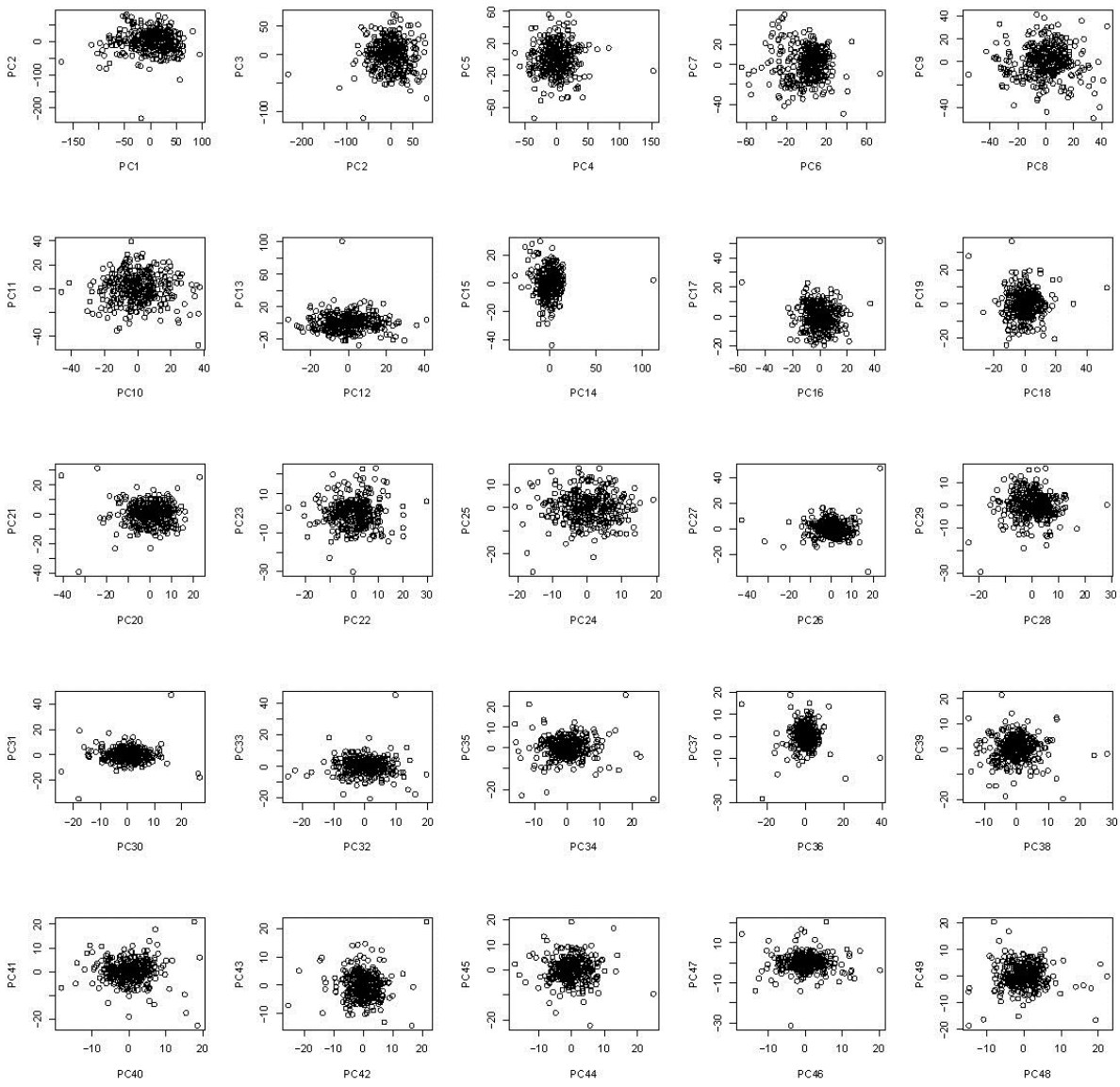
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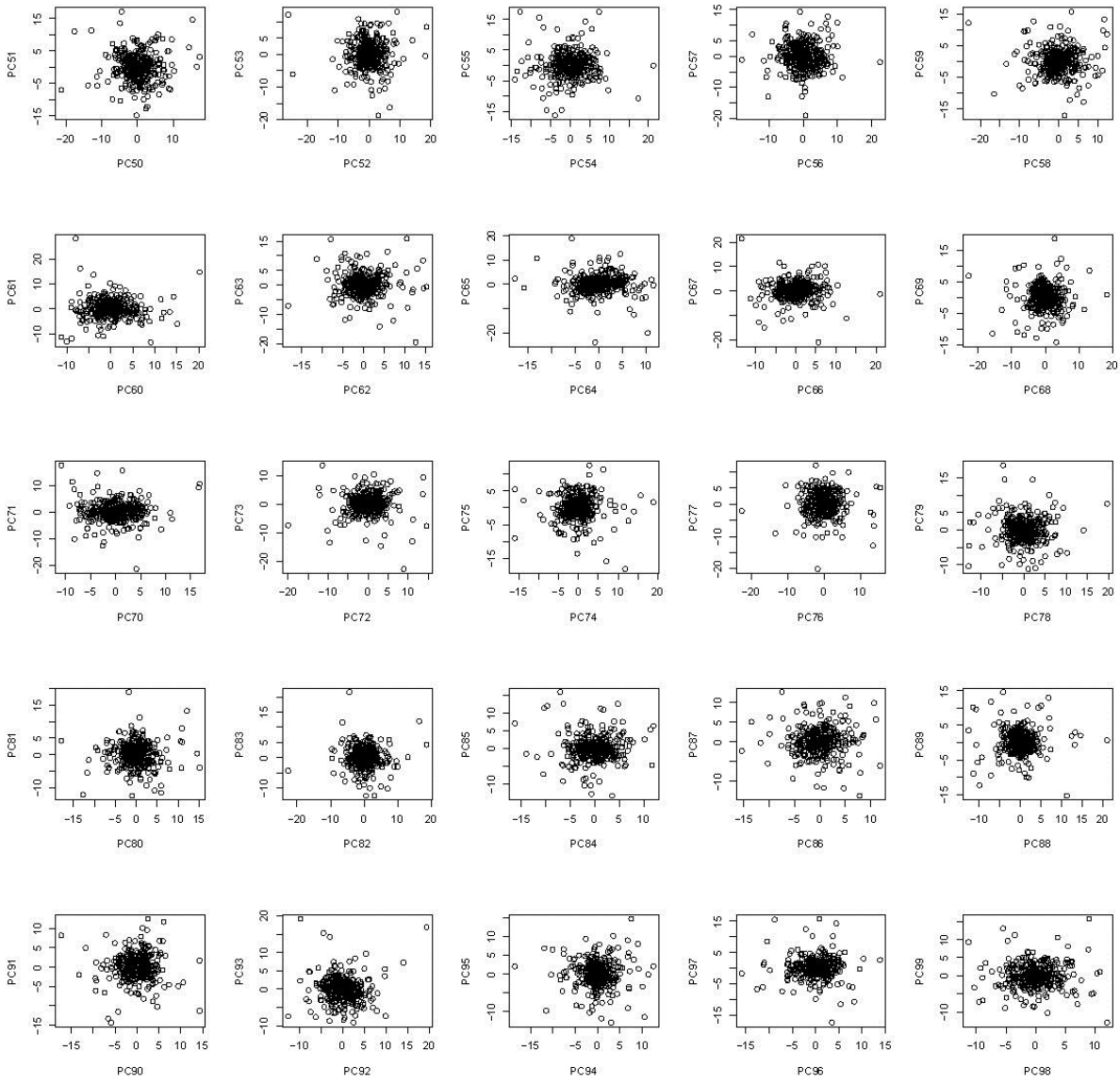
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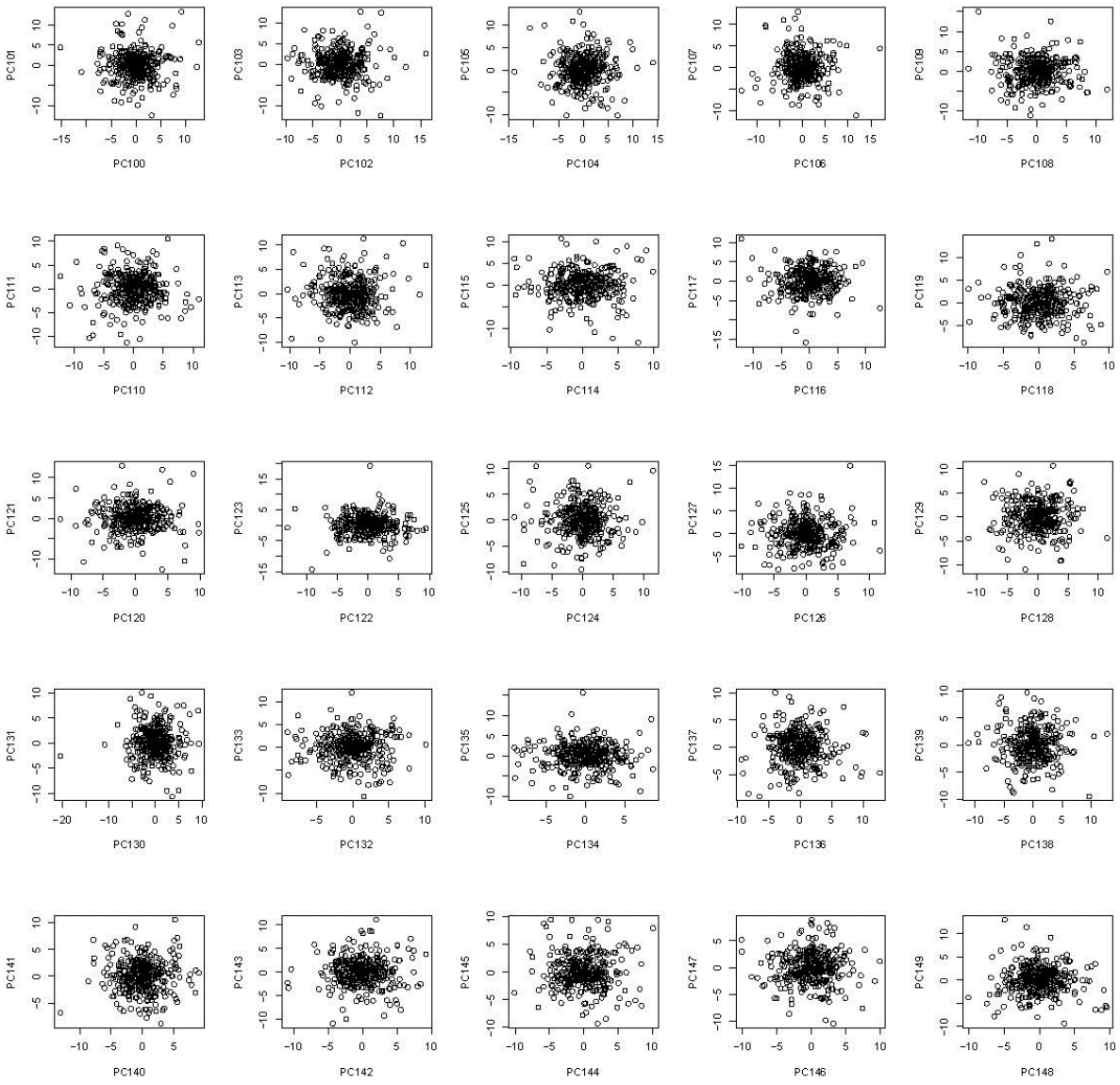
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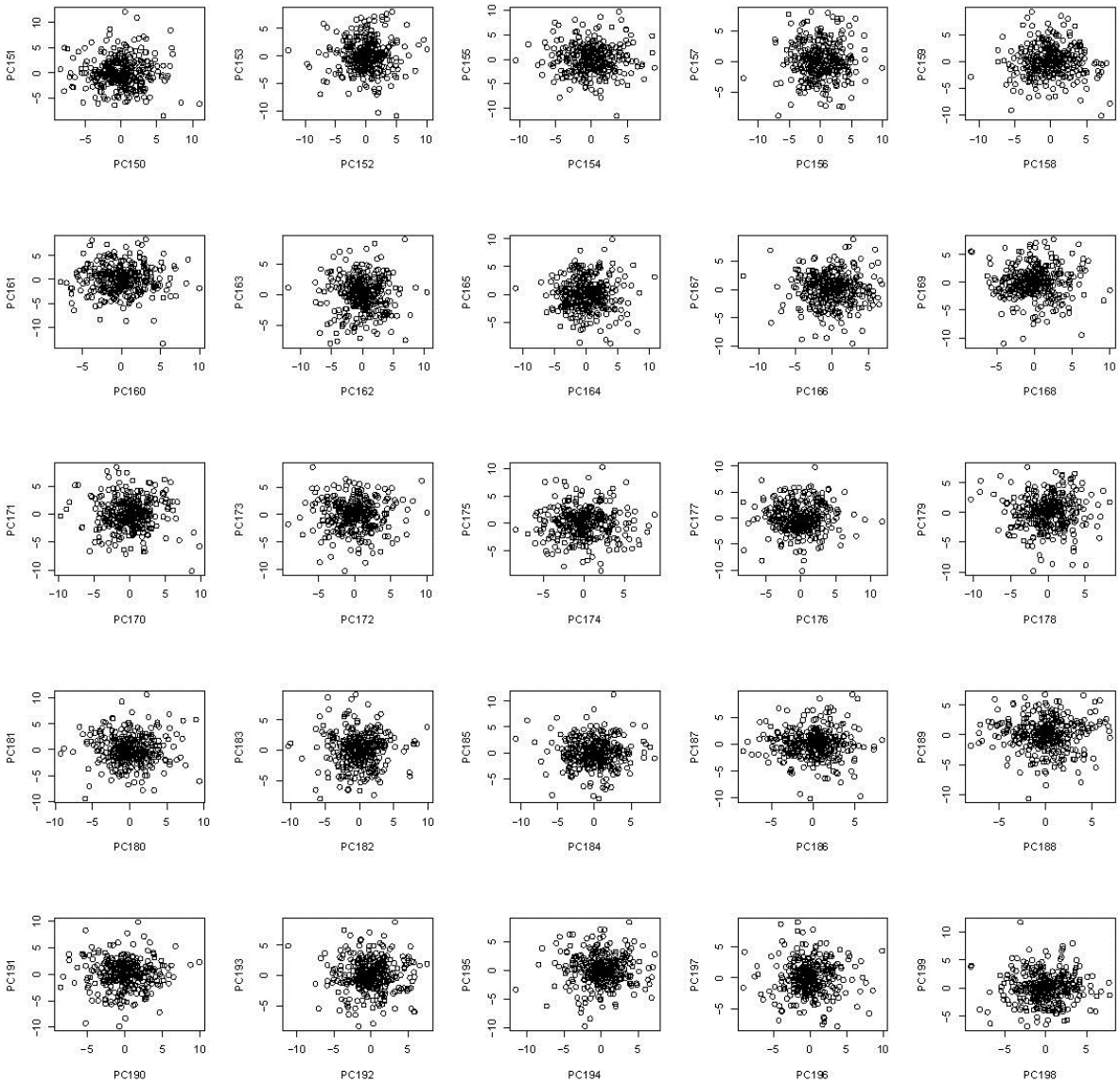
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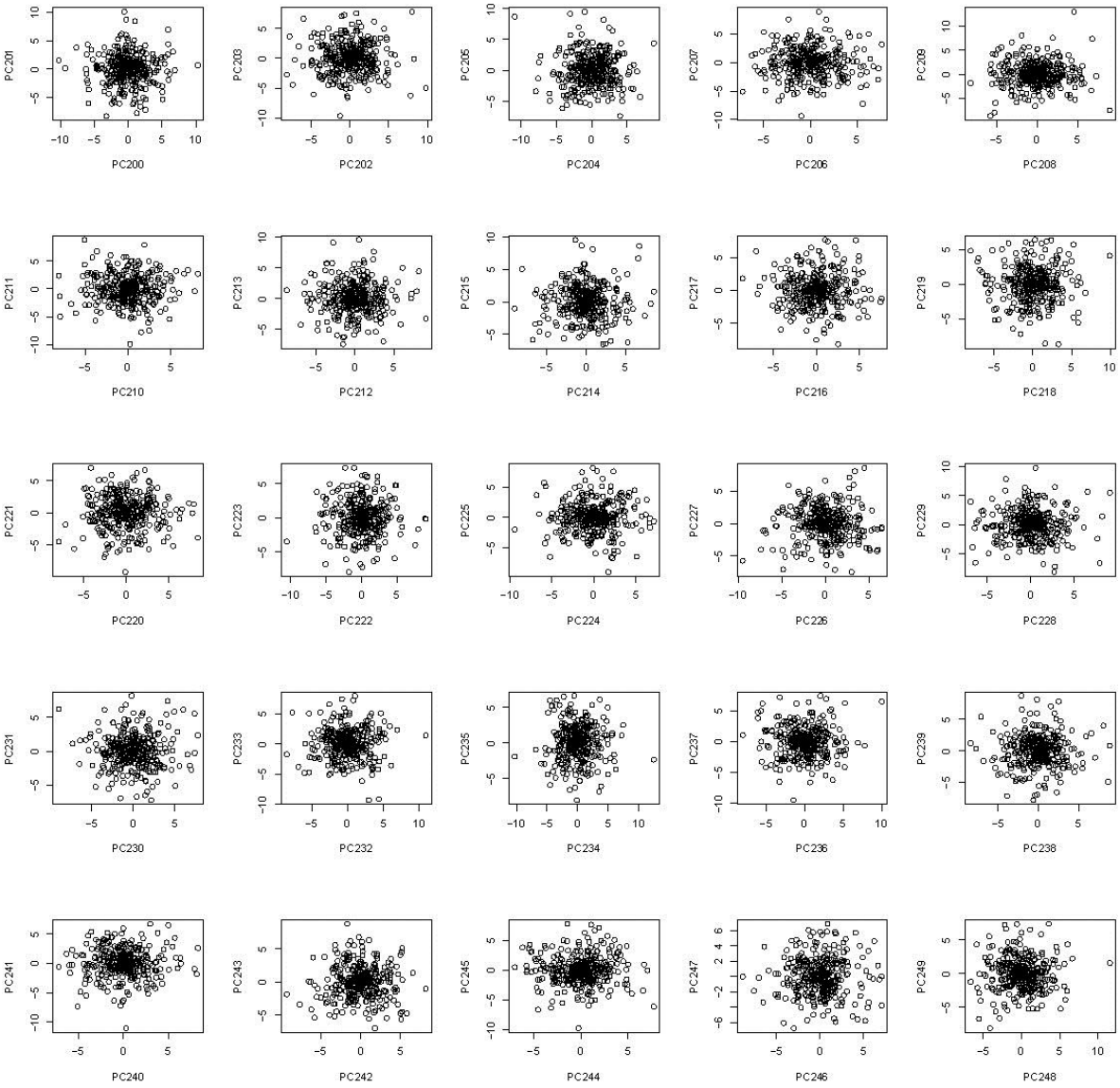
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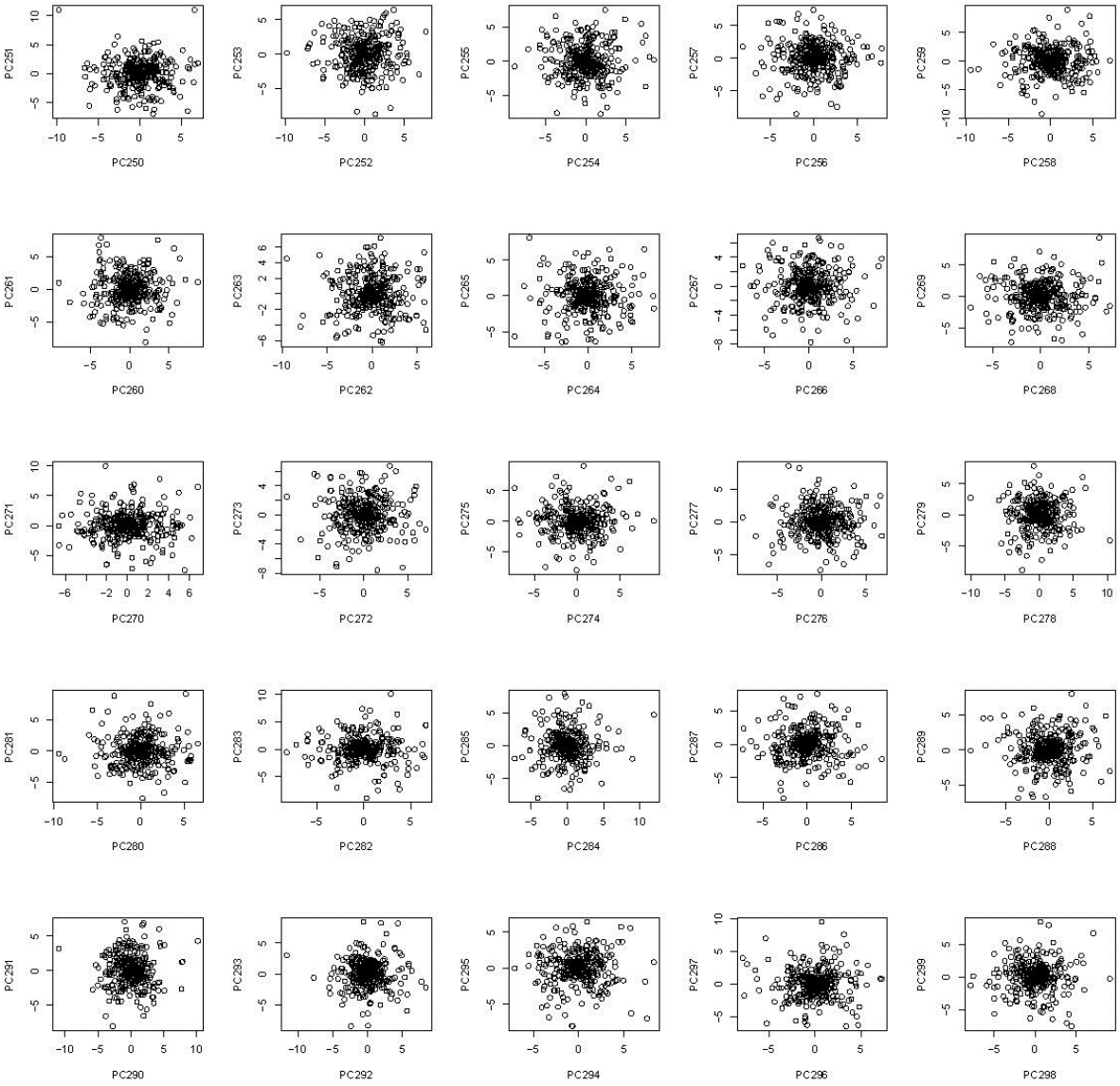
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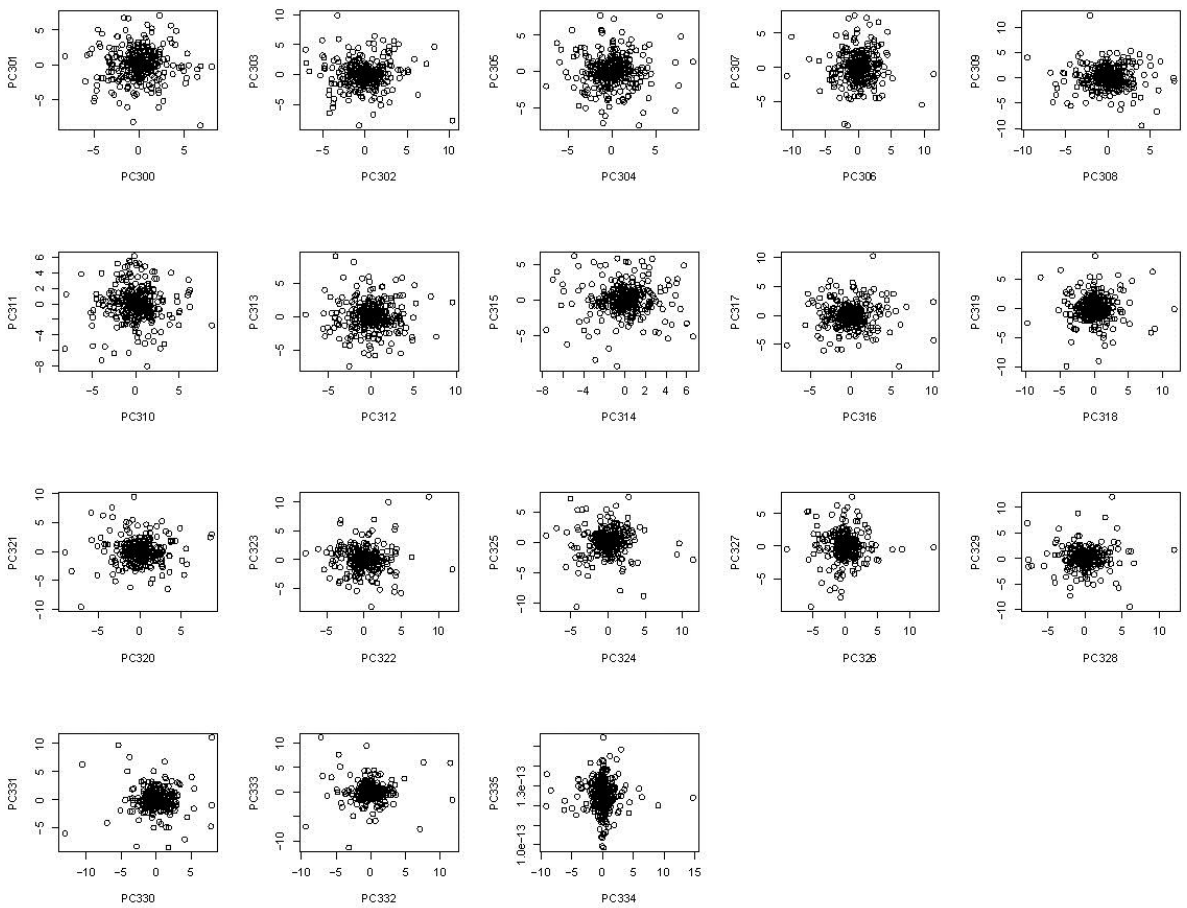


Figure S1 Scores plots of PCs against their adjacent vectors. Demonstrates a homogenous population with no clear substructure or independent clustering of groups of individuals.

