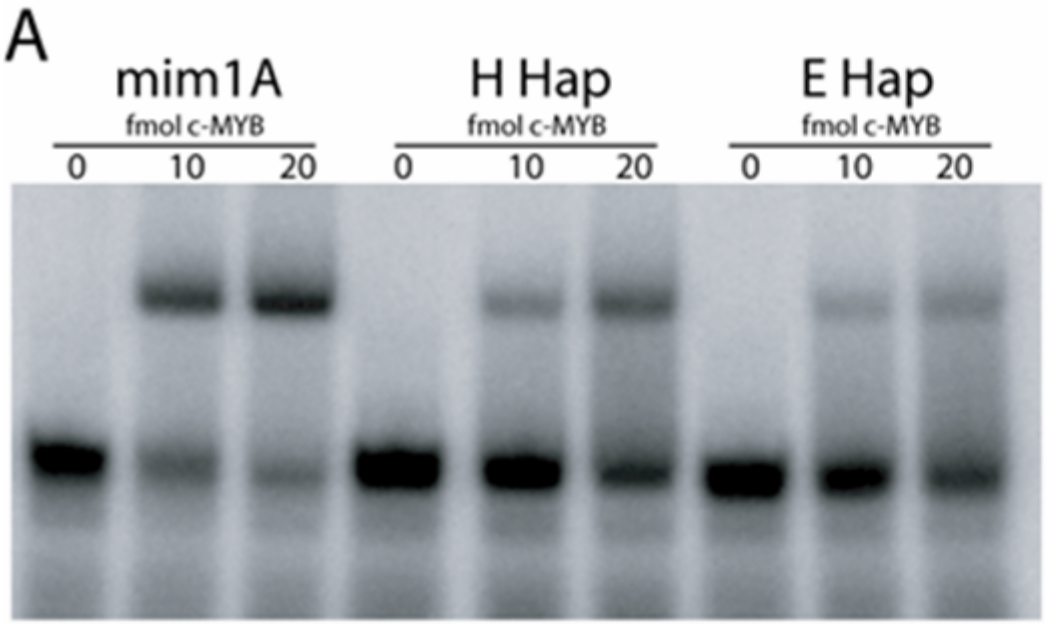
GSTP1_MSP1_2

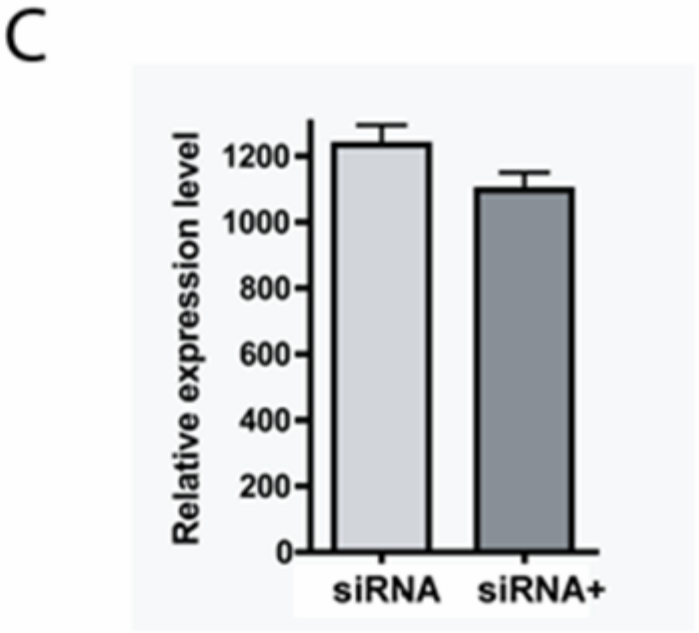


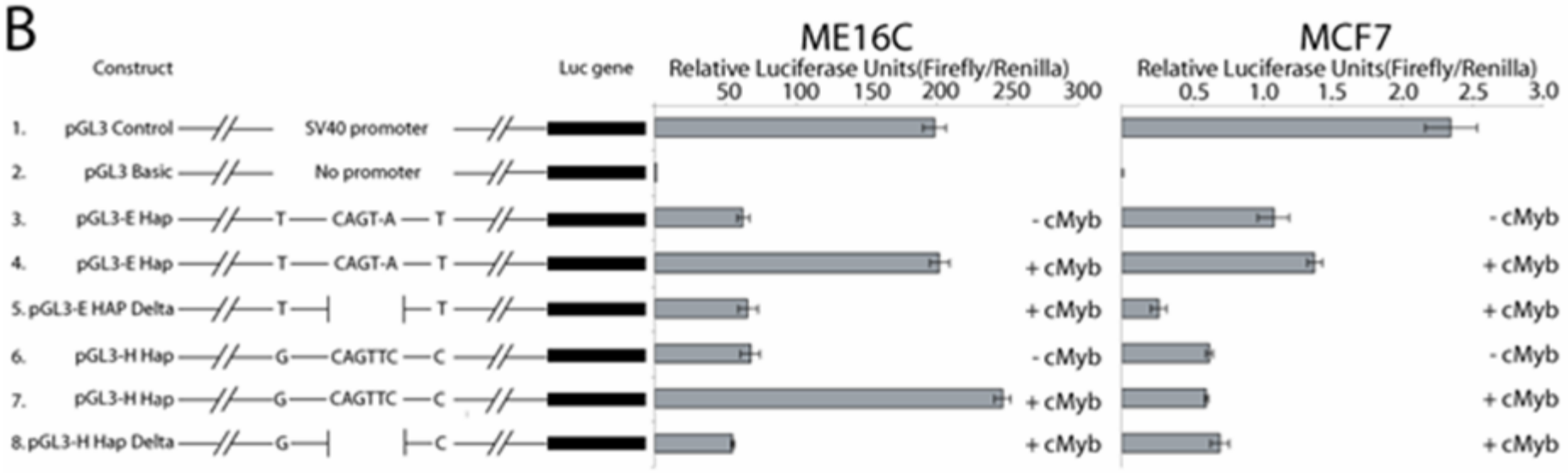
P = 0.039

Sequencing of 400bp upstream of the GSTP1 genome







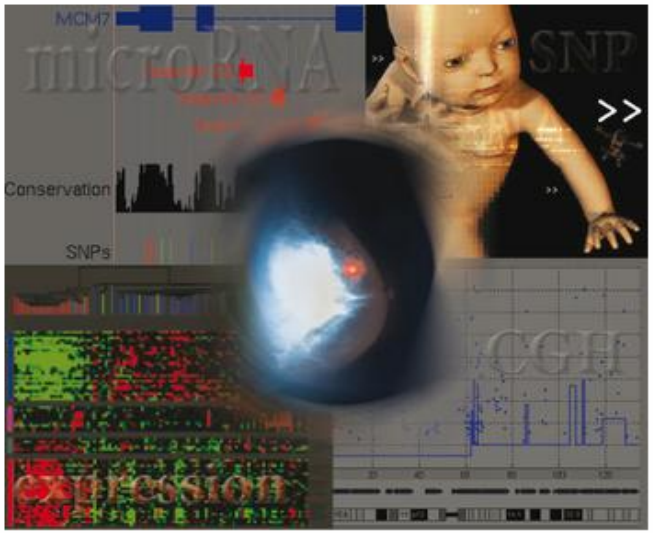


Rønneberg et al, *Cancer Res* 2008

miRNA

Espen Enerly, postdoc

Variation in regulation of gene expression: SNPs in regulatory RNA and their targets.



Introduction

There are indications that microRNA genes are involved in human tumourigenesis. Expression profiles of microRNAs can be used to classify tumors. Comparative DNA Hybridization (CGH) show that loss, amplifications and fragile sites often overlap with genomic location of microRNAs. They have a striking propensity to target genes known to or suspected to have roles in growth control, including both oncogenes and tumor suppressor genes.

Single Nucleotide Polymorphisms (SNPs) affects the miRNA pathways in several aspects. SNPs upstream of the gene might affect the transcription of individual or clusters of miRNAs, SNPs in the mature unit might affect the binding to an mRNA, SNPs in the mRNA of the target gene might prevent or generate binding sites for miRNAs, and SNPs in genes involved in miRNA processing might affect the whole microRNA pathway.

Aim

1. Identify SNP/haplotypes that affect expression or target binding of miRNAs involved in breast cancer.

2. Integrate miRNA and other data from various platforms (CGH, expression, SNPs) to generate a comprehensive understanding of the influence from miRNA deregulation in susceptibility, aggressiveness and treatment response of breast cancer.