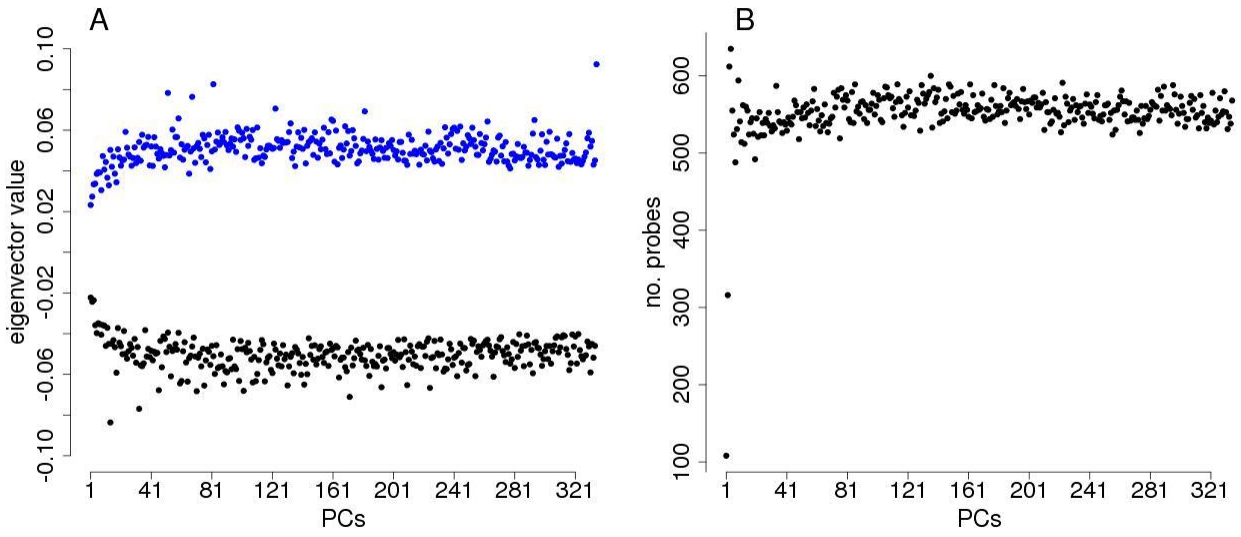


Figure S2 Selection of probes driving PCs**.** (S2A) Maximum (blue) and minimum (black) eigenvector values for each PC. The eigenvector values represent the extent of the correlation between a probe and a PC, with 0 indicating no association. Selection of probes driving each PC is based on the optimal number of probes for each PC that have the same eigenvector value cut off. As multiple probes can contribute a small amount of variance to each PC it is reasonable that a low cut off value can pick up many of the significant probes driving each PC. Probes that have an eigenvector value of greater than 0.02 or less than -0.02 were selected for further biological enrichment analysis as this incorporated all the maximally and minimally expressed probes in this section. (S2B) Selection of probes at this cut off value enabled approximately similar numbers of probes to be selected for each PC. The slightly lower number of probes that are selected in the initial PCs is due to the lower maximum and minimum eigenvector values in these PCs as shown in (S2A).

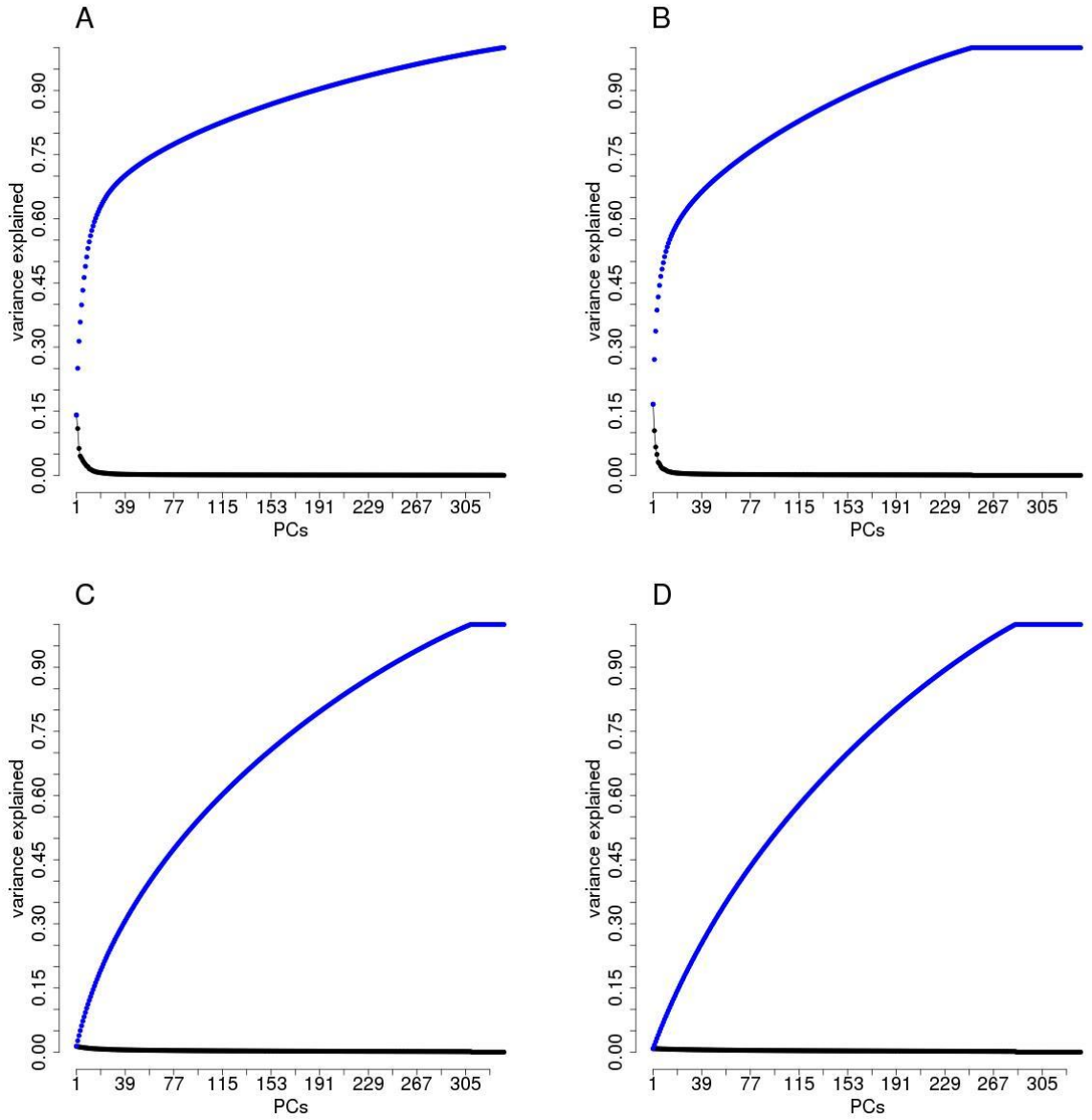


Figure S3 Variance explained by PCs. Calculated from the eigenvalues obtained from the Singular Value Decomposition. Variance explained by each PC is plotted in black and cumulative variance in blue. A) Normalized dataset, B) Corrected with linear models, C) PC25 corrected D) PC50 corrected. All variances add up to 1. Cum

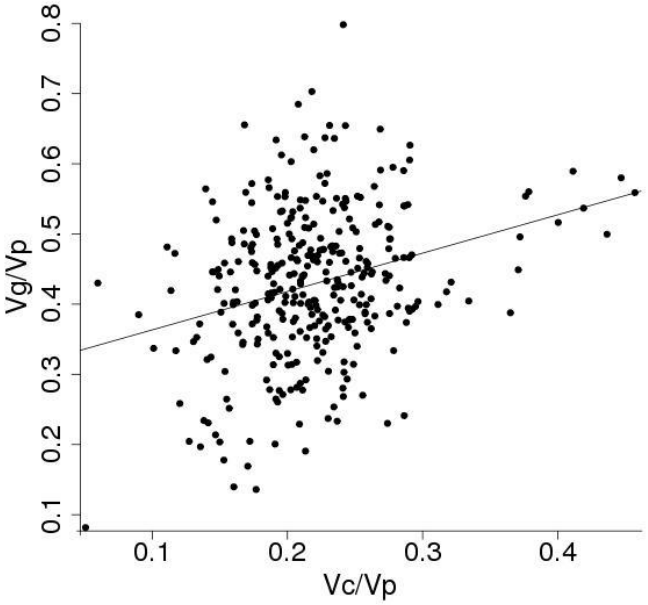
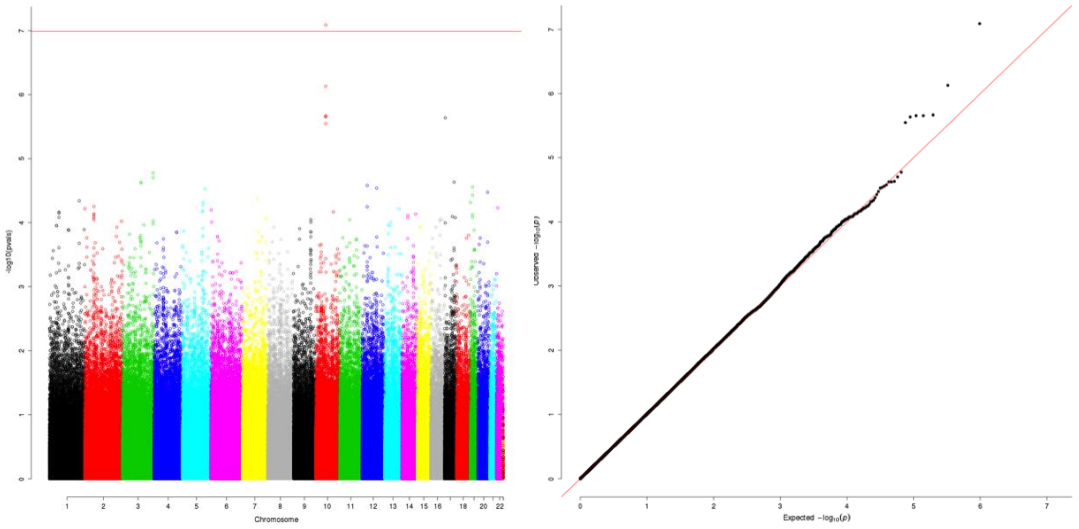
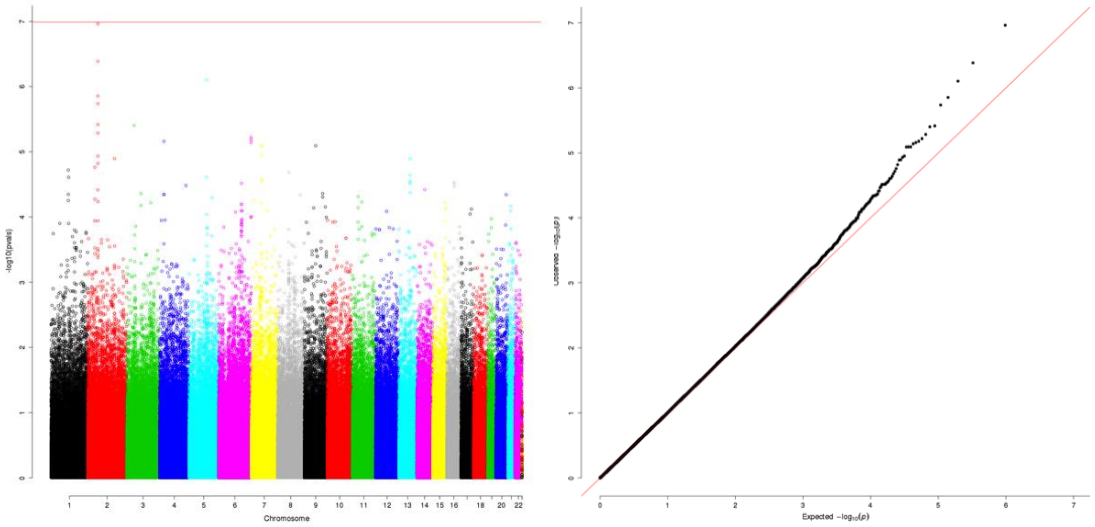


Figure S4 Correlation between additive genetic and common environmental factors. Significant association (p = 8.57e-08 and R2=0.08) between the common environment and genetic components estimated in an AC and AE models. The proportion of common environment variance was calculated by dividing the variance attributed to common environment (Vc) by the total phenotypic variance (Vp). The proportion of genetic variability (heritability) was calculated by dividing the additive genetic component (Vg) by the total phenotypic variance (Vp). This result indicates that the heritability estimates obtained are confounded with common environment variance and therefore inflated upwards by common family effects.

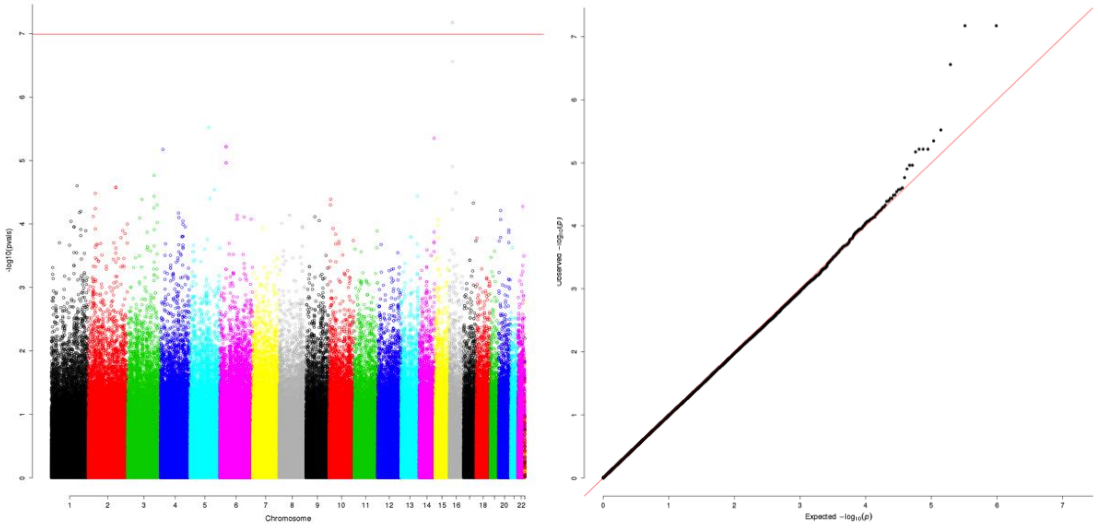
PC22



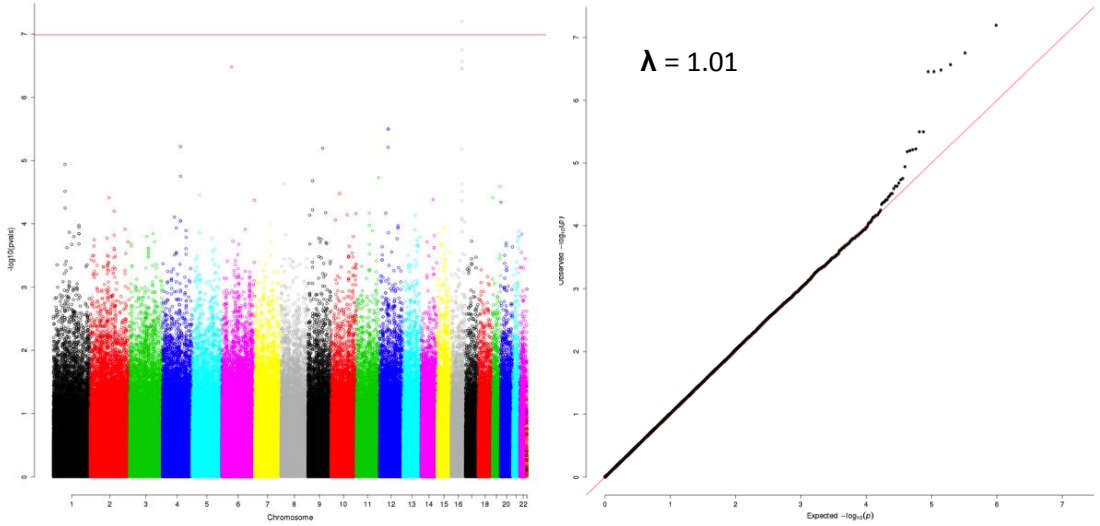
PC35



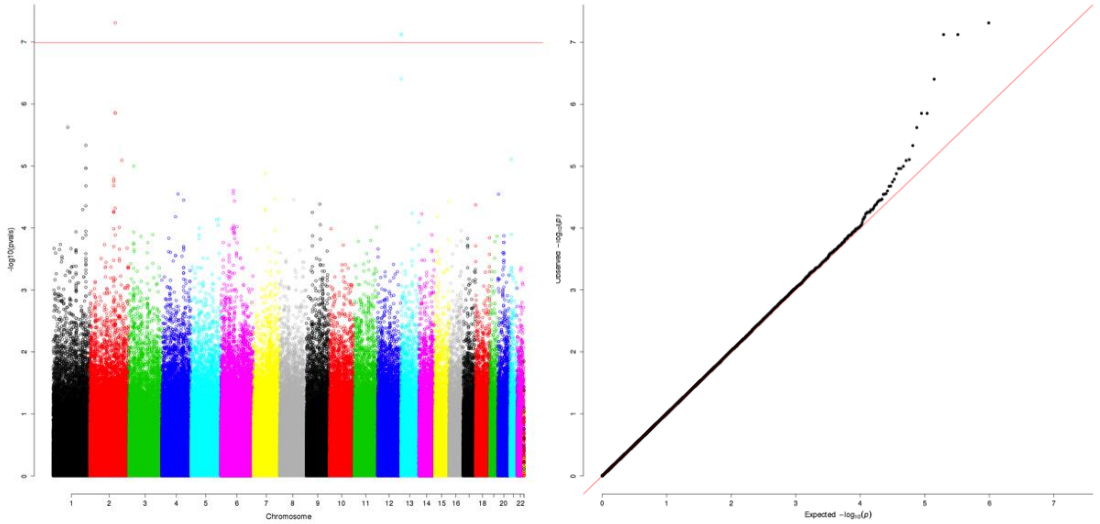
PC81



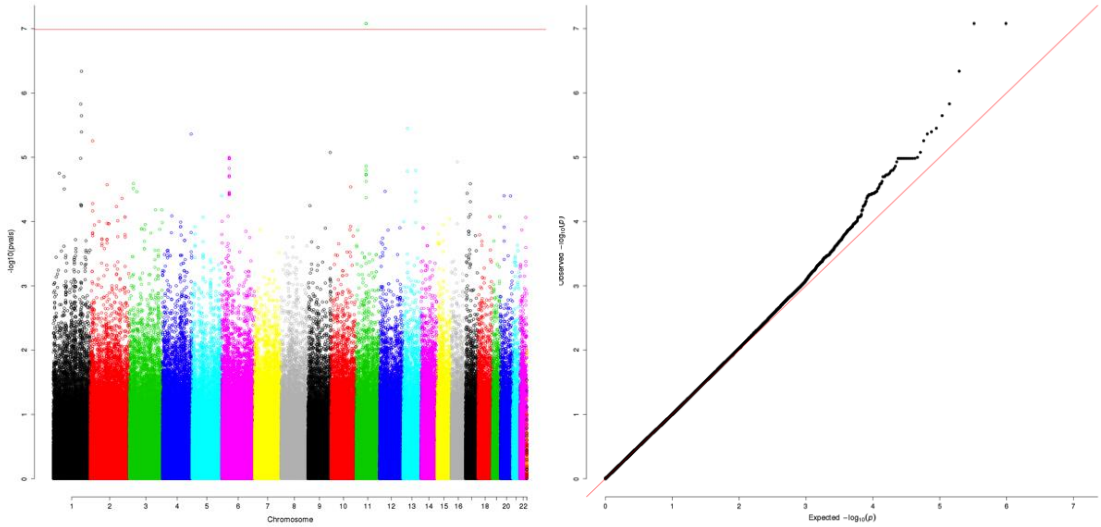
PC100



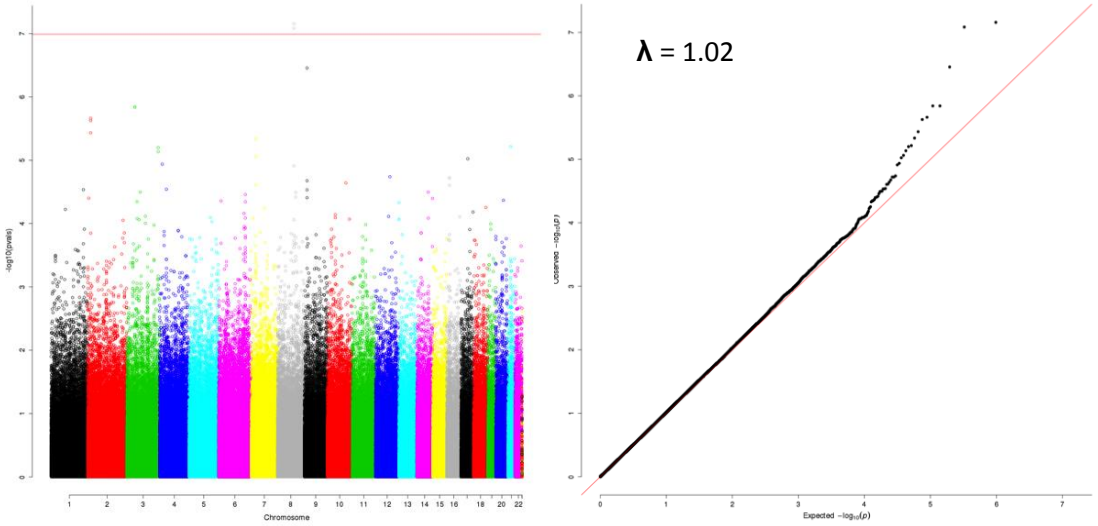
PC106



PC110



PC119



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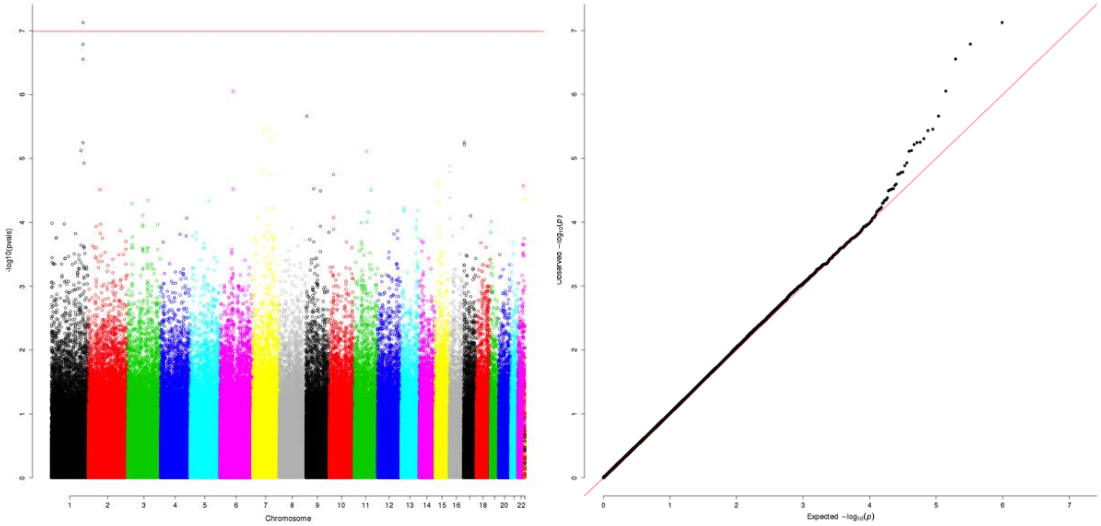

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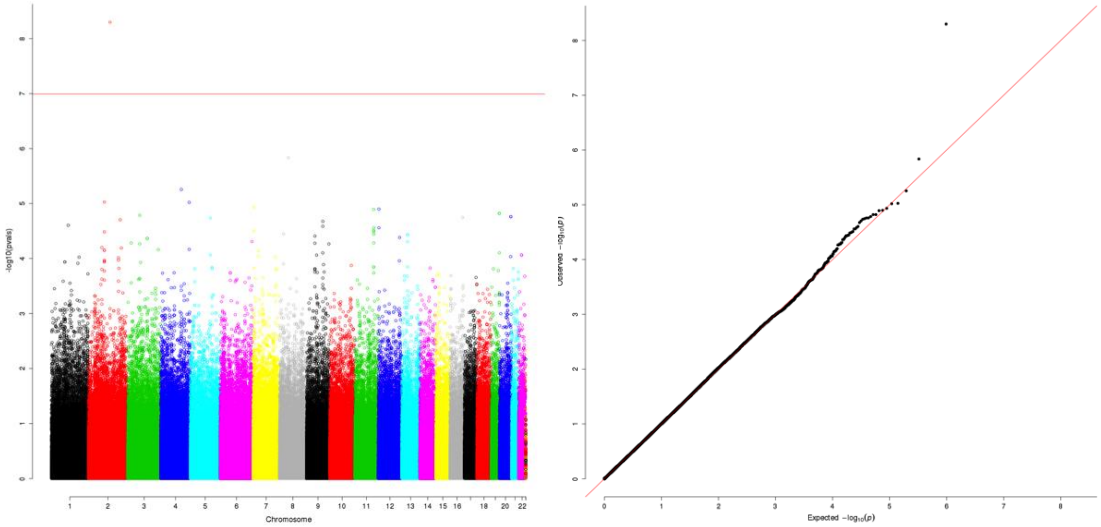

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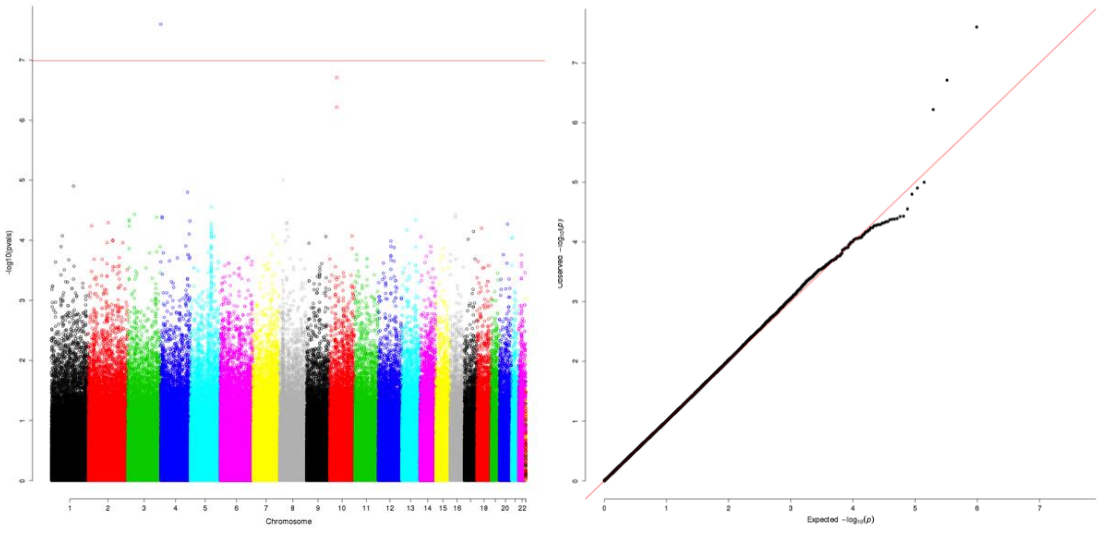

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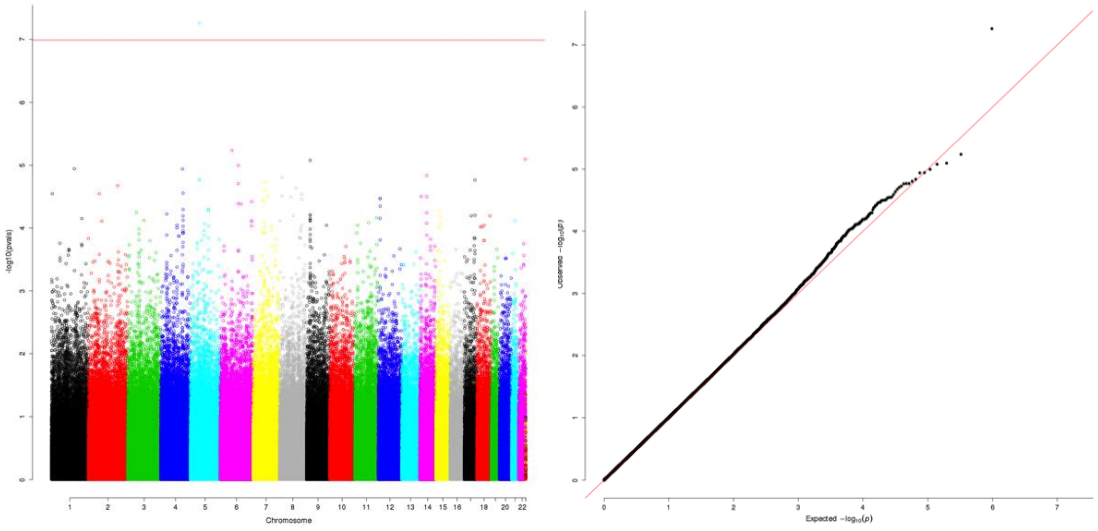

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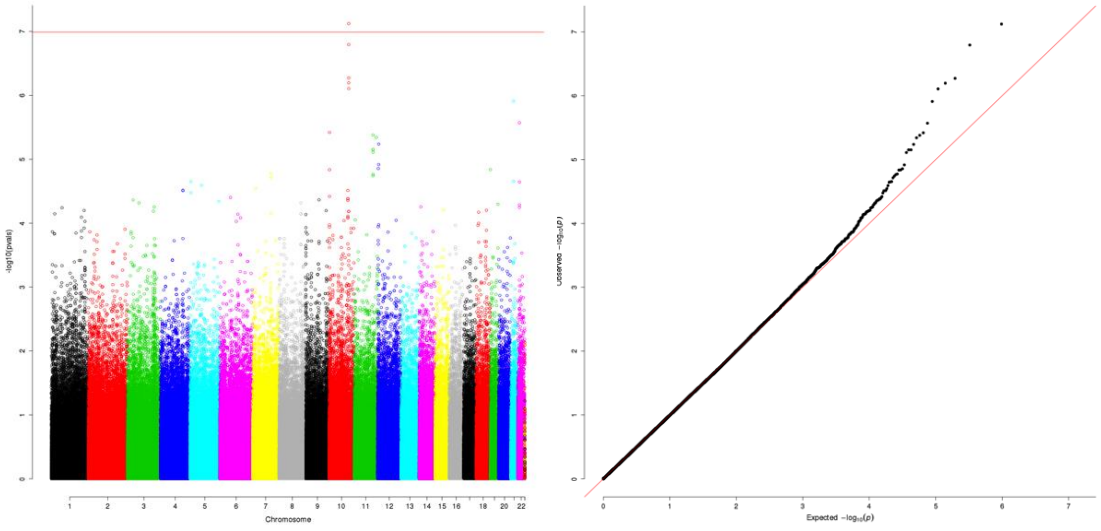

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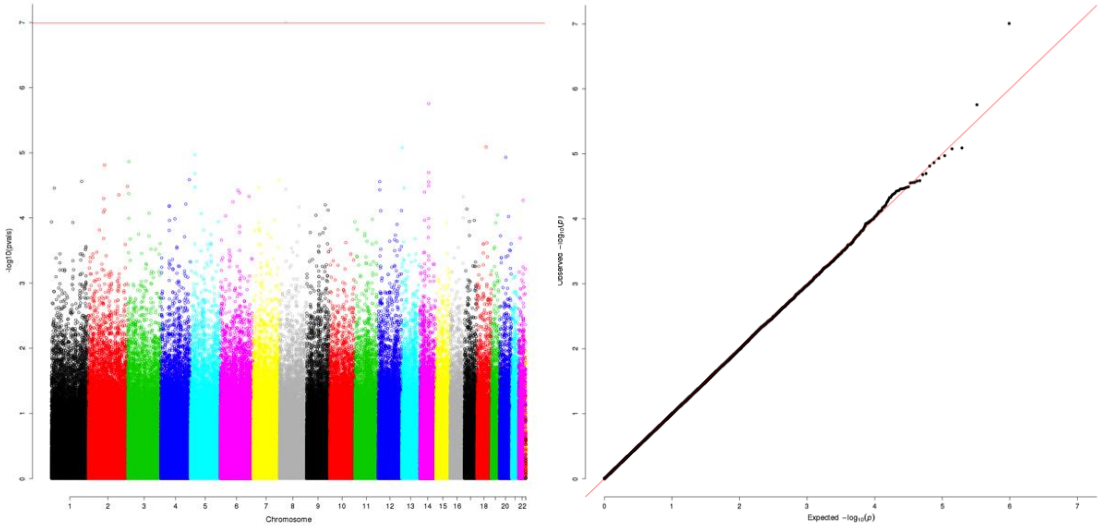

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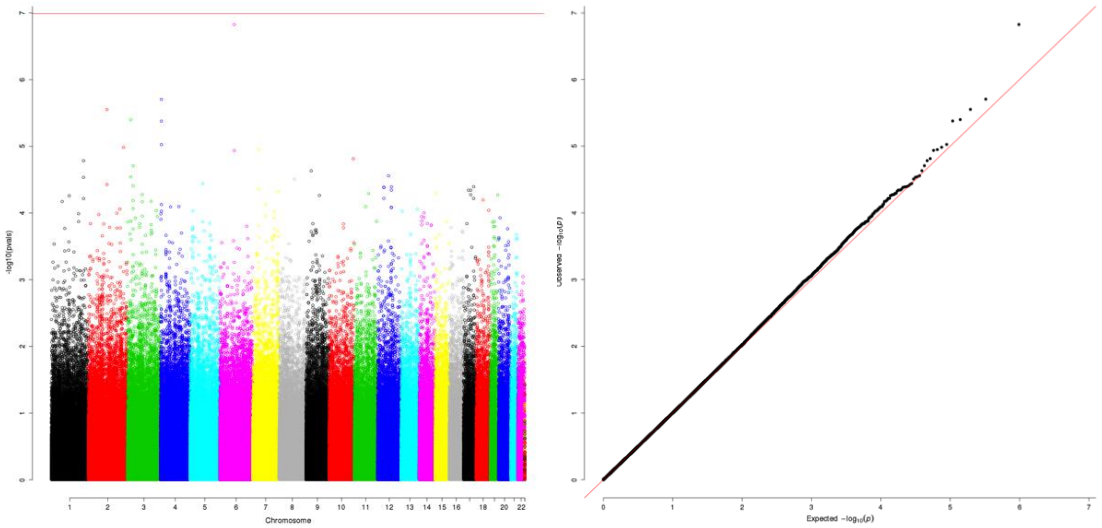

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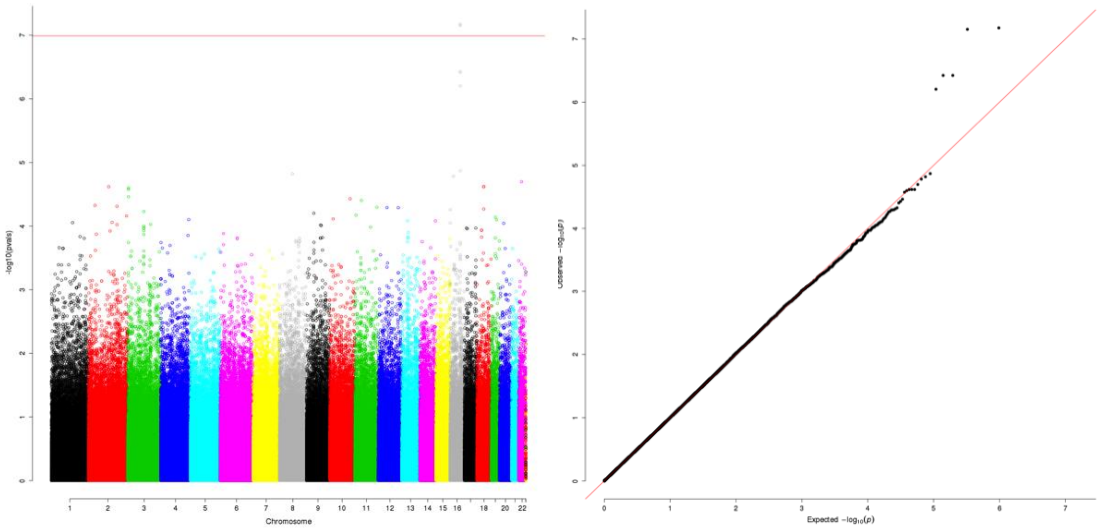
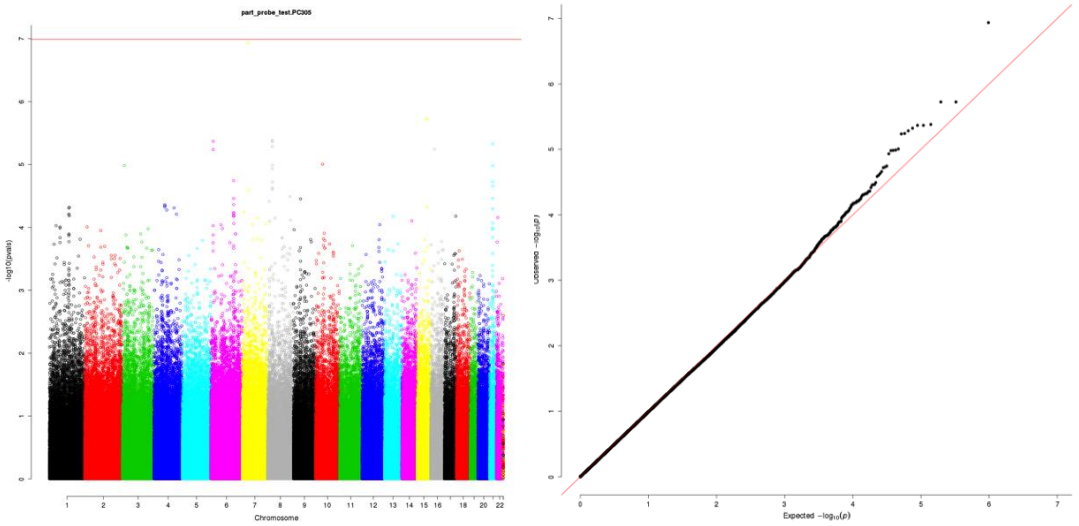
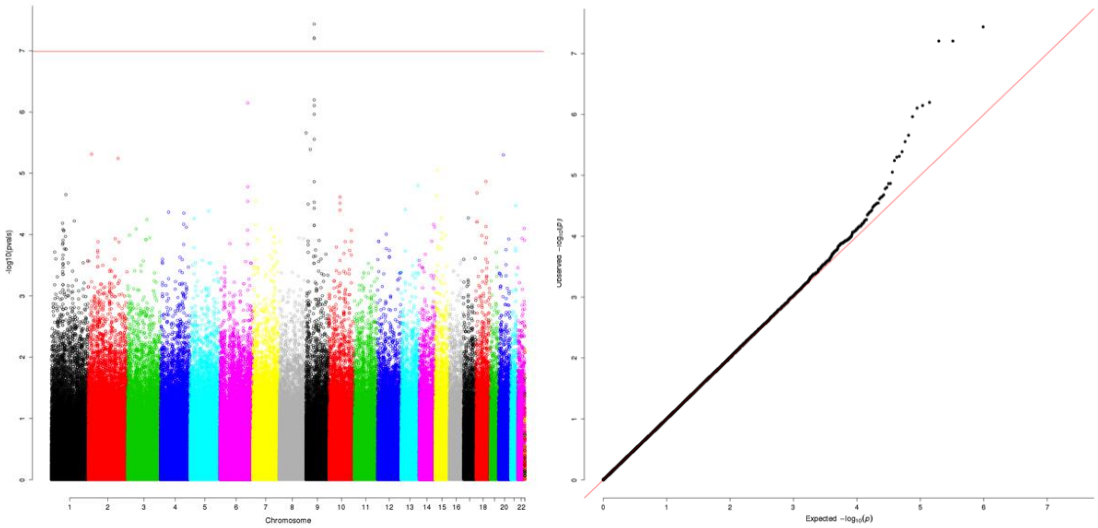