Support

Key member: Dr. Espen Enerly
Collaborator: Ravi Sachidanandam (Cold Spring Harbor Laboratory)
The project is supported by EMBIO

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SNPs in miRNA targets

Miriam

Aure

MSc student

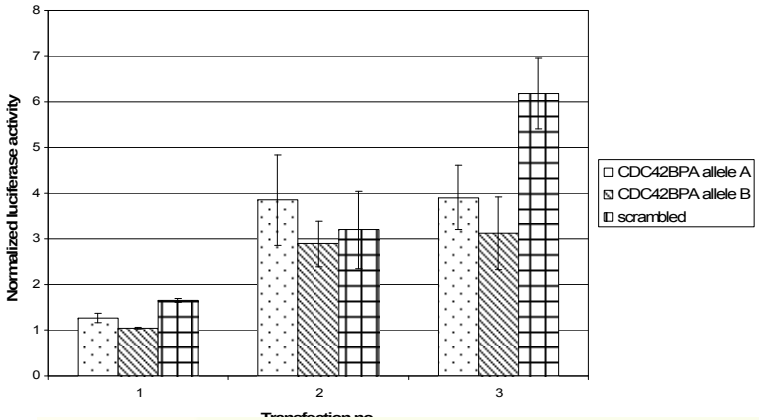
miRNA target prediction program combined with dbSNP

81 selected SNPs genotyped in 82 breast cancer patients

65 SNPs successfully genotyped

32 monomorphic SNPs

33 polymorphic SNPs



4 genes with a SNP in the miRNA binding site chosen for luciferase experiments

CDC42BPA and hsa-miR-520a

CENTB1 and hsa-miR-501

OAS3 and hsa-miR-506

AQP10 and hsa-miR-199b

miRNA Targeting Project

Cold Spring Harbor Laboratory

miRNA Targets | Common miRNA Targets | Targets to miRNA(s) | Find miRNAs for sequences | TF motifs for accessions

Candidate SNPs from *in silico* predictions for functional validation

85	31	27	22	8
miRNA with SNPs in binding sites	Existing frekuency for both SNP alleles	mRNA translated to protein	monoklonal antibody for western blotting	miRNA bindings-sites selected for functional validation

+ experimental control

Enhancer of zeste homolog 2, EZH2:

2 validated miR-101 bindingssites in 3' UTR

SNP in one of them av setene

Materialer og metoder

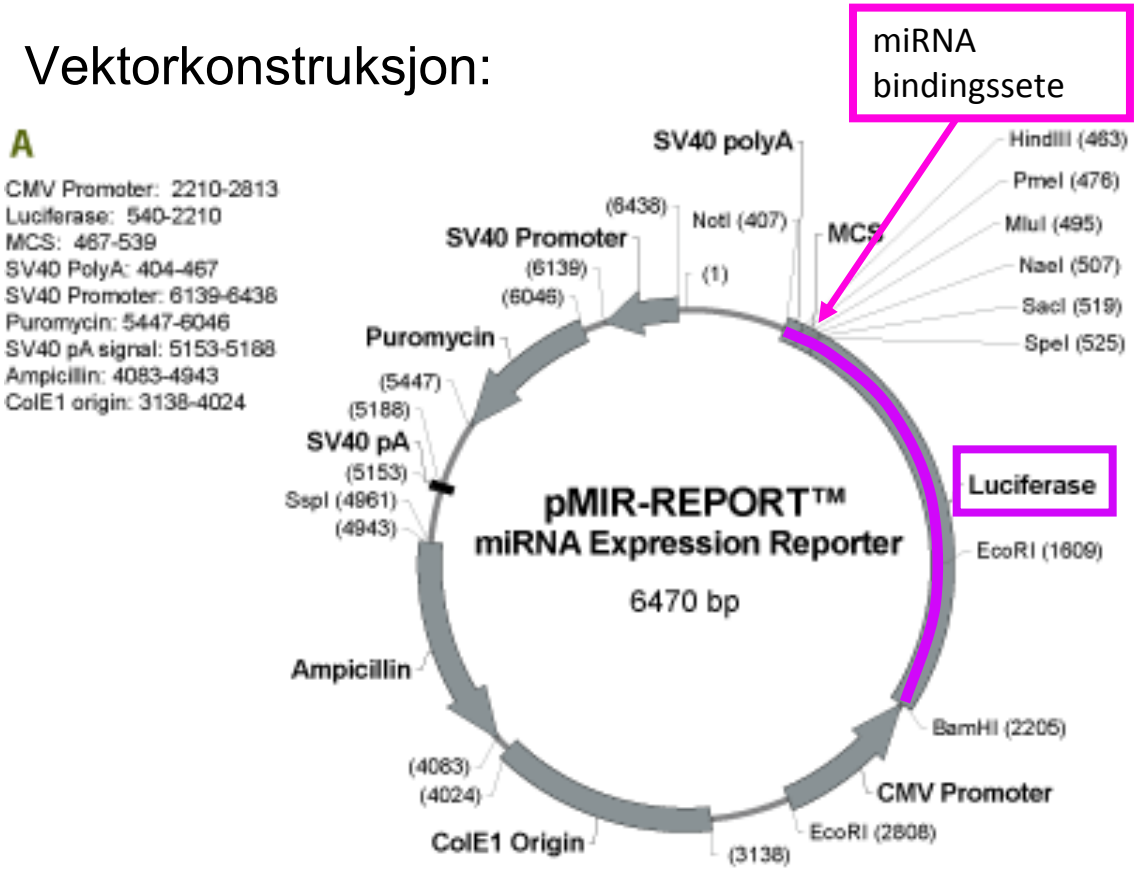
In silico predikerte affinitetsscore og genotypefrekvens