PC305



PC323



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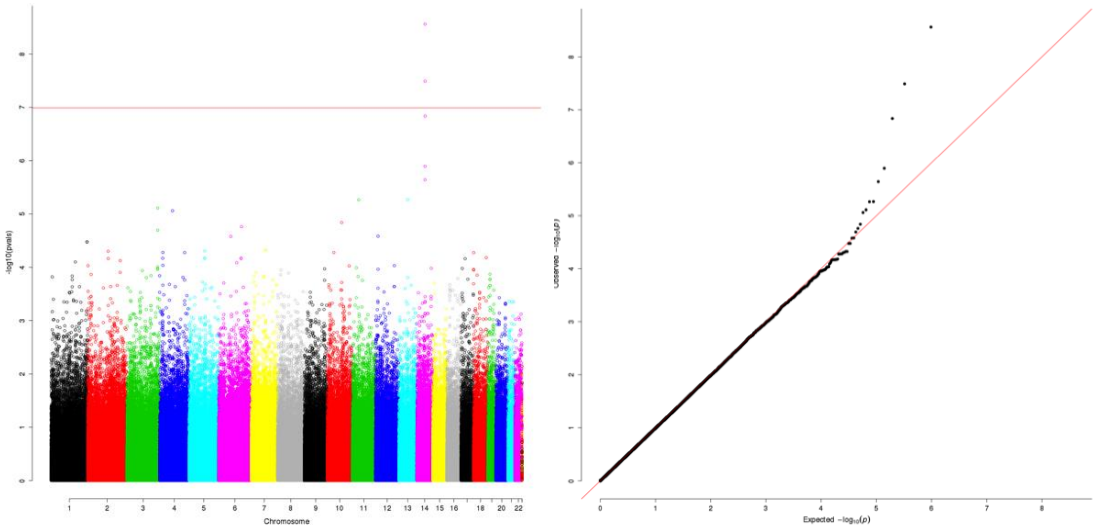
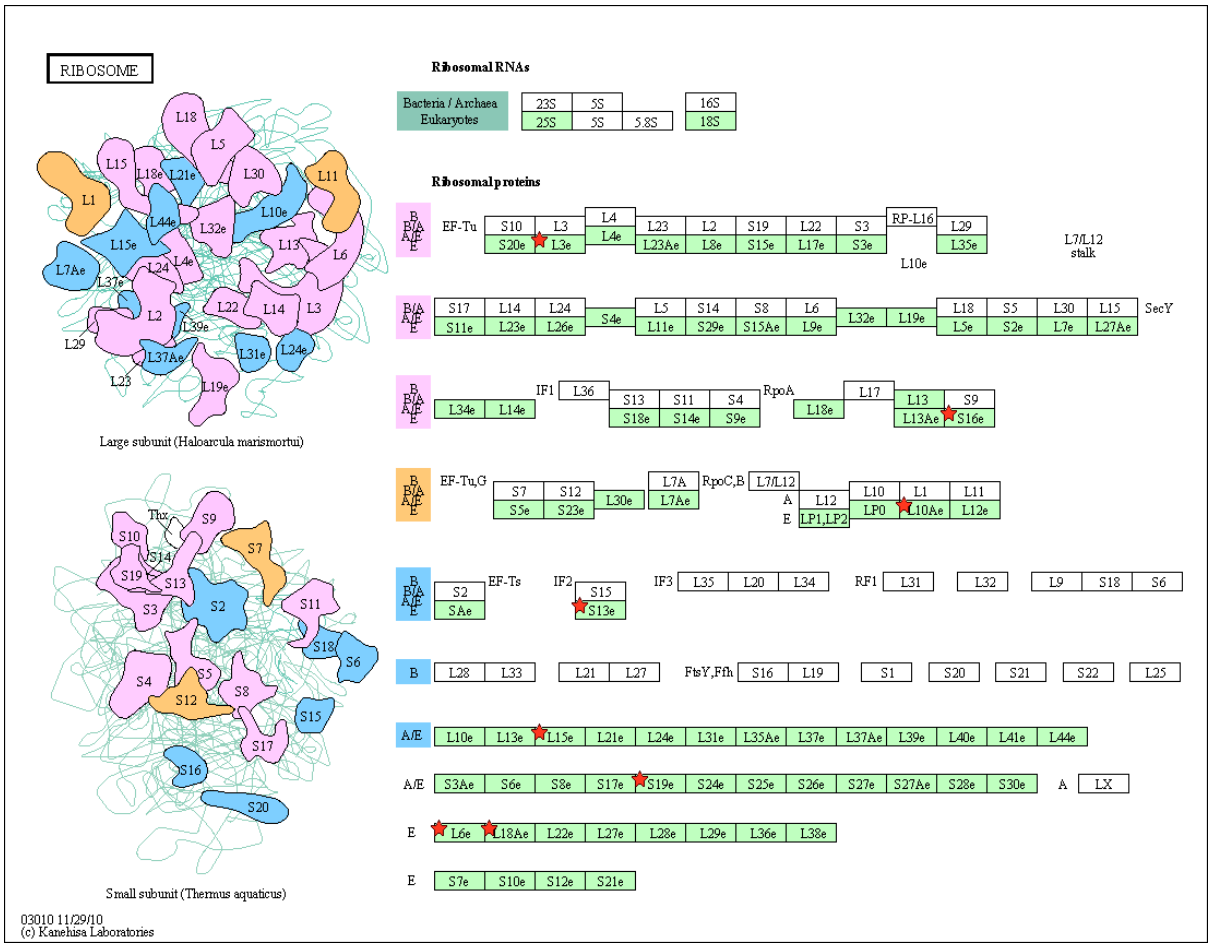
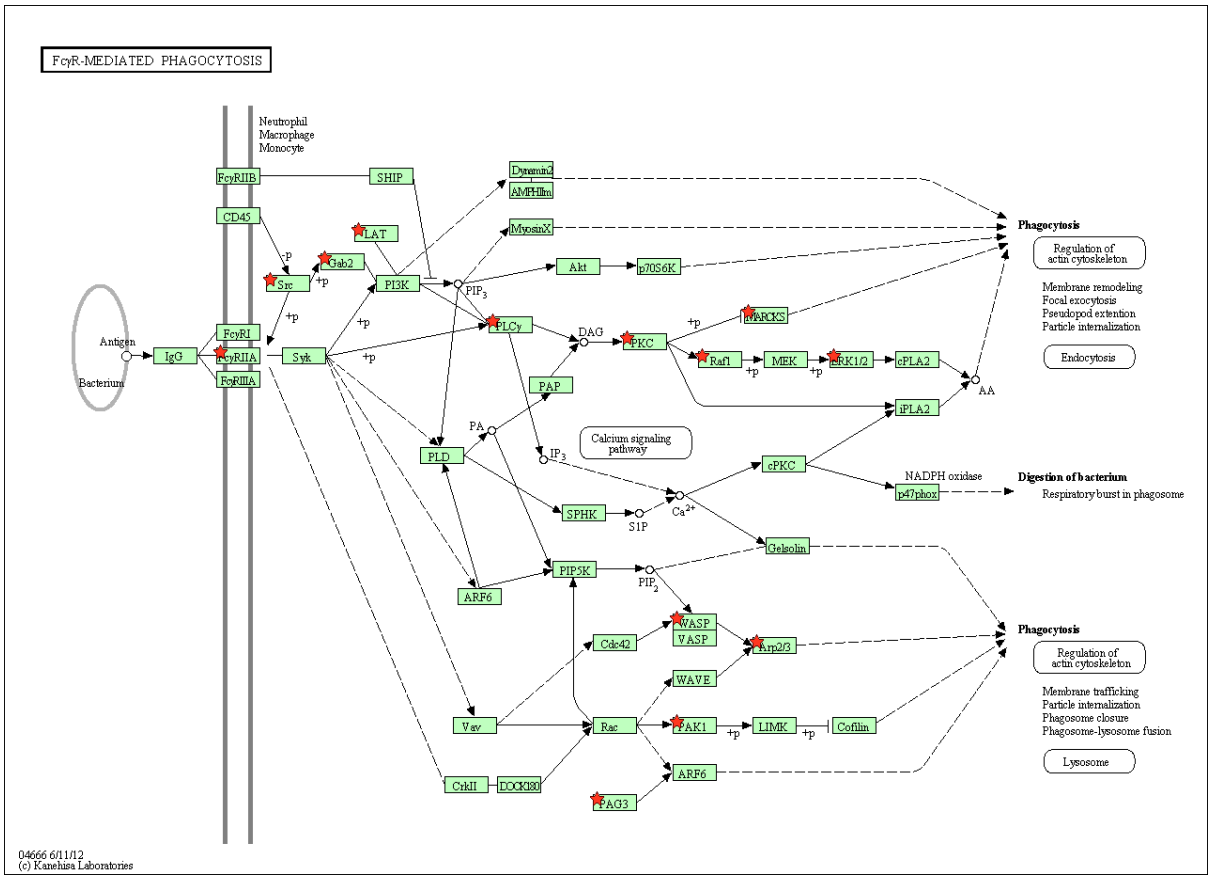


Figure S5 Manhattan and QQ plots. Manhattan and QQ plots for each PC with a significant SNP associated in Table S1. The significance value cut-off is drawn as a red line drawn on the Manhattan plots and is based on the Bonferroni correction for each PC. The QQ plot shows the expected p-values vs. the observed p-values in the study and the lambda value gives a numerical estimation of any inflation in the statistics.

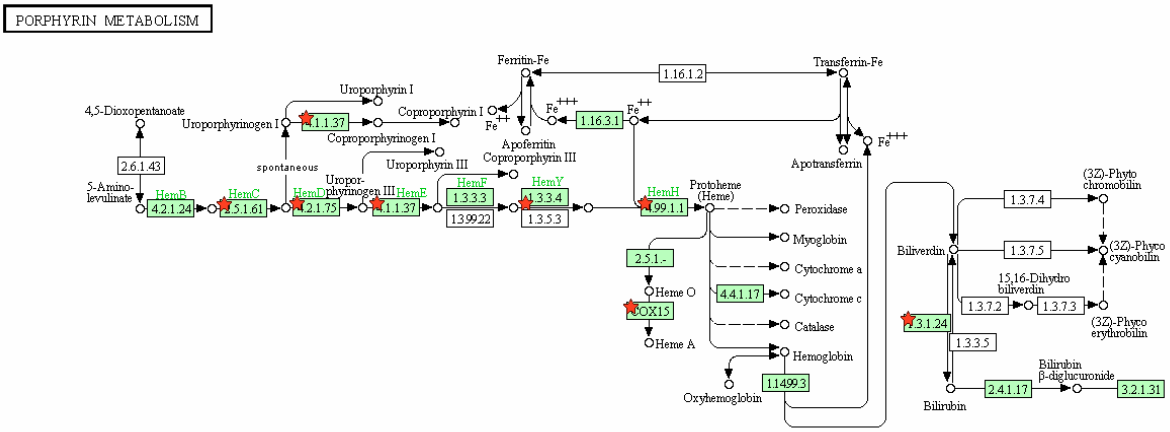
PC1


RIBOSOME
Large subunit (Haloarcula marismortui)
Small subunit (Thermus aquaticus)
03010 11/29/10
(c) Kanehisa Laboratories
Ribosomal RNAs
Bacteria / Archaea
Eukaryotes
23S 5S 5.8S 16S
25S 5S 18S
Ribosomal proteins
EF-Tu
RP-L16
L10e
L7/L12 stalk
SecY
IF1
RpoA
EF-Tu,G
L7A
L7Ae
RpoC,B
L7/L12
L12
LP1,LP2
EF-Ts
IF2
IF3
RF1
FtsY,Ffh
Thx

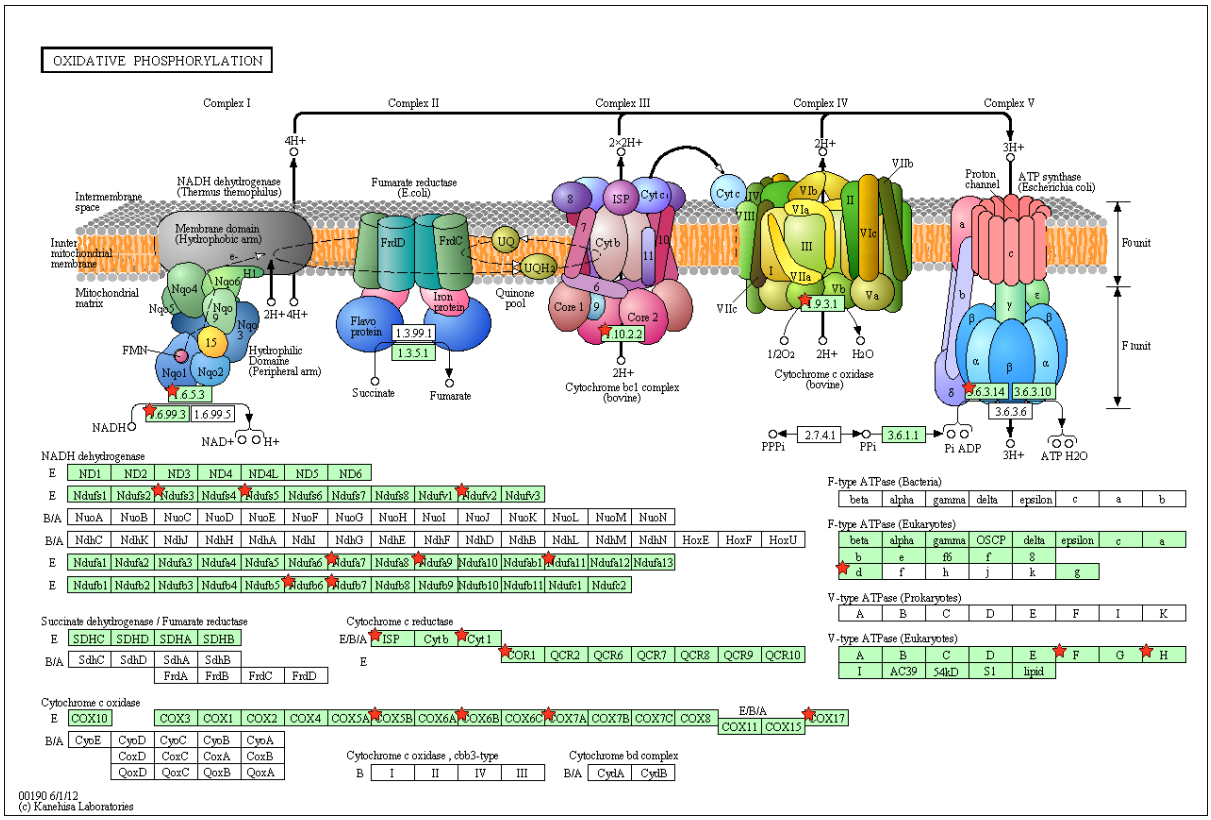
PC3


FcγR-MEDIATED PHAGOCYTOSIS
Neutrophil
Macrophage
Monocyte
FcγRIIB
SHIP
CD45
LAT
Gab2
Src
PI3K
Dynamin2
AMPHIIm
MyosinX
Akt
p70S6K
Phagocytosis
Regulation of actin cytoskeleton
Membrane remodeling
Focal exocytosis
Pseudopod extention
Particle internalization
Endocytosis
Antigen
IgG
Bacterium
FcγRI
FcγRIIA
FcγRIIIA
Syk
PLCγ
DAG
PKC
pPAK/KS
Raf1
MEK
ERK1/2
cPLA2
AA
PAP
PA
iPLA2
PLD
Calcium signaling pathway
IP3
cPKC
NADPH oxidase
p47phox
Digestion of bacterium
Respiratory burst in phagosome
SPHK
S1P
Ca2+
Gelsolin
PIP5K
PIP2
ARF6
WASP
VASP
Cdc42
Arp2/3
Phagocytosis
Regulation of actin cytoskeleton
WAVE
Membrane trafficking
Particle internalization
Phagosome closure
Phagosome-lysosome fusion
Vav
Rac
PAK1
LIMK
Cofilin
Lysosome
CrkII
DOCK180
PAG3
04666 6/11/12
(c) Kanehisa Laboratories

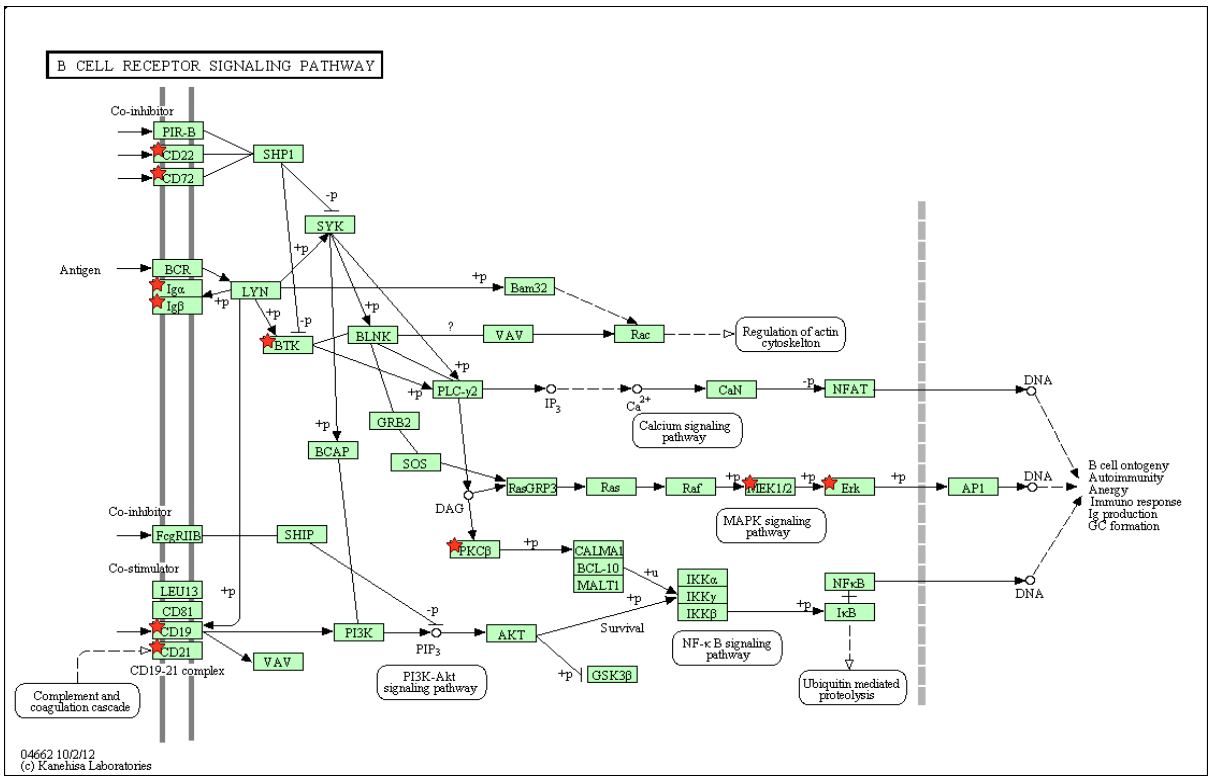
PC7

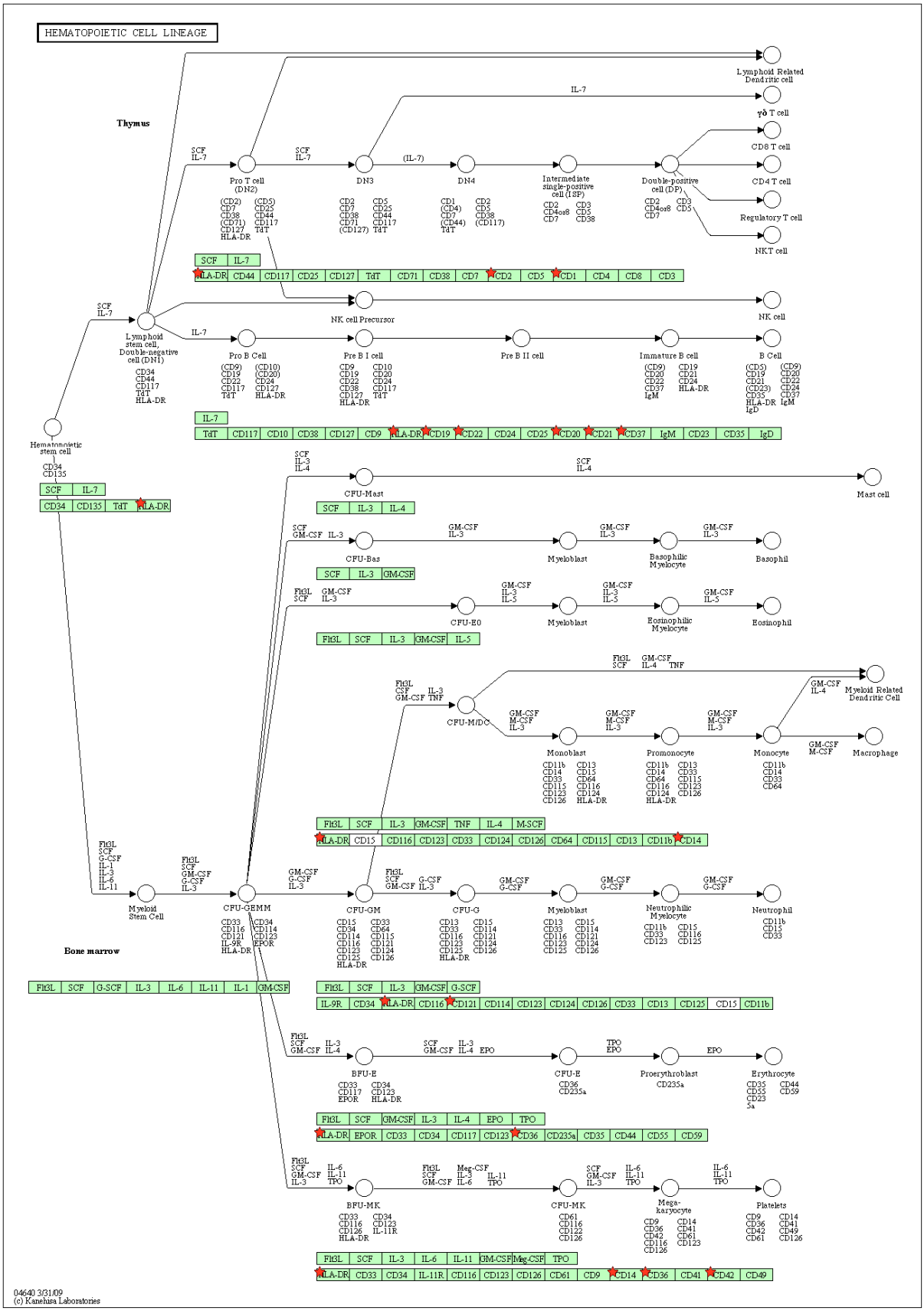

PORPHYRIN METABOLISM
Ferritin-Fe
1.16.1.2
Transferrin-Fe
Uroporphyrin I
4,5-Dioxopentanoate
Uroporphyrinogen I
4.1.1.37
Coproporphyrin I
Fe++
Fe+++
1.16.3.1
Coproporphyrinogen I
Apoferritin
Coproporphyrin III
Apotransferrin
2.6.1.43
spontaneous
Uroporphyrin III
5-Amino-levulinate
HemB
4.2.1.24
HemC
2.5.1.61
HemD
4.2.1.75
Uropor-phyrinogen III
HemE
4.1.1.37
HemF
1.3.3.3
1.3.99.22
HemY
1.3.3.4
1.3.5.3
HemH
4.99.1.1
Protoheme (Heme)
Peroxidase
Myoglobin
Cytochrome a
Cytochrome c
Catalase
Hemoglobin
Oxyhemoglobin
1.14.99.3
2.5.1.-
Heme O
4.4.1.17
COX15
Heme A
Biliverdin
1.3.7.4
(3Z)-Phyto chromobilin
1.3.7.5
(3Z)-Phyco cyanobilin
15,16-Dihydro biliverdin
1.3.7.2
1.3.7.3
(3Z)-Phyco erythrobilin
1.3.1.24
1.3.3.5
Bilirubin
Bilirubin β-diglucuronide
2.4.1.17
3.2.1.31

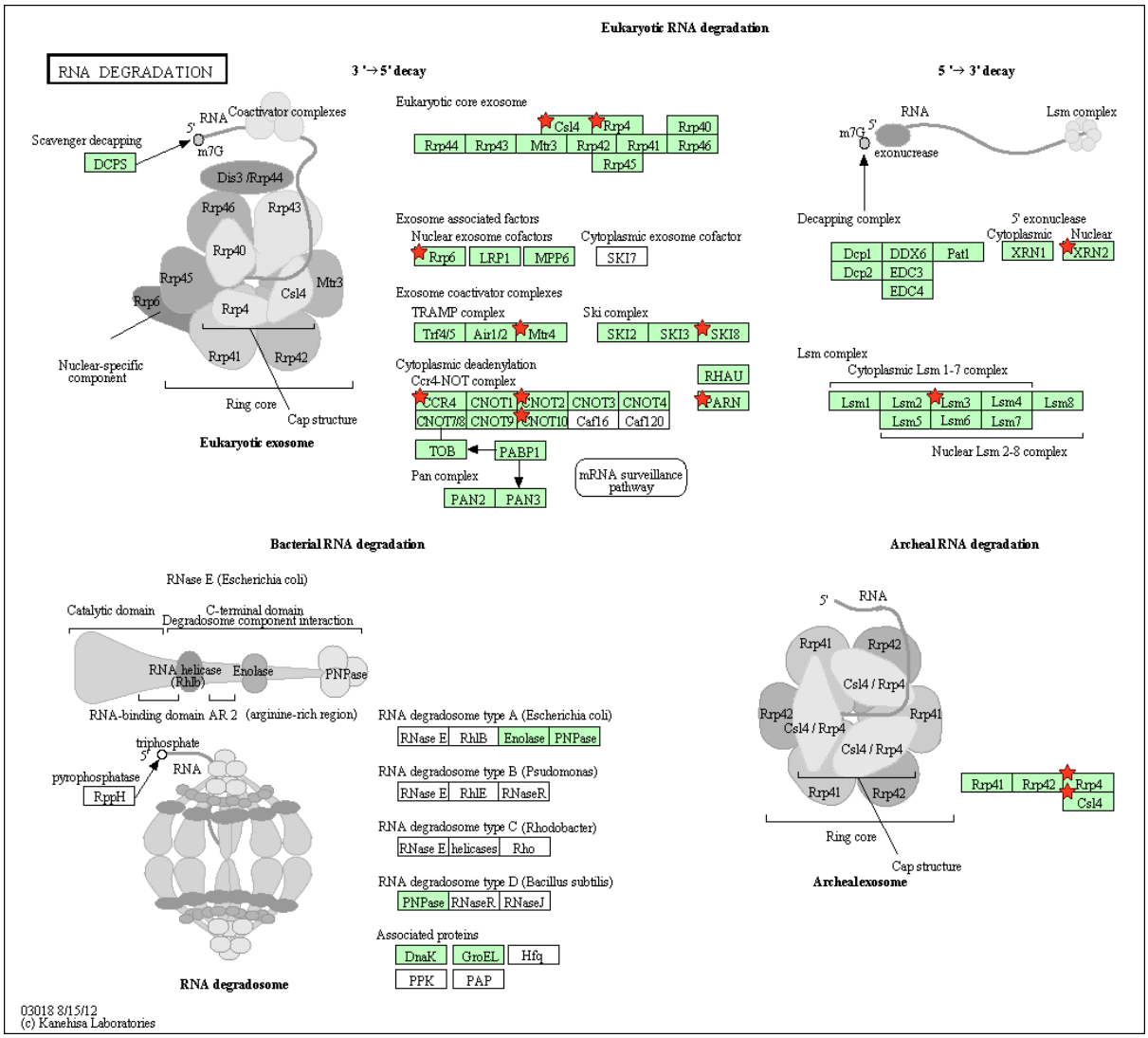
PC8

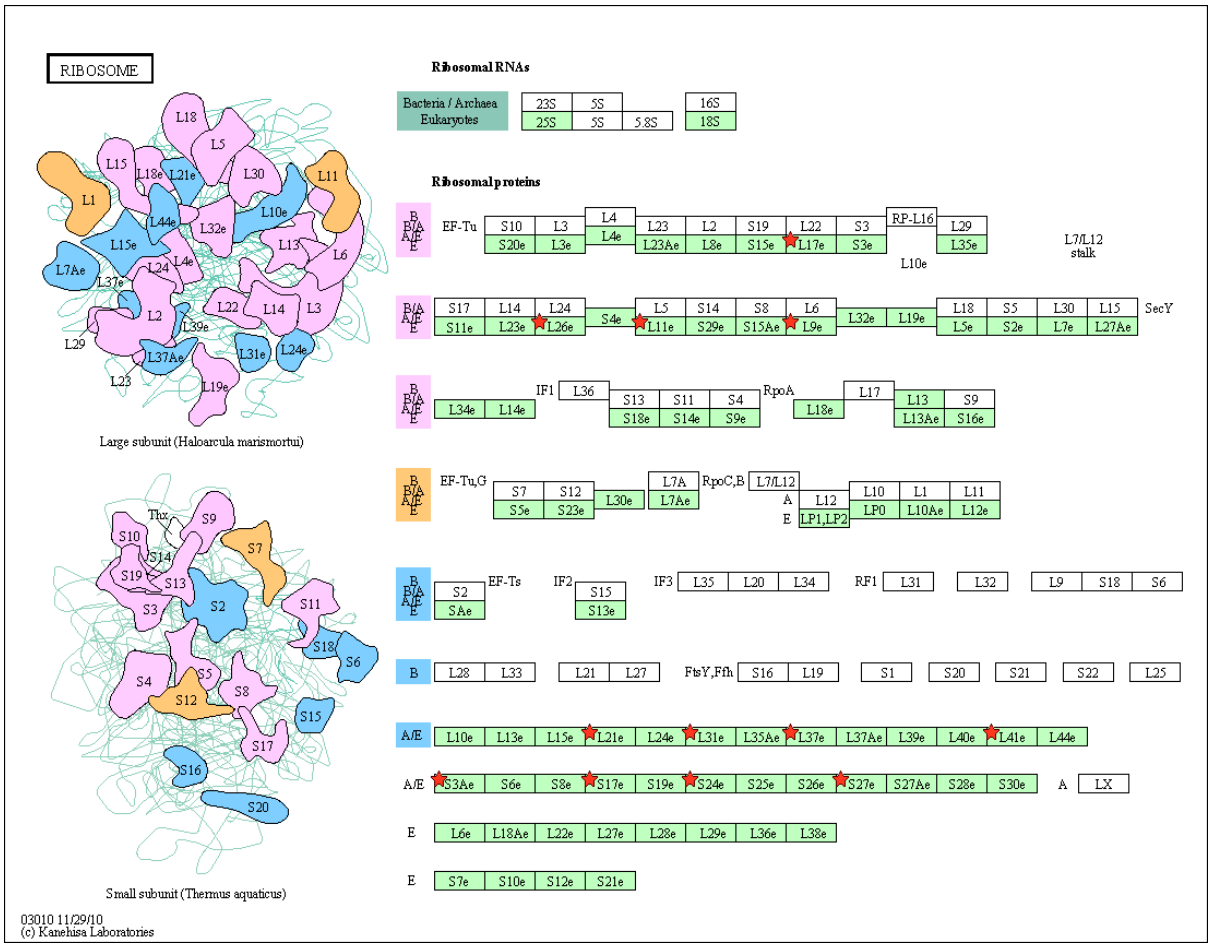

OXIDATIVE PHOSPHORYLATION
Complex I
Complex II
Complex III
Complex IV
Complex V
NADH dehydrogenase (Thermus thermophilus)
Fumarate reductase (E.coli)
Proton channel
ATP synthase (Escherichia coli)
Intermembrane space
Inner mitochondrial membrane
Mitochondrial matrix
Membrane domain (Hydrophobic arm)
Hydrophilic Domain (Peripheral arm)
Quinone pool
Cytochrome bc1 complex (bovine)
Cytochrome c oxidase (bovine)
F0 unit
F1 unit
NADH dehydrogenase
Succinate dehydrogenase / Fumarate reductase
Cytochrome c reductase
Cytochrome c oxidase
Cytochrome c oxidase , cbb3-type
Cytochrome bd complex
F-type ATPase (Bacteria)
F-type ATPase (Eukaryotes)
V-type ATPase (Prokaryotes)
V-type ATPase (Eukaryotes)
00190 6/1/12
(c) Kanehisa Laboratories

PC12


B CELL RECEPTOR SIGNALING PATHWAY
Co-inhibitor
PIR-B
CD22
CD72
SHP1
SYK
Antigen
BCR
Igα
Igβ
LYN
Bam32
BTK
BLNK
VAV
Rac
Regulation of actin cytoskelton
PLC-γ2
CaN
NFAT
DNA
Calcium signaling pathway
GRB2
BCAP
SOS
RasGRP3
Ras
Raf
MEK1/2
Erk
AP1
DNA
B cell ontogeny
Autoimmunity
Anergy
Immuno response
Ig production
GC formation
MAPK signaling pathway
DAG
Co-inhibitor
FcgRIIB
SHIP
PKCβ
CALMA1
BCL-10
MALT1
IKKα
IKKγ
IKKβ
NFκB
IκB
Co-stimulator
LEU13
CD81
CD19
CD21
CD19-21 complex
PI3K
PIP3
AKT
Survival
GSK3β
NF-κ B signaling pathway
PI3K-Akt signaling pathway
Ubiquitin mediated proteolysis
Complement and coagulation cascade
04662 10/2/12
(c) Kanehisa Laboratories


HEMATOPOIETIC CELL LINEAGE
Thymus
Bone marrow
Lymphoid Related Dendritic cell
γδ T cell
CD8 T cell
CD4 T cell
Regulatory T cell
NKT cell
NK cell Precursor
NK cell
Pro T cell (DN2)
DN3
DN4
Intermediate single-positive cell (ISP)
Double-positive cell (DP)
Lymphoid stem cell, Double-negative cell (DN1)
Pro B Cell
Pre B I cell
Pre B II cell
Immature B cell
B Cell
Hematopoietic stem cell
CFU-Mast
Mast cell
CFU-Bas
Myeloblast
Basophilic Myelocyte
Basophil
CFU-E0
Eosinophilic Myelocyte
Eosinophil
CFU-M/DC
Monoblast
Promonocyte
Monocyte
Myeloid Related Dendritic Cell
Macrophage
Myeloid Stem Cell
CFU-GEMM
CFU-GM
CFU-G
Neutrophilic Myelocyte
Neutrophil
BFU-E
CFU-E
Proerythroblast
Erythrocyte
BFU-MK
CFU-MK
Mega-karyocyte
Platelets
0464O 3/31/09
(c) Kanehisa Laboratories


Eukaryotic RNA degradation
RNA DEGRADATION
3 '→ 5' decay
5 '→ 3' decay
Coactivator complexes
RNA
5'
Scavenger decapping
DCPS
m7G
Dis3 /Rrp44
Rrp46
Rrp43
Rrp40
Rrp45
Csl4
Mtr3
Rrp6
Rrp4
Rrp41
Rrp42
Nuclear-specific component
Ring core
Cap structure
Eukaryotic exosome
Eukaryotic core exosome
Csl4
Rrp4
Rrp40
Rrp44
Rrp43
Mtr3
Rrp42
Rrp41
Rrp46
Rrp45
Exosome associated factors
Nuclear exosome cofactors
Cytoplasmic exosome cofactor
Rrp6
LRP1
MPP6
SKI7
Exosome coactivator complexes
TRAMP complex
Ski complex
Trf4/5
Air1/2
Mtr4
SKI2
SKI3
SKI8
Cytoplasmic deadenylation
Ccr4-NOT complex
RHAU
CCR4
CNOT1
CNOT2
CNOT3
CNOT4
PARN
CNOT7/8
CNOT9
CNOT10
Caf16
Caf120
TOB
PABP1
Pan complex
PAN2
PAN3
mRNA surveillance pathway
RNA
Lsm complex
m7G
5'
exonucrease
Decapping complex
5' exonuclease
Cytoplasmic
Nuclear
Dcp1
DDX6
Pat1
XRN1
XRN2
Dcp2
EDC3
EDC4
Lsm complex
Cytoplasmic Lsm 1-7 complex
Lsm1
Lsm2
Lsm3
Lsm4
Lsm8
Lsm5
Lsm6
Lsm7
Nuclear Lsm 2-8 complex
Bacterial RNA degradation
Archeal RNA degradation
RNase E (Escherichia coli)
Catalytic domain
C-terminal domain
Degradosome component interaction
RNA helicase (RhlB)
Enolase
PNPase
RNA-binding domain
AR 2 (arginine-rich region)
triphosphate
5'
RNA
pyrophosphatase
RppH
RNA degradosome
RNA degradosome type A (Escherichia coli)
RNase E
RhlB
Enolase
PNPase
RNA degradosome type B (Psudomonas)
RNase E
RhlE
RNaseR
RNA degradosome type C (Rhodobacter)
RNase E
helicases
Rho
RNA degradosome type D (Bacillus subtilis)
PNPase
RNaseR
RNaseJ
Associated proteins
DnaK
GroEL
Hfq
PPK
PAP
5'
RNA
Rrp41
Rrp42
Csl4 / Rrp4
Rrp42
Rrp41
Csl4 / Rrp4
Csl4 / Rrp4
Rrp41
Rrp42
Ring core
Cap structure
Archealexosome
Rrp41
Rrp42
Rrp4
Csl4
03018 8/15/12
(c) Kanehisa Laboratories


RIBOSOME
Large subunit (Haloarcula marismortui)
Small subunit (Thermus aquaticus)
Ribosomal RNAs
Bacteria / Archaea
Eukaryotes
23S
5S
5.8S
16S
18S
Ribosomal proteins
EF-Tu
RP-L16
L10e
L7/L12 stalk
SecY
IF1
RpoA
EF-Tu,G
L7/L12
EF-Ts
IF2
IF3
RF1
FtsY,Ffh
03010 11/29/10
(c) Kanehisa Laboratories

PC25

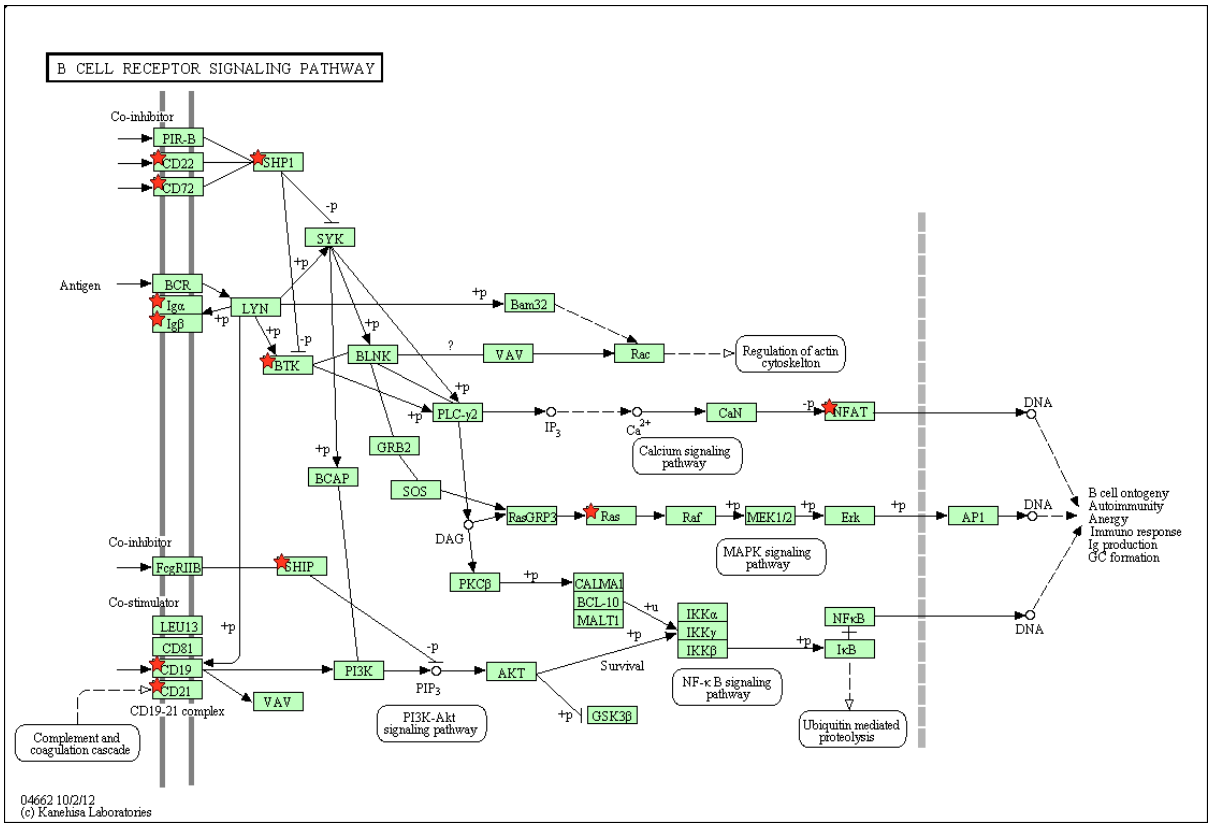


Figure S6 Pathway diagrams of enriched biological networks. Figures generated from the KEGG pathway database. Pathway analysis for PC1-50 was performed using DAVID Bioinformatics Resources 6.7, Functional Annotation Tool. These pathways were significant after multiple correction (FDR) (Table S2). Components highlighted with red stars represent probes present within the corresponding PC. PC1 shows enrichment for ribosomal components. PC3 is enriched for Fc gamma R-mediated phagocytosis. PC7 is enriched for porphyrin metabolism. PC8 shows enrichment for enzymatic subunits involved oxidative phosphorylation, PC12 is enriched in components involved in the B-cell receptor signaling pathway and hematopoietic cell lineage. PC13 is enriched for RNA degradation. PC18 shows enrichment for ribosomal components and PC25 shows enrichment for B-cell reception signaling.

Table S1 Results from the GWAS for each PC. Probes that were found to be significant after a Bonferroni correction (0.05/488,462 SNPs) on each PC are listed in this table. Though none of these are significant after correcting for all PCs, they are significant at an empirical p-value of 0.05 for each PC after 1000 permutations. PC – principal component, CHR – chromosome, SNP – SNP ID, BP – base pair, BETA – regression coefficient, STAT – Coefficient T-statistic, P – Asymptotic p-value for t-statistic, EMP – empirical p-value after 1000 permutations.

PC	CHR	SNP	BP	BETA	STAT	P	EMP
22	10	rs11004899	56960734	3.754	5.487	8.14E-08	0.036
35	2	rs1516174	51724845	2.826	5.43	1.089E-07	0.049
81	16	rs9673242	14078070	-3.404	-5.524	6.69E-08	0.021
81	16	rs1004637	14113245	-3.404	-5.524	6.69E-08	0.021
100	16	rs7190803	77375823	-1.444	-5.535	6.33E-08	0.021
106	2	rs10497190	158347486	-1.741	-5.585	4.87E-08	0.021
106	13	rs17072974	21351926	2.275	5.501	7.53E-08	0.027
106	13	rs12428031	21355249	2.275	5.501	7.53E-08	0.027
110	11	rs10501384	59950456	2.555	5.482	8.31E-08	0.033
110	11	rs17542525	59958103	2.555	5.482	8.31E-08	0.033
119	8	rs4596672	88124581	-1.641	-5.488	8.23E-08	0.032
119	8	rs2974279	88144159	-1.385	-5.517	6.95E-08	0.028
156	1	rs825113	221564768	1.762	5.503	7.45E-08	0.026
157	2	rs11674634	132055980	-1.305	-6.005	5.02E-09	0.004
175	4	rs6848983	298010	1.736	5.71	2.50E-08	0.005
214	5	rs1279627	55966337	-1.095	-5.562	5.50E-08	0.019
225	10	rs7919814	109720733	-1.055	-5.502	7.52E-08	0.03
245	8	rs17128272	19257994	-1.516	-5.449	9.85E-08	0.042
323	9	rs10813262	30474037	1.542	5.538	6.22E-08	0.044
323	9	rs4878432	30490252	1.542	5.538	6.22E-08	0.044
323	9	rs7866981	30548222	1.568	5.639	3.65E-08	0.034
324	14	rs10498517	64832534	1.619	6.112	2.74E-09	0.002
324	14	rs4902382	64834310	1.44	5.662	3.24E-08	0.017

Table S2 Pathway analysis for the first 50 PCs Pathway analysis for PC1-50 was performed using DAVID Bioinformatics Resources 6.7, Functional Annotation Tool. PC – principal component, Term – name of KEGG pathway, Count – count of probes in each hit, % – percentage of all probes submitted for that PC that are present within the pathway, P – the p-value that is calculated using a modified Fischer's exact test for enrichment, FDR – correction of p-values and using the Benjamini-Hochberg FDR method.

PC	Term	Count	%	P	FDR
1	Ribosome	8	7.9	1.00E-06	4.50E-05
3	Fc gamma R-mediated phagocytosis	14	2.7	4.30E-05	5.40E-03
7	Porphyrin metabolism	7	1.5	1.60E-04	2.00E-02
8	Proteasome	12	2.6	2.70E-07	4.00E-05
	Oxidative phosphorylation	18	3.9	1.20E-06	8.70E-05
	Huntington's disease	21	4.6	1.90E-06	9.00E-05
	Parkinson's disease	15	3.3	8.50E-05	3.10E-03
	Alzheimer's disease	15	3.3	1.10E-03	3.00E-02
12	Hematopoietic cell lineage	13	2.5	1.40E-05	2.00E-03
	B cell receptor signaling pathway	10	1.9	5.60E-04	3.80E-02
	Antigen processing and presentation	10	1.9	1.20E-03	5.30E-02
	Graft-versus-host disease	7	1.3	1.30E-03	4.40E-02
	Non-small cell lung cancer	8	1.5	1.50E-03	4.00E-02
	Asthma	6	1.2	2.00E-03	4.40E-02
13	RNA degradation	11	2.3	1.30E-05	1.80E-03
	Oxidative phosphorylation	15	3.1	7.80E-05	5.60E-03
	Ribosome	11	2.3	5.00E-04	2.40E-02
18	Ribosome	14	2.9	9.40E-07	1.00E-04

24	B cell receptor signaling pathway	14	2.9	2.00E-07	2.70E-05
25	B cell receptor signaling pathway	11	2.2	1.10E-04	1.60E-02
26	Primary immunodeficiency	8	1.7	7.90E-05	1.20E-02
32	Oxidative phosphorylation	13	2.7	2.90E-04	3.70E-02

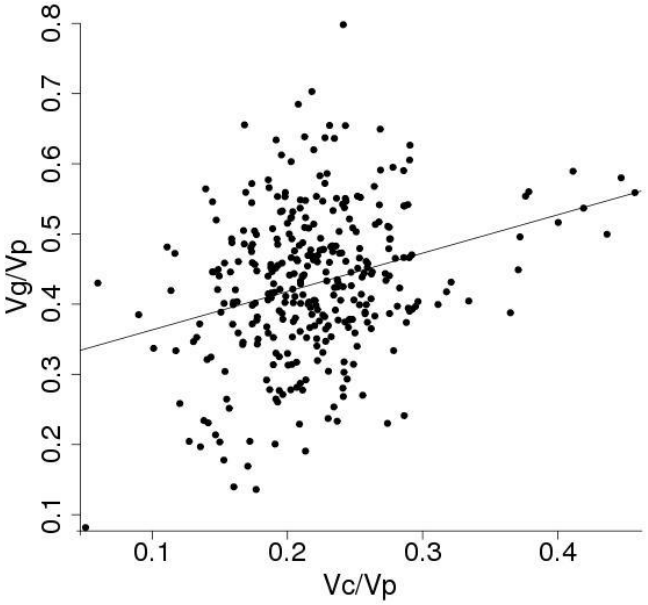


Figure S4 Correlation between additive genetic and common environmental factors. Significant association (p = 8.57e-08 and R2=0.08) between the common environment and genetic components estimated in an AC and AE models. The proportion of common environment variance was calculated by dividing the variance attributed to common environment (Vc) by the total phenotypic variance (Vp). The proportion of genetic variability (heritability) was calculated by dividing the additive genetic component (Vg) by the total phenotypic variance (Vp). This result indicates that the heritability estimates obtained are confounded with common environment variance and therefore inflated upwards by common family effects.