Gene	Predicted miRNA partner	Predicted pairing of target region (top) and miRNA (bottom)	SNP	Allele	Binding affinity score	Genotype frequency (82 breast cancer patients)
EZH2	hsa-miR-101	5' UCAGGAACCUCG-AGUACUGUG 3' 3' AGUC--AAUAGUGUCAUGACAU 5' 5'GCAGUU-(16nt)-CAAAGUACUGUA 3' 3'AGUCAA---UA---GUGUCAUGACAU 5'	rs8829	T	-	1
				G	-	0
				Score difference	-	
PTPRJ	hsa-miR-34b	5′ CAAU-GGC-AAUGGCACUGCCU 3′ 3′ GUUAGUCGAUUACUGUGACGGA 5′	rs2210992	T	655	0,39
				C	251	0,61
				Score difference	404	
Lass6	hsa-miR-505	5′ AGGAAGCCAG–GGUGUUGAC 3′ 3′ UCCUUUGGUCGUUCACAACUG 5′	rs8304	T	601	0,67
				G	222	0,33
				Score difference	379	
MCC	hsa-miR-34a	5′ AA-GAC-AGCUGAGAACGCUGCCA 3′ 3′ UUGUUGGUCGAUUCU-GUGACGGU 5′	rs2227947	C	479	0,32
				T	319	0,68
				Score difference	160	

Resultater

Luciferase reporter assay

Vektorkonstruksjon:

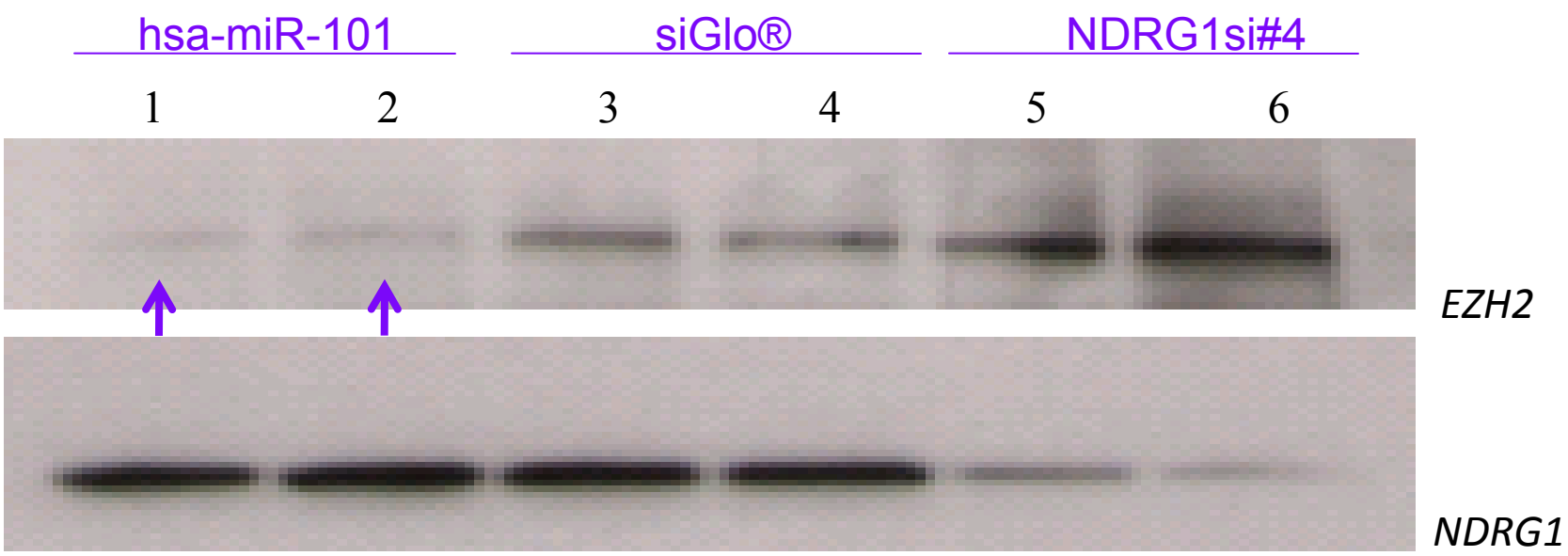


- Hver av SNP allelene i de predikerte, utvalgte miRNA bindingssetene
- Kontrollvektorer med tilfeldig baserekkefølge av bindingssetene → vil ikke binde predikert miRNA partner

mRNA:

Materialer og metoder

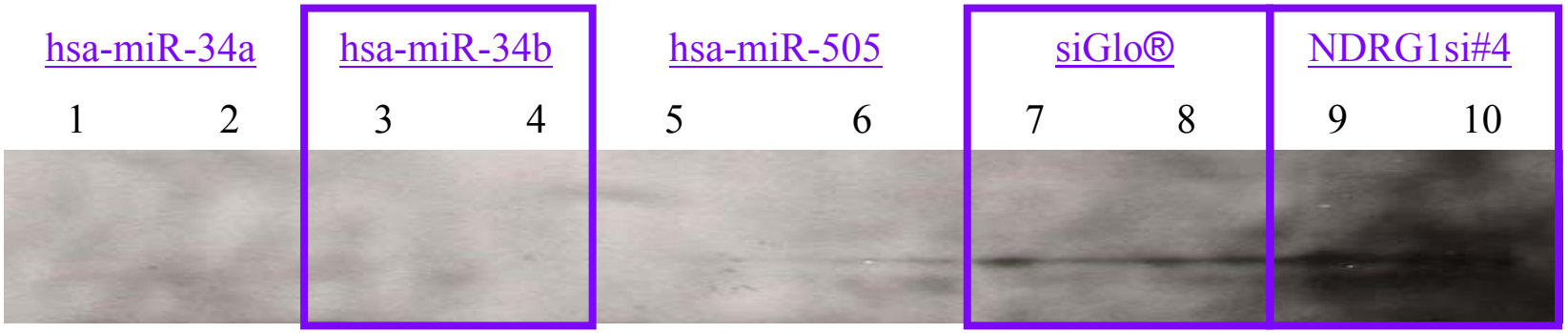
Western blotting med antistoff mot EZH2 av 293T celler transfektert med miR-101



293T celler: homozygot **T** for EZH2 rs8829

Resultater

Western blotting med antistoff mot PTPRJ



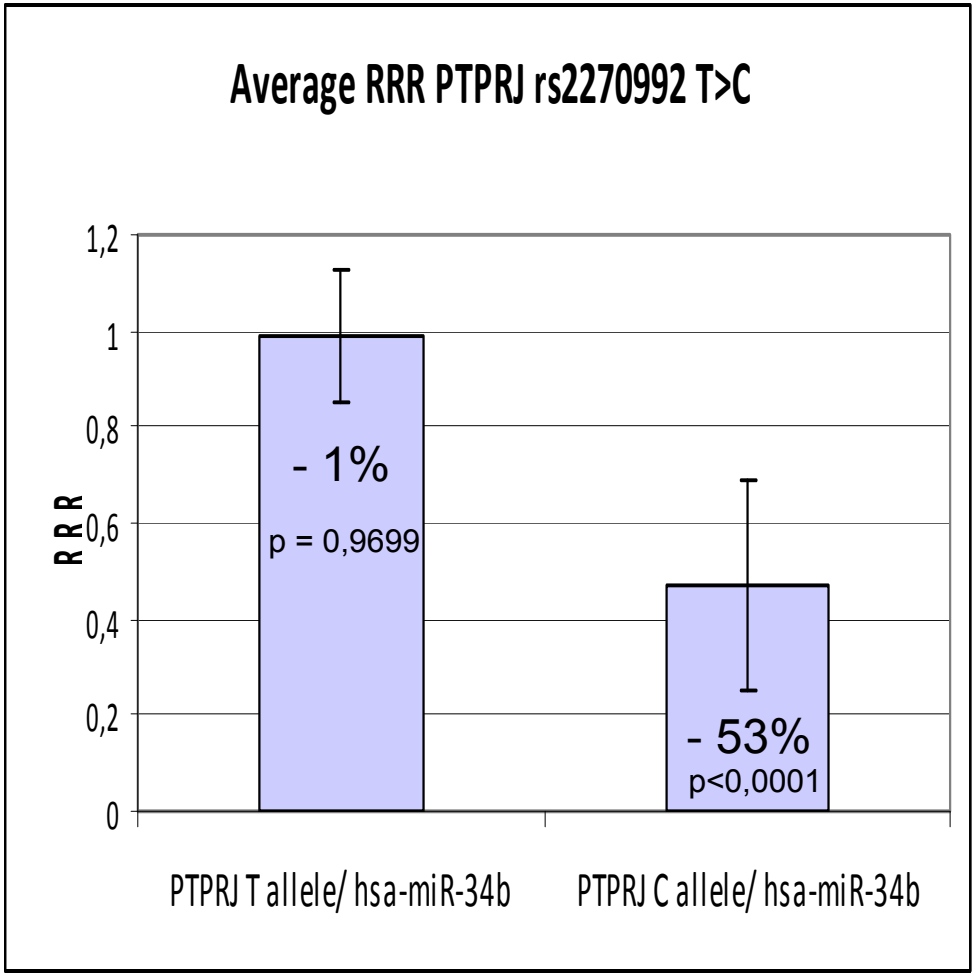
MCF-7 celler: heterozygot TC for PTPRJ rs2270992