Table S1 Results from the GWAS for each PC. Probes that were found to be significant after a Bonferroni correction (0.05/488,462 SNPs) on each PC are listed in this table. Though none of these are significant after correcting for all PCs, they are significant at an empirical p-value of 0.05 for each PC after 1000 permutations. PC – principal component, CHR – chromosome, SNP – SNP ID, BP – base pair, BETA – regression coefficient, STAT – Coefficient T-statistic, P – Asymptotic p-value for t-statistic, EMP – empirical p-value after 1000 permutations.

PC	CHR	SNP	BP	BETA	STAT	P	EMP
22	10	rs11004899	56960734	3.754	5.487	8.14E-08	0.036
35	2	rs1516174	51724845	2.826	5.43	1.089E-07	0.049
81	16	rs9673242	14078070	-3.404	-5.524	6.69E-08	0.021
81	16	rs1004637	14113245	-3.404	-5.524	6.69E-08	0.021
100	16	rs7190803	77375823	-1.444	-5.535	6.33E-08	0.021
106	2	rs10497190	158347486	-1.741	-5.585	4.87E-08	0.021
106	13	rs17072974	21351926	2.275	5.501	7.53E-08	0.027
106	13	rs12428031	21355249	2.275	5.501	7.53E-08	0.027
110	11	rs10501384	59950456	2.555	5.482	8.31E-08	0.033
110	11	rs17542525	59958103	2.555	5.482	8.31E-08	0.033
119	8	rs4596672	88124581	-1.641	-5.488	8.23E-08	0.032
119	8	rs2974279	88144159	-1.385	-5.517	6.95E-08	0.028
156	1	rs825113	221564768	1.762	5.503	7.45E-08	0.026
157	2	rs11674634	132055980	-1.305	-6.005	5.02E-09	0.004
175	4	rs6848983	298010	1.736	5.71	2.50E-08	0.005
214	5	rs1279627	55966337	-1.095	-5.562	5.50E-08	0.019
225	10	rs7919814	109720733	-1.055	-5.502	7.52E-08	0.03
245	8	rs17128272	19257994	-1.516	-5.449	9.85E-08	0.042
323	9	rs10813262	30474037	1.542	5.538	6.22E-08	0.044
323	9	rs4878432	30490252	1.542	5.538	6.22E-08	0.044
323	9	rs7866981	30548222	1.568	5.639	3.65E-08	0.034
324	14	rs10498517	64832534	1.619	6.112	2.74E-09	0.002
324	14	rs4902382	64834310	1.44	5.662	3.24E-08	0.017

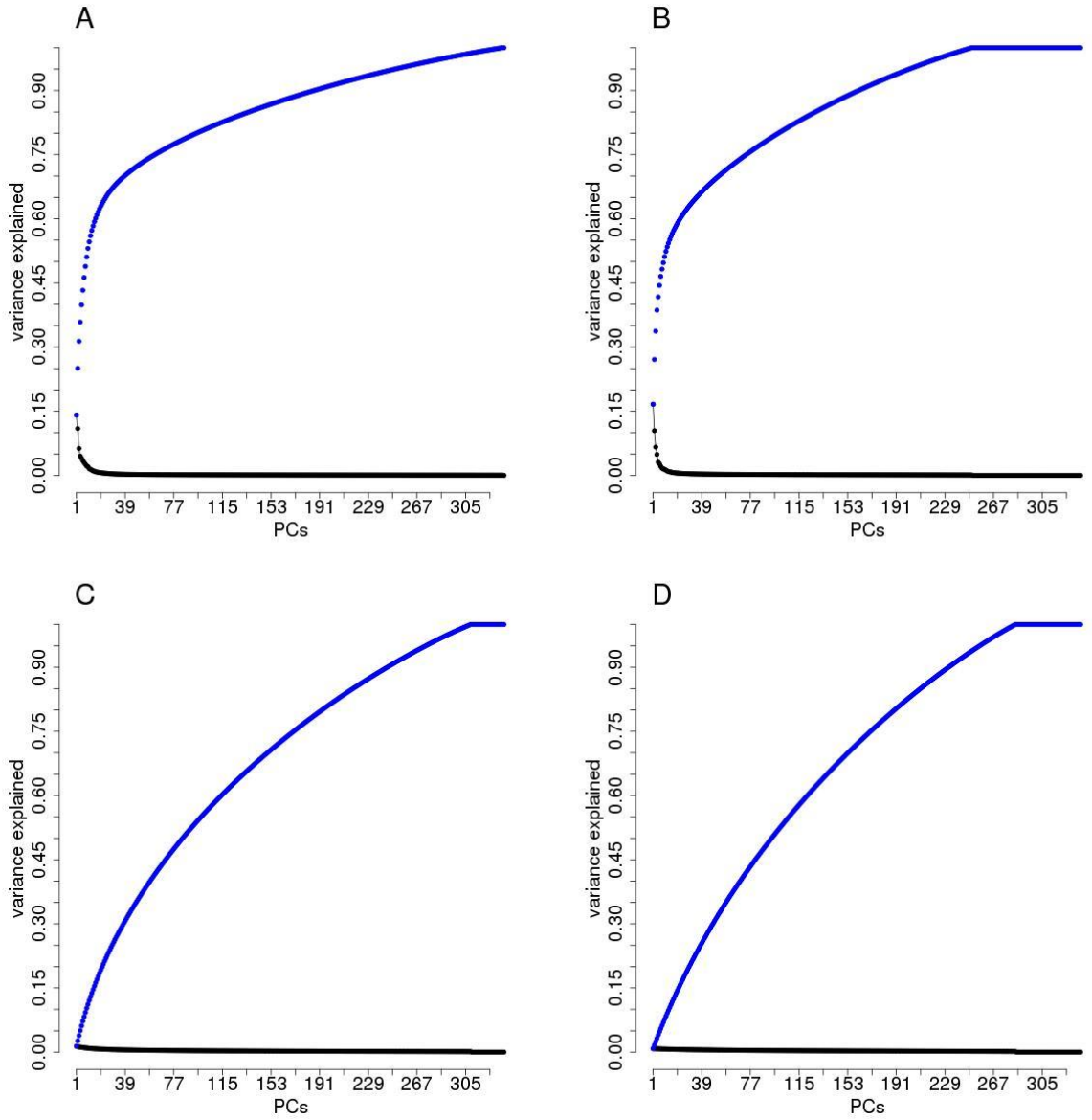


Figure S3 Variance explained by PCs. Calculated from the eigenvalues obtained from the Singular Value Decomposition. Variance explained by each PC is plotted in black and cumulative variance in blue. A) Normalized dataset, B) Corrected with linear models, C) PC25 corrected D) PC50 corrected. All variances add up to 1. Cum

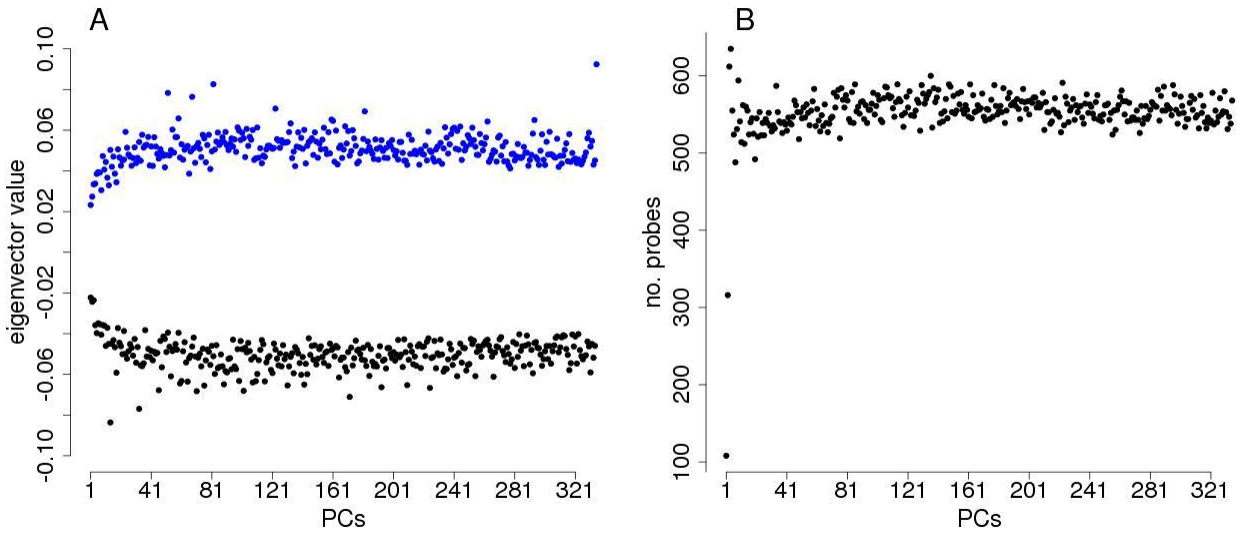
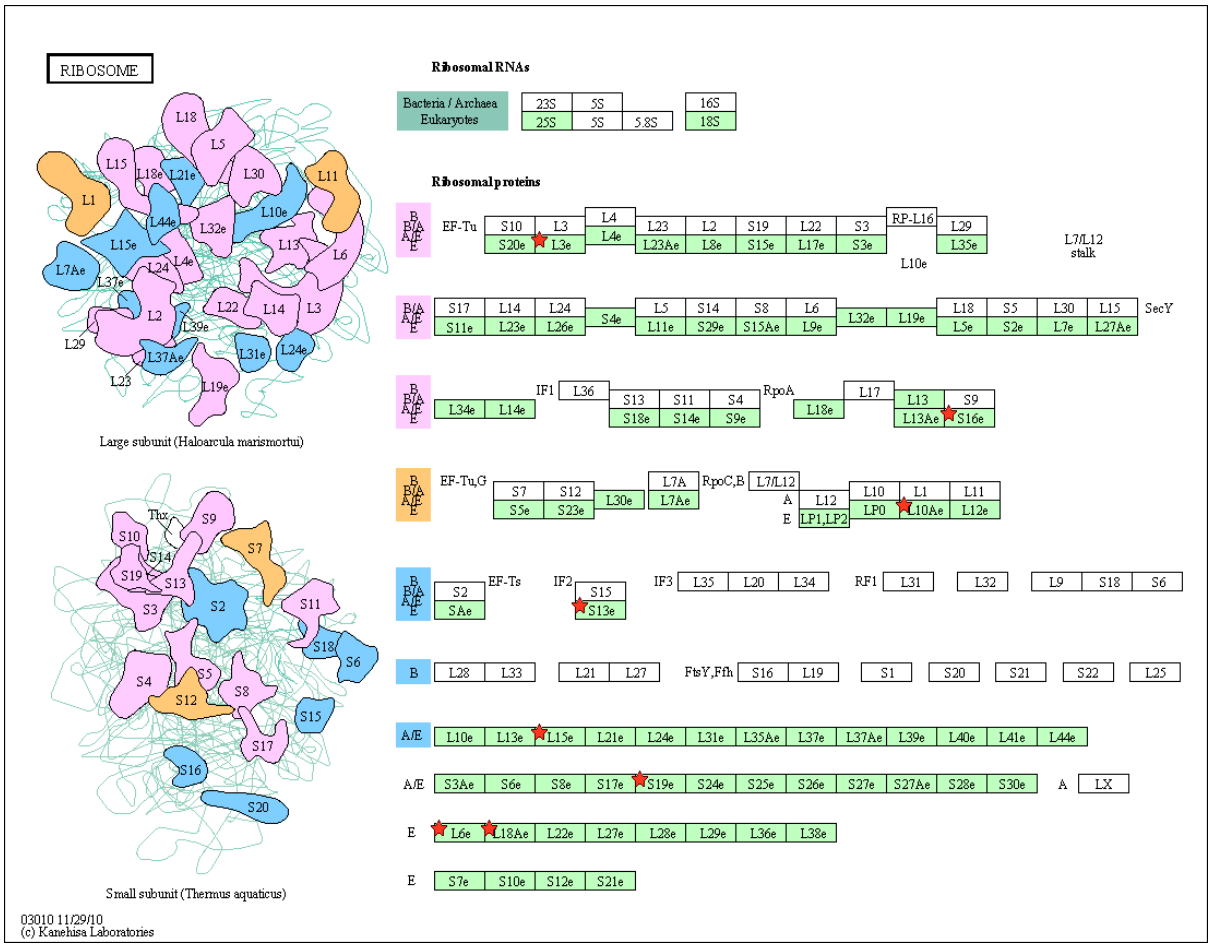
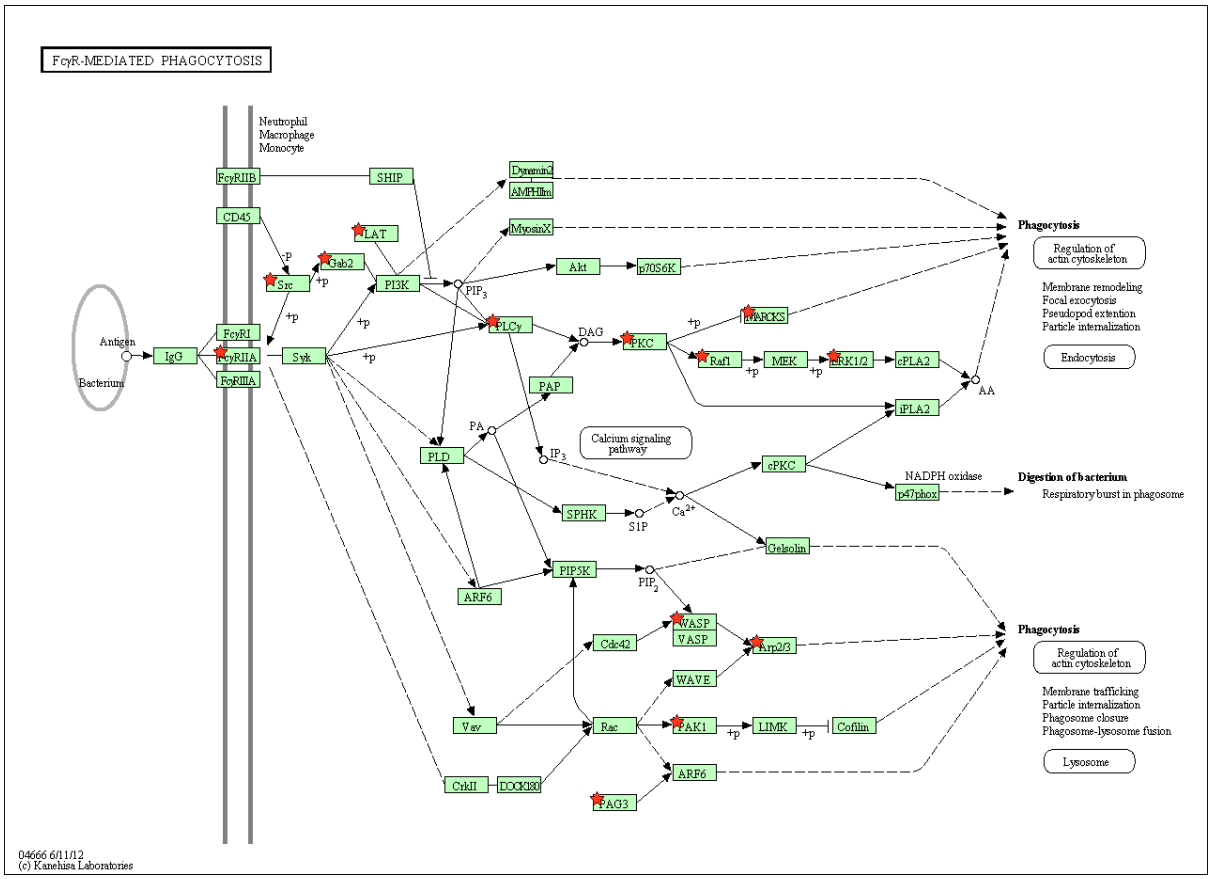


Figure S2 Selection of probes driving PCs**.** (S2A) Maximum (blue) and minimum (black) eigenvector values for each PC. The eigenvector values represent the extent of the correlation between a probe and a PC, with 0 indicating no association. Selection of probes driving each PC is based on the optimal number of probes for each PC that have the same eigenvector value cut off. As multiple probes can contribute a small amount of variance to each PC it is reasonable that a low cut off value can pick up many of the significant probes driving each PC. Probes that have an eigenvector value of greater than 0.02 or less than -0.02 were selected for further biological enrichment analysis as this incorporated all the maximally and minimally expressed probes in this section. (S2B) Selection of probes at this cut off value enabled approximately similar numbers of probes to be selected for each PC. The slightly lower number of probes that are selected in the initial PCs is due to the lower maximum and minimum eigenvector values in these PCs as shown in (S2A).

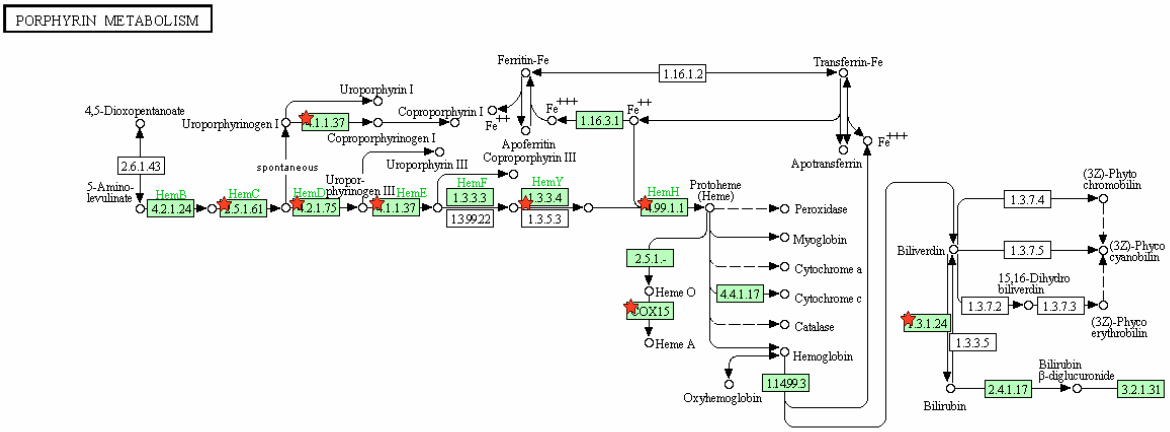
PC1


RIBOSOME
Large subunit (Haloarcula marismortui)
Small subunit (Thermus aquaticus)
03010 11/29/10
(c) Kanehisa Laboratories
Ribosomal RNAs
Bacteria / Archaea
Eukaryotes
23S 5S 5.8S 16S
25S 5S 18S
Ribosomal proteins
EF-Tu
RP-L16
L10e
L7/L12 stalk
SecY
IF1
RpoA
EF-Tu,G
L7A
L7Ae
RpoC,B
L7/L12
L12
LP1,LP2
EF-Ts
IF2
IF3
RF1
FtsY,Ffh
Thx

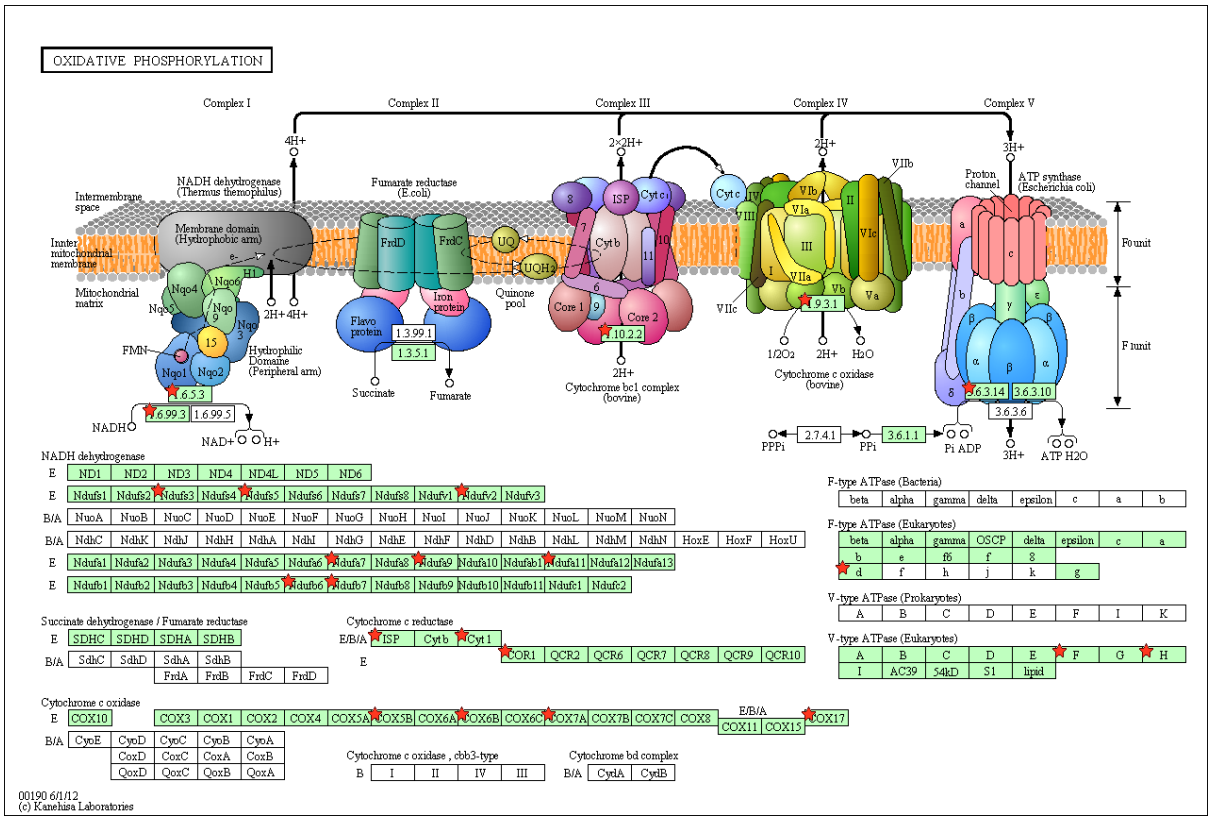
PC3


FcγR-MEDIATED PHAGOCYTOSIS
Neutrophil
Macrophage
Monocyte
FcγRIIB
SHIP
CD45
LAT
Gab2
Src
PI3K
Dynamin2
AMPHIIm
MyosinX
Akt
p70S6K
Phagocytosis
Regulation of actin cytoskeleton
Membrane remodeling
Focal exocytosis
Pseudopod extention
Particle internalization
Endocytosis
Antigen
IgG
Bacterium
FcγRI
FcγRIIA
FcγRIIIA
Syk
PLCγ
DAG
PKC
pPAK/KS
Raf1
MEK
ERK1/2
cPLA2
AA
PAP
PA
iPLA2
PLD
Calcium signaling pathway
IP3
cPKC
NADPH oxidase
p47phox
Digestion of bacterium
Respiratory burst in phagosome
SPHK
S1P
Ca2+
Gelsolin
PIP5K
PIP2
ARF6
WASP
VASP
Cdc42
Arp2/3
Phagocytosis
Regulation of actin cytoskeleton
WAVE
Membrane trafficking
Particle internalization
Phagosome closure
Phagosome-lysosome fusion
Vav
Rac
PAK1
LIMK
Cofilin
Lysosome
CrkII
DOCK180
PAG3
04666 6/11/12
(c) Kanehisa Laboratories

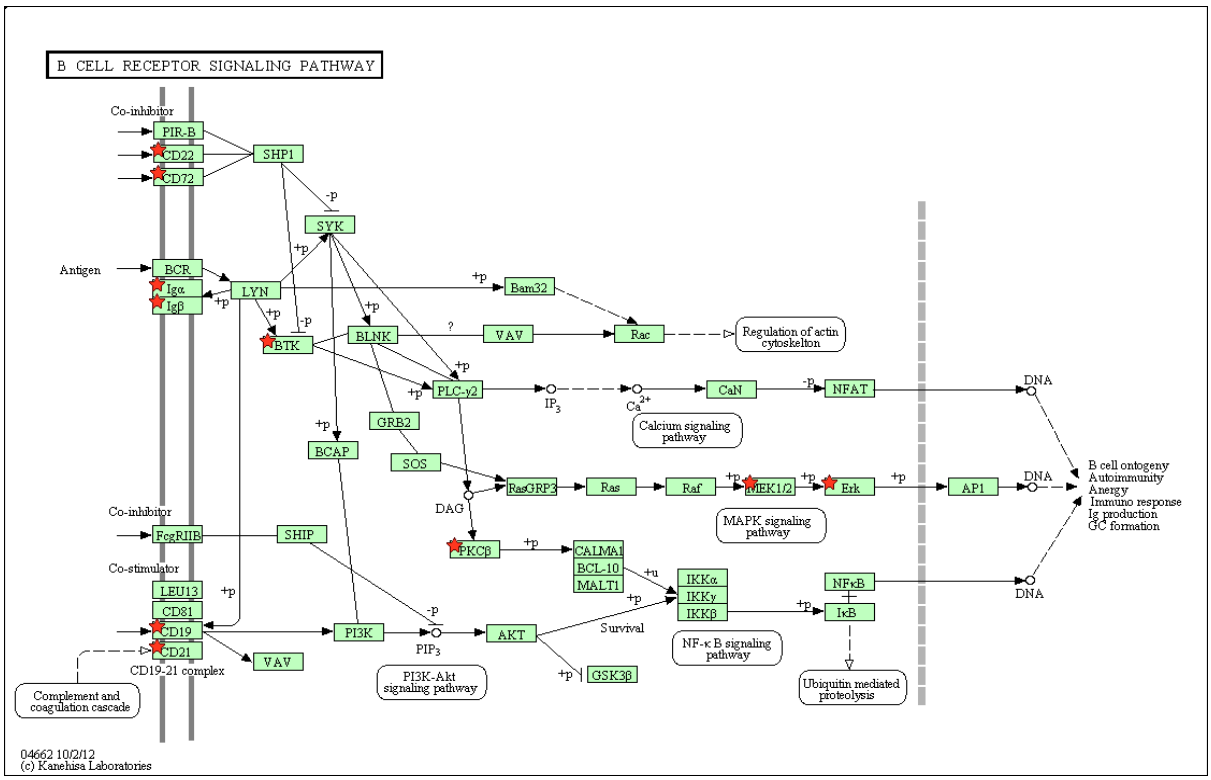
PC7

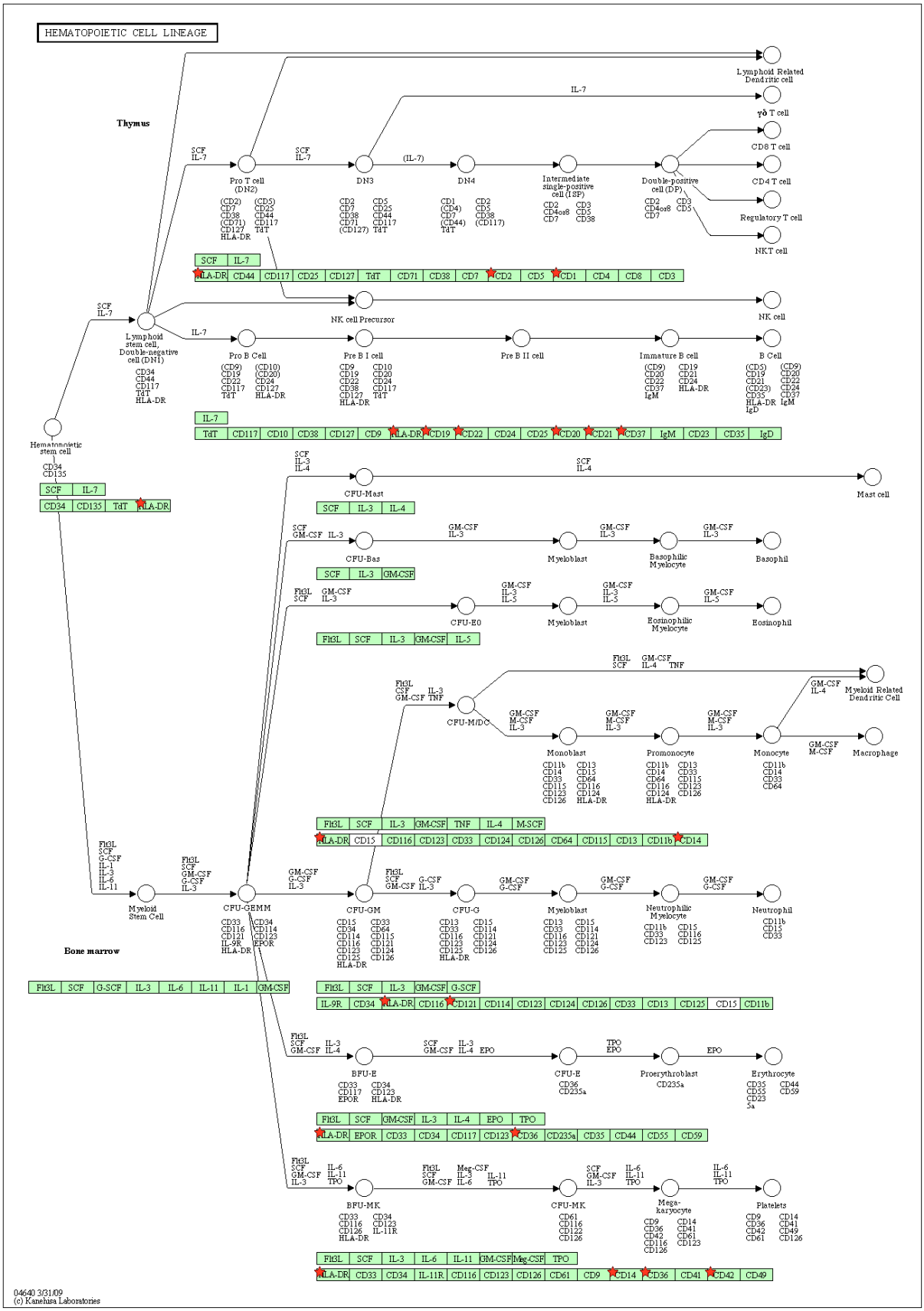

PORPHYRIN METABOLISM
Ferritin-Fe
1.16.1.2
Transferrin-Fe
Uroporphyrin I
4,5-Dioxopentanoate
Uroporphyrinogen I
4.1.1.37
Coproporphyrin I
Fe++
Fe+++
1.16.3.1
Coproporphyrinogen I
Apoferritin
Coproporphyrin III
Apotransferrin
2.6.1.43
spontaneous
Uroporphyrin III
5-Amino-levulinate
HemB
4.2.1.24
HemC
2.5.1.61
HemD
4.2.1.75
Uropor-phyrinogen III
HemE
4.1.1.37
HemF
1.3.3.3
1.3.99.22
HemY
1.3.3.4
1.3.5.3
HemH
4.99.1.1
Protoheme (Heme)
Peroxidase
Myoglobin
Cytochrome a
Cytochrome c
Catalase
Hemoglobin
Oxyhemoglobin
1.14.99.3
2.5.1.-
Heme O
4.4.1.17
COX15
Heme A
Biliverdin
1.3.7.4
(3Z)-Phyto chromobilin
1.3.7.5
(3Z)-Phyco cyanobilin
15,16-Dihydro biliverdin
1.3.7.2
1.3.7.3
(3Z)-Phyco erythrobilin
1.3.1.24
1.3.3.5
Bilirubin
Bilirubin β-diglucuronide
2.4.1.17
3.2.1.31

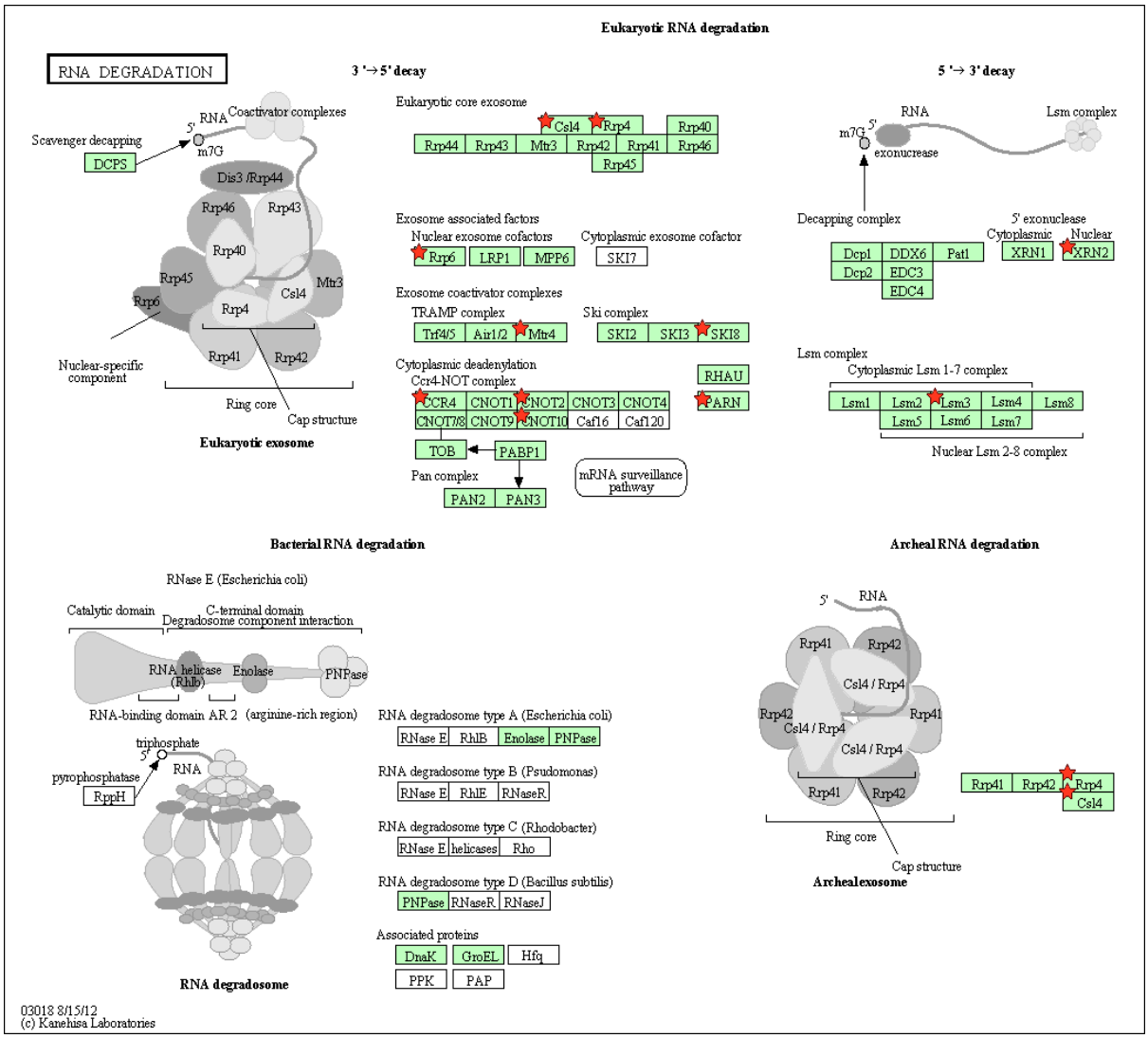
PC8

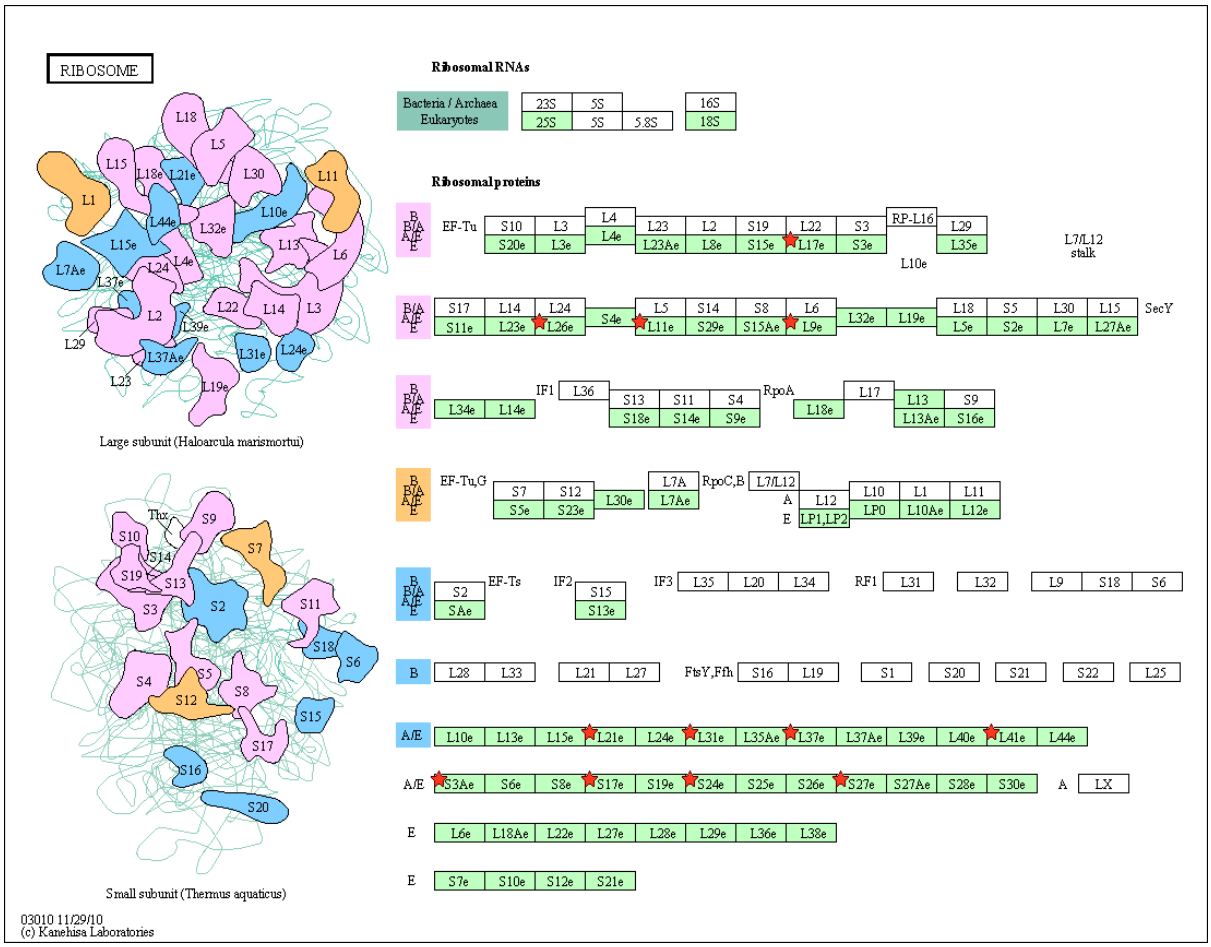

OXIDATIVE PHOSPHORYLATION
Complex I
Complex II
Complex III
Complex IV
Complex V
NADH dehydrogenase (Thermus thermophilus)
Fumarate reductase (E.coli)
Proton channel
ATP synthase (Escherichia coli)
Intermembrane space
Inner mitochondrial membrane
Mitochondrial matrix
Membrane domain (Hydrophobic arm)
Hydrophilic Domain (Peripheral arm)
Quinone pool
Cytochrome bc1 complex (bovine)
Cytochrome c oxidase (bovine)
F0 unit
F1 unit
NADH dehydrogenase
Succinate dehydrogenase / Fumarate reductase
Cytochrome c reductase
Cytochrome c oxidase
Cytochrome c oxidase , cbb3-type
Cytochrome bd complex
F-type ATPase (Bacteria)
F-type ATPase (Eukaryotes)
V-type ATPase (Prokaryotes)
V-type ATPase (Eukaryotes)
00190 6/1/12
(c) Kanehisa Laboratories

PC12


B CELL RECEPTOR SIGNALING PATHWAY
Co-inhibitor
PIR-B
CD22
CD72
SHP1
SYK
Antigen
BCR
Igα
Igβ
LYN
Bam32
BTK
BLNK
VAV
Rac
Regulation of actin cytoskelton
PLC-γ2
CaN
NFAT
DNA
Calcium signaling pathway
GRB2
BCAP
SOS
RasGRP3
Ras
Raf
MEK1/2
Erk
AP1
DNA
B cell ontogeny
Autoimmunity
Anergy
Immuno response
Ig production
GC formation
MAPK signaling pathway
DAG
Co-inhibitor
FcgRIIB
SHIP
PKCβ
CALMA1
BCL-10
MALT1
IKKα
IKKγ
IKKβ
NFκB
IκB
Co-stimulator
LEU13
CD81
CD19
CD21
CD19-21 complex
PI3K
PIP3
AKT
Survival
GSK3β
NF-κ B signaling pathway
PI3K-Akt signaling pathway
Ubiquitin mediated proteolysis
Complement and coagulation cascade
04662 10/2/12
(c) Kanehisa Laboratories


HEMATOPOIETIC CELL LINEAGE
Thymus
Bone marrow
Lymphoid Related Dendritic cell
γδ T cell
CD8 T cell
CD4 T cell
Regulatory T cell
NKT cell
NK cell Precursor
NK cell
Pro T cell (DN2)
DN3
DN4
Intermediate single-positive cell (ISP)
Double-positive cell (DP)
Lymphoid stem cell, Double-negative cell (DN1)
Pro B Cell
Pre B I cell
Pre B II cell
Immature B cell
B Cell
Hematopoietic stem cell
CFU-Mast
Mast cell
CFU-Bas
Myeloblast
Basophilic Myelocyte
Basophil
CFU-E0
Eosinophilic Myelocyte
Eosinophil
CFU-M/DC
Monoblast
Promonocyte
Monocyte
Myeloid Related Dendritic Cell
Macrophage
Myeloid Stem Cell
CFU-GEMM
CFU-GM
CFU-G
Neutrophilic Myelocyte
Neutrophil
BFU-E
CFU-E
Proerythroblast
Erythrocyte
BFU-MK
CFU-MK
Mega-karyocyte
Platelets
0464O 3/31/09
(c) Kanehisa Laboratories


Eukaryotic RNA degradation
RNA DEGRADATION
3 '→ 5' decay
5 '→ 3' decay
Coactivator complexes
RNA
5'
Scavenger decapping
DCPS
m7G
Dis3 /Rrp44
Rrp46
Rrp43
Rrp40
Rrp45
Csl4
Mtr3
Rrp6
Rrp4
Rrp41
Rrp42
Nuclear-specific component
Ring core
Cap structure
Eukaryotic exosome
Eukaryotic core exosome
Csl4
Rrp4
Rrp40
Rrp44
Rrp43
Mtr3
Rrp42
Rrp41
Rrp46
Rrp45
Exosome associated factors
Nuclear exosome cofactors
Cytoplasmic exosome cofactor
Rrp6
LRP1
MPP6
SKI7
Exosome coactivator complexes
TRAMP complex
Ski complex
Trf4/5
Air1/2
Mtr4
SKI2
SKI3
SKI8
Cytoplasmic deadenylation
Ccr4-NOT complex
RHAU
CCR4
CNOT1
CNOT2
CNOT3
CNOT4
PARN
CNOT7/8
CNOT9
CNOT10
Caf16
Caf120
TOB
PABP1
Pan complex
PAN2
PAN3
mRNA surveillance pathway
RNA
Lsm complex
m7G
5'
exonucrease
Decapping complex
5' exonuclease
Cytoplasmic
Nuclear
Dcp1
DDX6
Pat1
XRN1
XRN2
Dcp2
EDC3
EDC4
Lsm complex
Cytoplasmic Lsm 1-7 complex
Lsm1
Lsm2
Lsm3
Lsm4
Lsm8
Lsm5
Lsm6
Lsm7
Nuclear Lsm 2-8 complex
Bacterial RNA degradation
Archeal RNA degradation
RNase E (Escherichia coli)
Catalytic domain
C-terminal domain
Degradosome component interaction
RNA helicase (RhlB)
Enolase
PNPase
RNA-binding domain
AR 2 (arginine-rich region)
triphosphate
5'
RNA
pyrophosphatase
RppH
RNA degradosome
RNA degradosome type A (Escherichia coli)
RNase E
RhlB
Enolase
PNPase
RNA degradosome type B (Psudomonas)
RNase E
RhlE
RNaseR
RNA degradosome type C (Rhodobacter)
RNase E
helicases
Rho
RNA degradosome type D (Bacillus subtilis)
PNPase
RNaseR
RNaseJ
Associated proteins
DnaK
GroEL
Hfq
PPK
PAP
5'
RNA
Rrp41
Rrp42
Csl4 / Rrp4
Rrp42
Rrp41
Csl4 / Rrp4
Csl4 / Rrp4
Rrp41
Rrp42
Ring core
Cap structure
Archealexosome
Rrp41
Rrp42
Rrp4
Csl4
03018 8/15/12
(c) Kanehisa Laboratories