- Predikert bindingspartner: miR-34b
- Også nedregulert av miR-34a og miR-505

Aligned miRNAs	Sequence alignment
hsa-miR-34b hsa-miR-34a	1 UAGGCAGUGUCAUUAGCUGAUUG 23 .||||||||| |||||||.||| 1 UGGCAGUGUC-UUAGCUGGUUGU 22
hsa-miR-34b hsa-miR-505	1 UAGGCAGUGUCA----UUAGCUGAUUG 23 .|||| || ||||.||. 1 CGUCAACACUU-GCUGGUUUCCU 22

Resultater

Luciferase reporter assay
PTPRJ – miR-34b

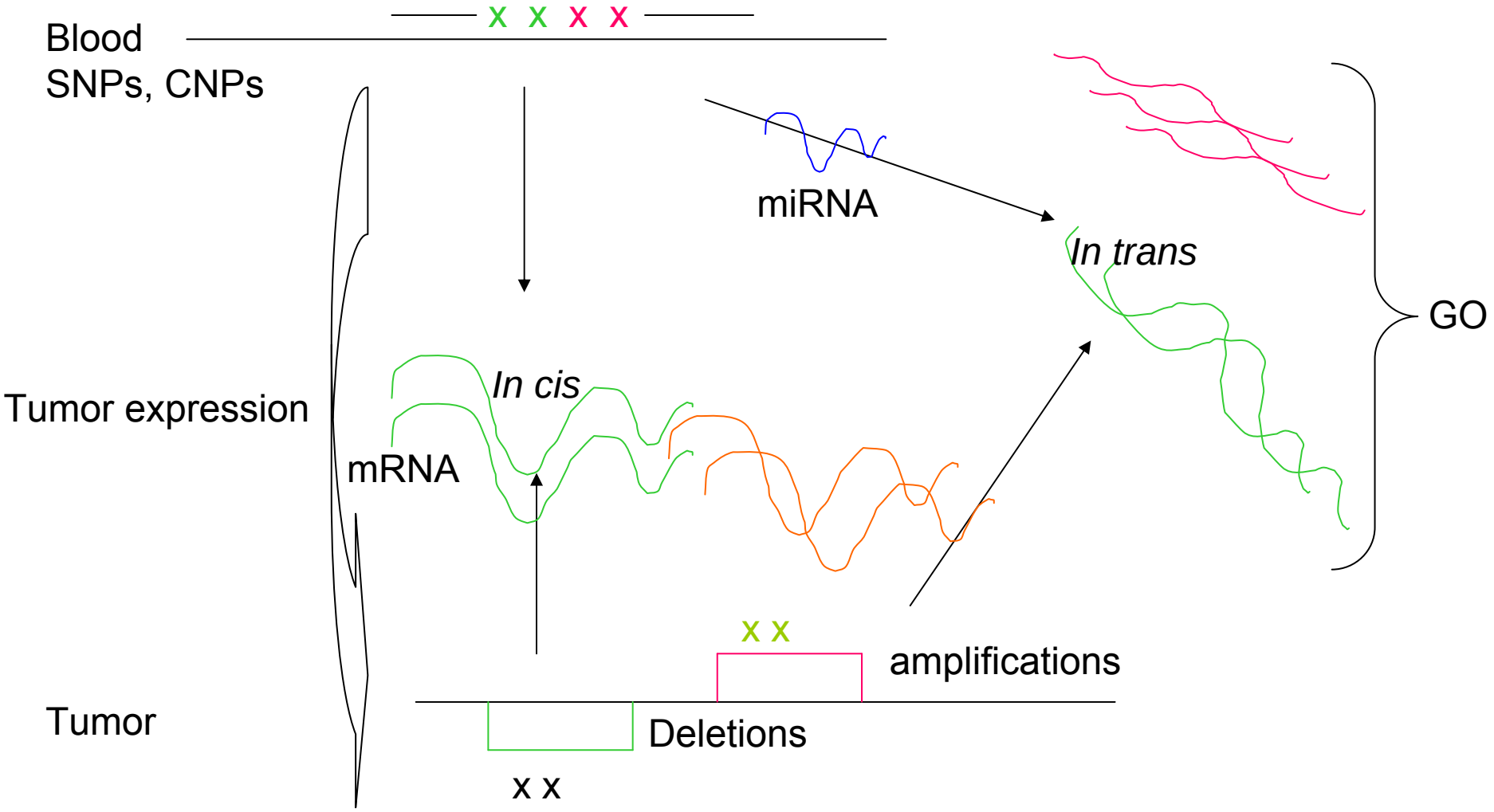


- Gjennomsnittlig RRR:
  - T allel = 0,99 (±0,14)
  - C allel = 0,47 (±0,22)
- T allel vs. C allele: p<0,0001
- T allel vs. PTPRJ kontroll: p = 0,9699
- C allel vs. PTPRJ kontroll: p<0,0001

$$RRR = \frac{\text{PTPRJ allel vektorkonstrukt}}{\text{PTPRJ kontroll vektorkonstrukt}}$$

Resultater

What comes first and what is the relative contribution of each event?



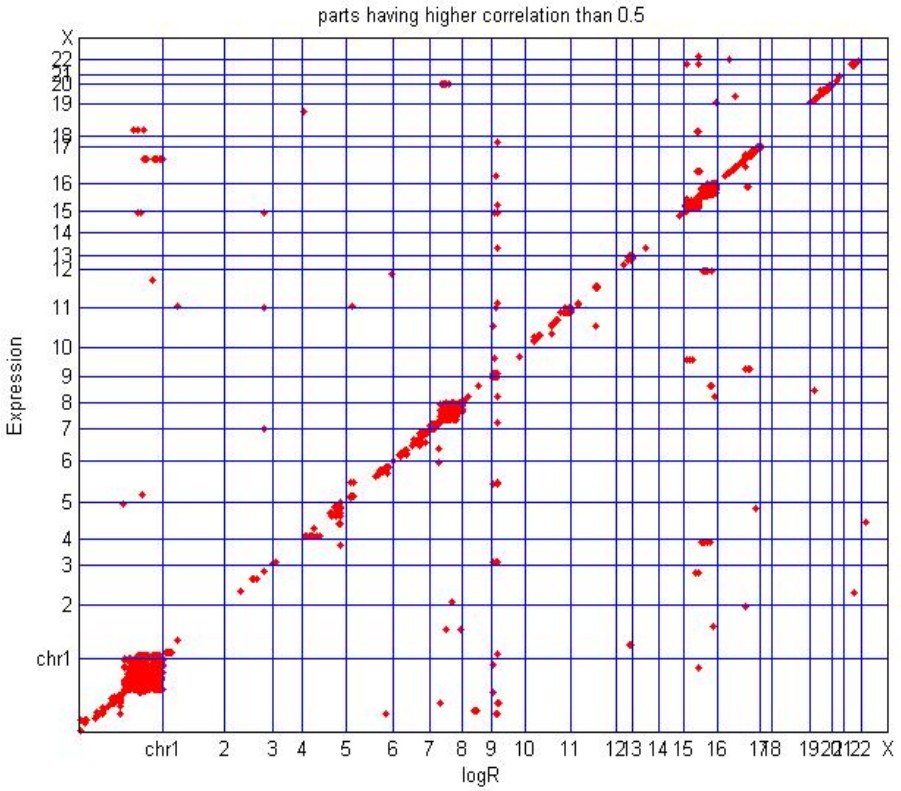
Structure of the data

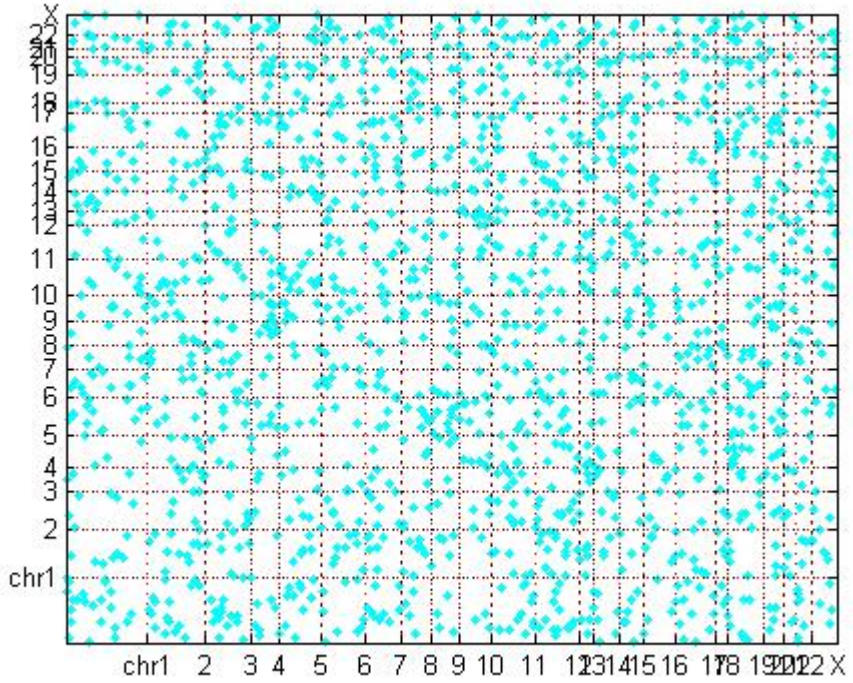
SNPs -	100 000 datapoints
CGH -	44/100/244 000 datapoints
mRNA values	44 000 datapoints
methylation	845 datapoints
miRNA	470 datapoints

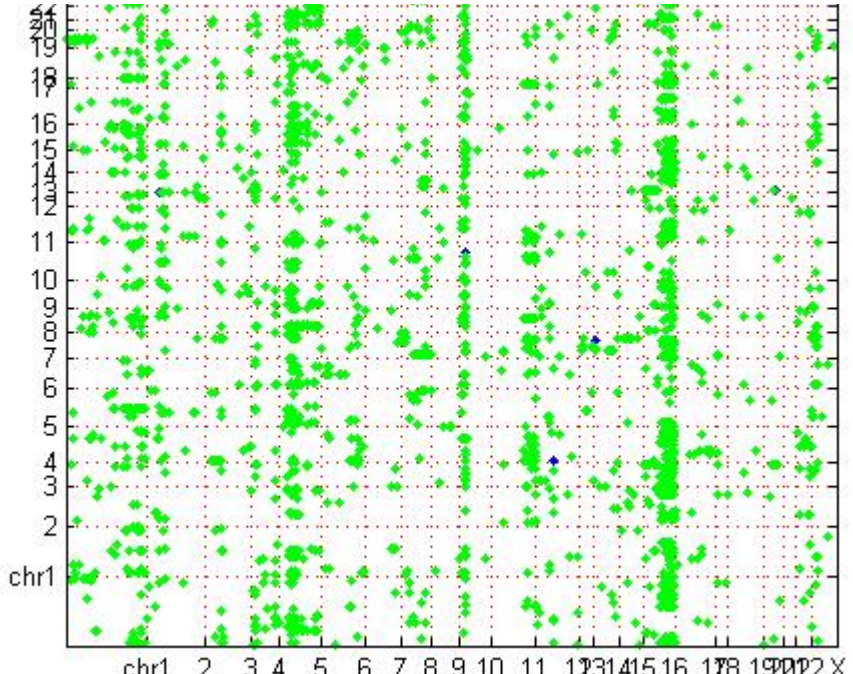
Sorted association analysis

	CGH no change	CGH high	CGH low
mRNA no change		Inhibition of mRNA- Absence of TF Methylation miRNA	Induction of mRNA- SNP regulator Presence of TF binding
mRNA high	Induction of mRNA- SNP regulator Presence of TF binding		???
mRNA low	Inhibition of mRNA- Absence of TF Methylation miRNA	Inhibition of mRNA- Methylation miRNA	

Sorted association analysis







Hiroko Solvang

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Rolf Kåresen, Ullevaal hospital
Bjørn Naume, DNR

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Zohar Yakhini, Agilent
Ole Christian Lingærde
Bettina Kulle
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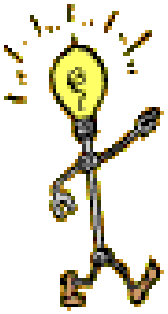
Therese sørlie

grethe ig alnæs

anya tsalenko

silje h. nordgard

arnoldo frigessi



bettina kulle

Illumina:
Daniel Peiffer
Kevin Gunderson