RIBOSOME
Large subunit (Haloarcula marismortui)
Small subunit (Thermus aquaticus)
Ribosomal RNAs
Bacteria / Archaea
Eukaryotes
23S
5S
5.8S
16S
18S
Ribosomal proteins
EF-Tu
RP-L16
L10e
L7/L12 stalk
SecY
IF1
RpoA
EF-Tu,G
L7/L12
EF-Ts
IF2
IF3
RF1
FtsY,Ffh
03010 11/29/10
(c) Kanehisa Laboratories

PC25

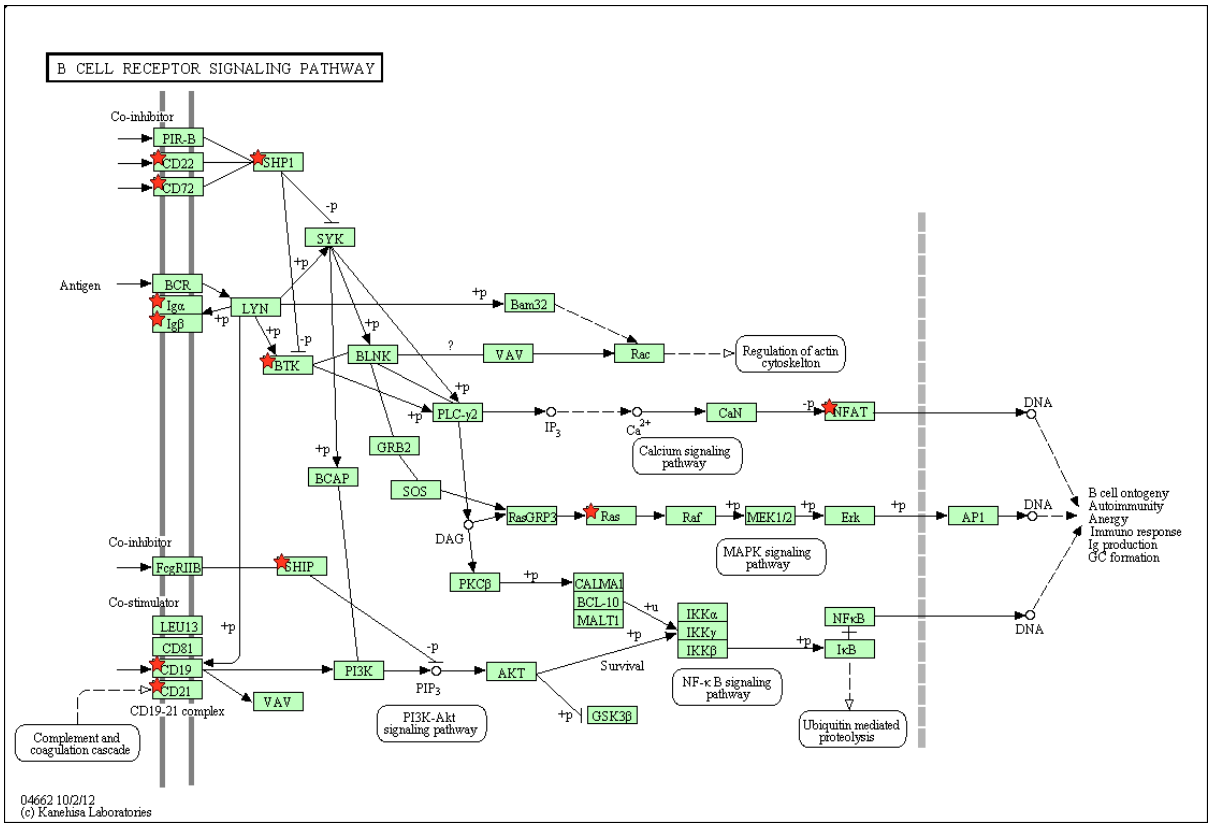
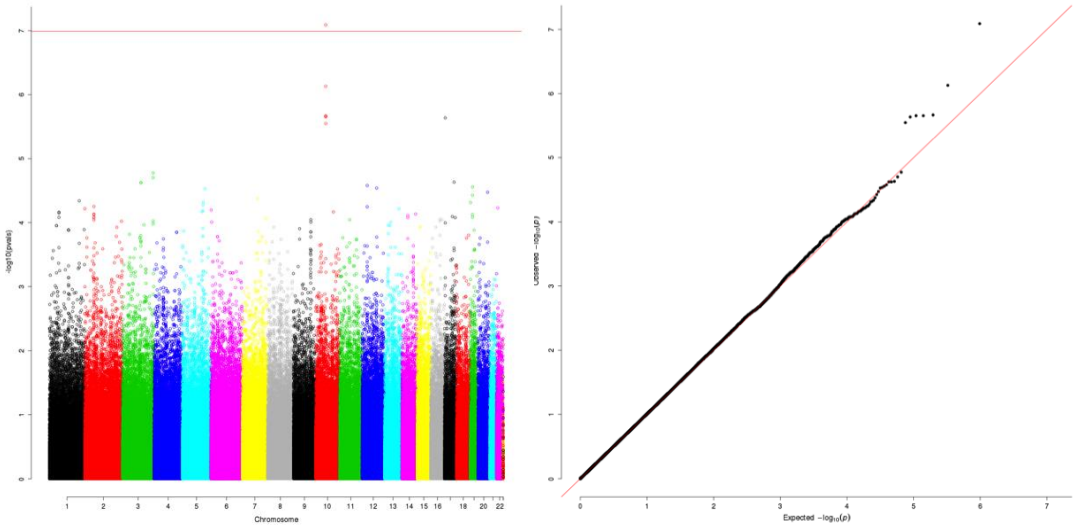
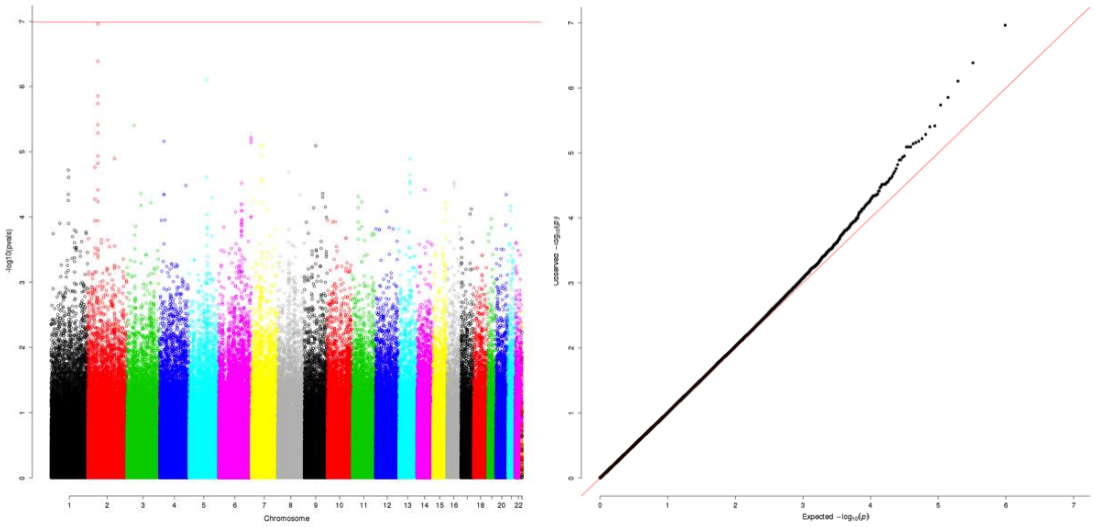


Figure S6 Pathway diagrams of enriched biological networks. Figures generated from the KEGG pathway database. Pathway analysis for PC1-50 was performed using DAVID Bioinformatics Resources 6.7, Functional Annotation Tool. These pathways were significant after multiple correction (FDR) (Table S2). Components highlighted with red stars represent probes present within the corresponding PC. PC1 shows enrichment for ribosomal components. PC3 is enriched for Fc gamma R-mediated phagocytosis. PC7 is enriched for porphyrin metabolism. PC8 shows enrichment for enzymatic subunits involved oxidative phosphorylation, PC12 is enriched in components involved in the B-cell receptor signaling pathway and hematopoietic cell lineage. PC13 is enriched for RNA degradation. PC18 shows enrichment for ribosomal components and PC25 shows enrichment for B-cell reception signaling.

PC22



PC35



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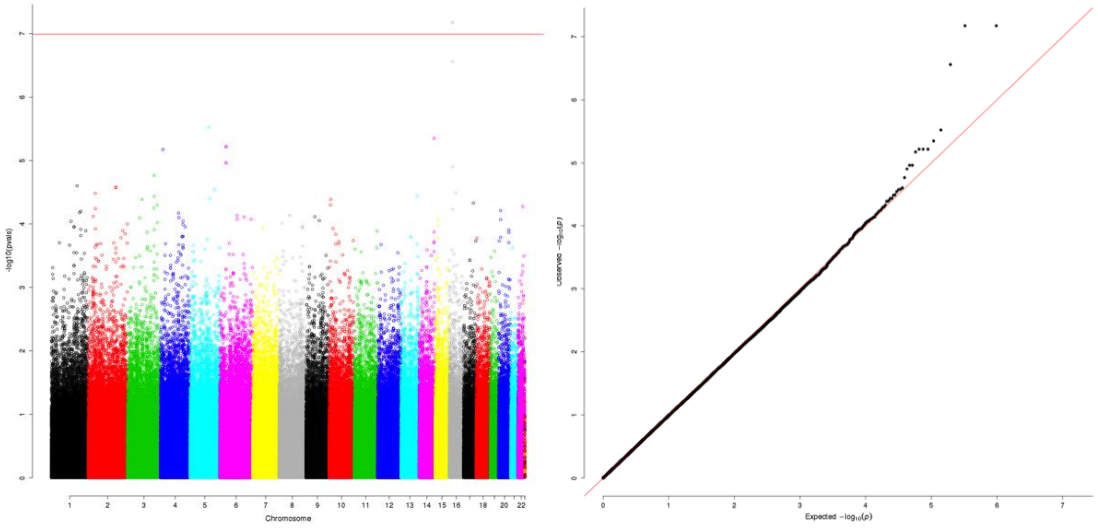
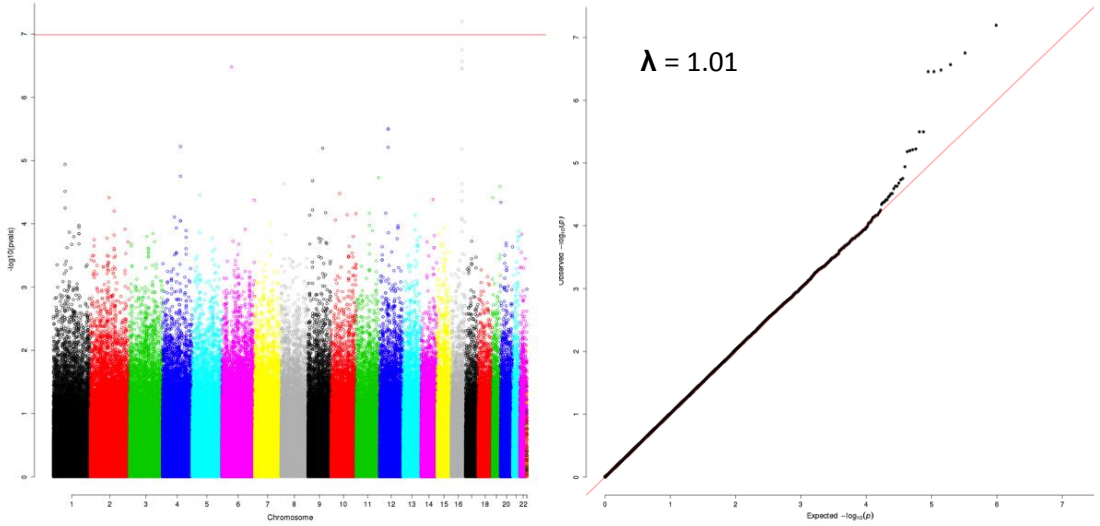


PC100



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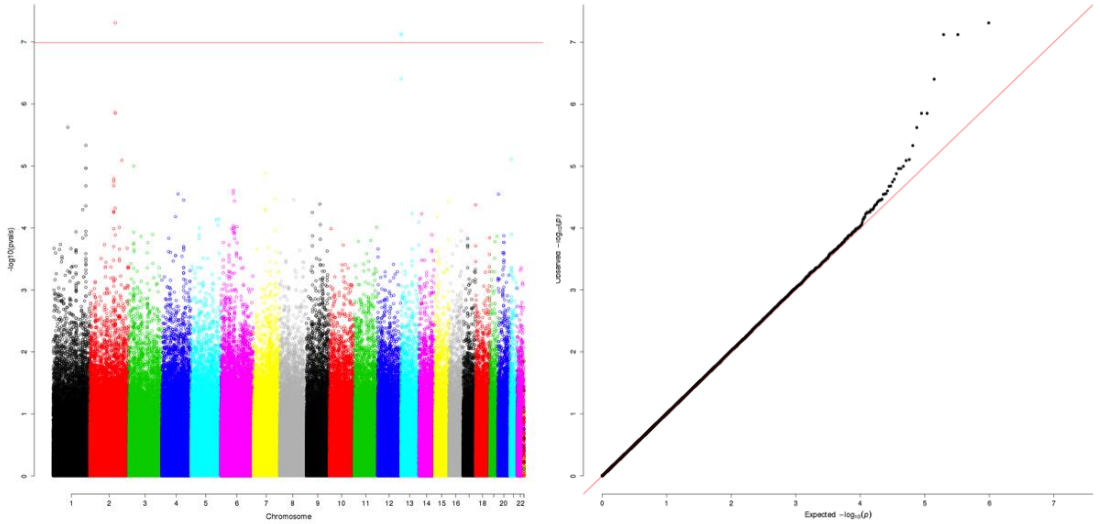

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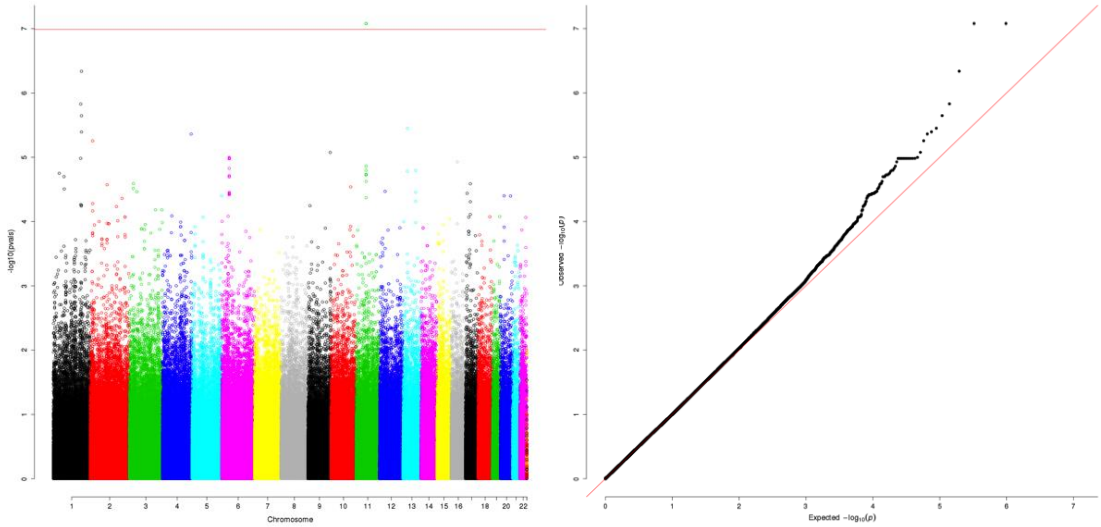

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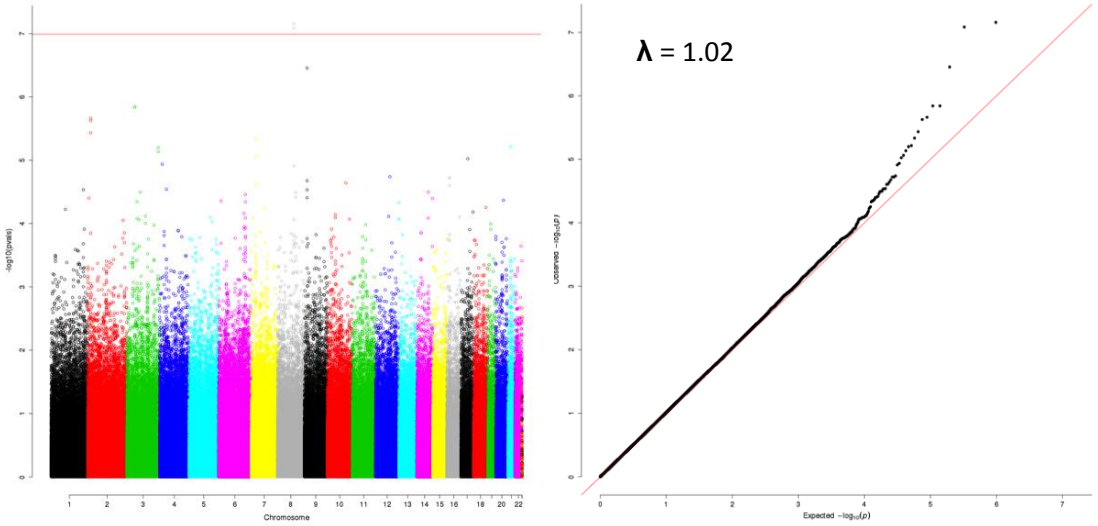

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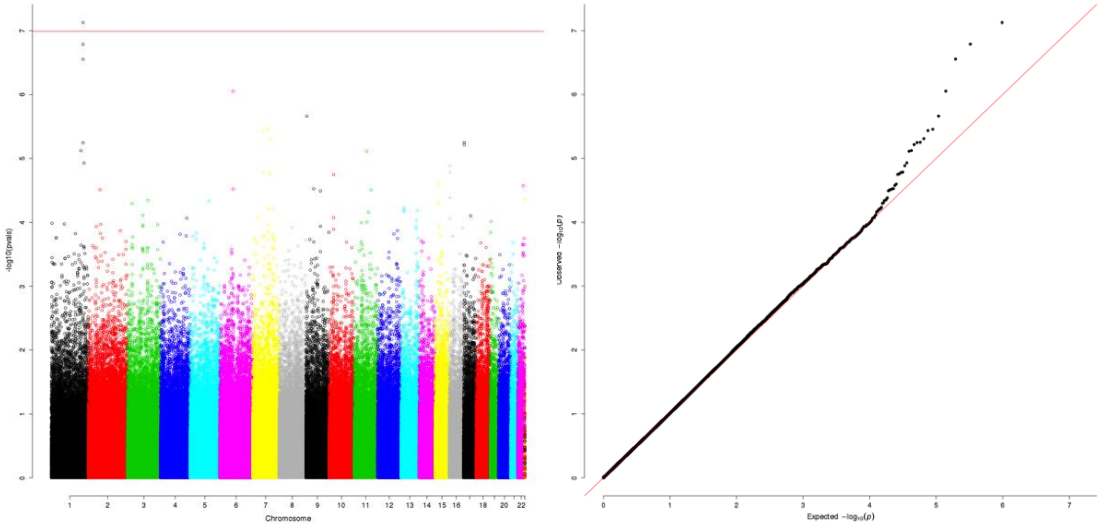

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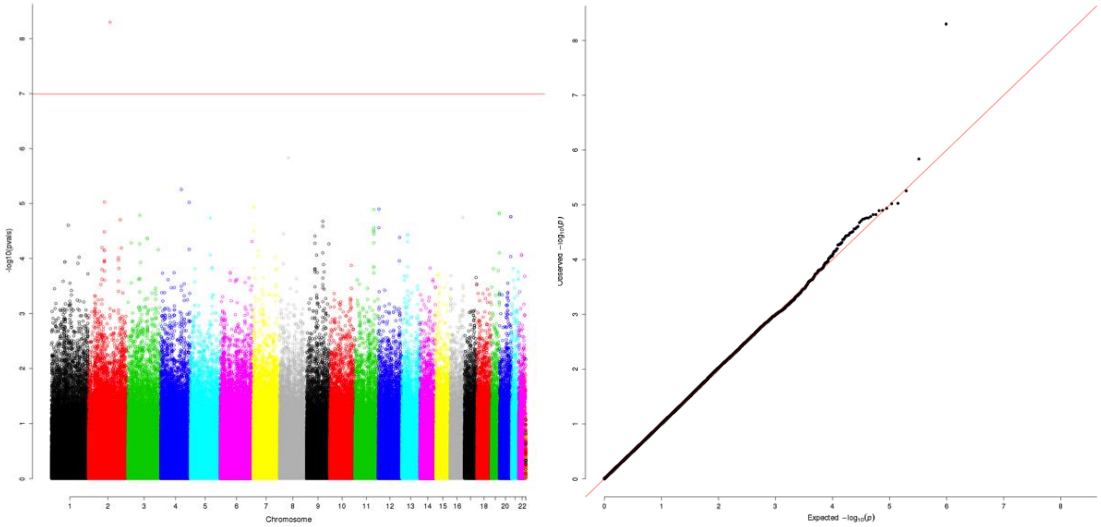

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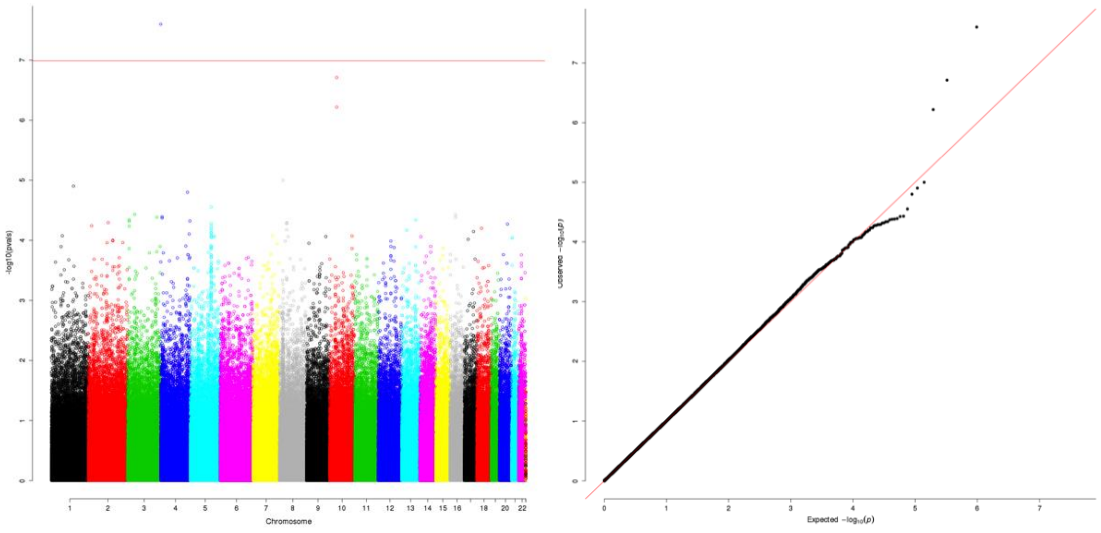

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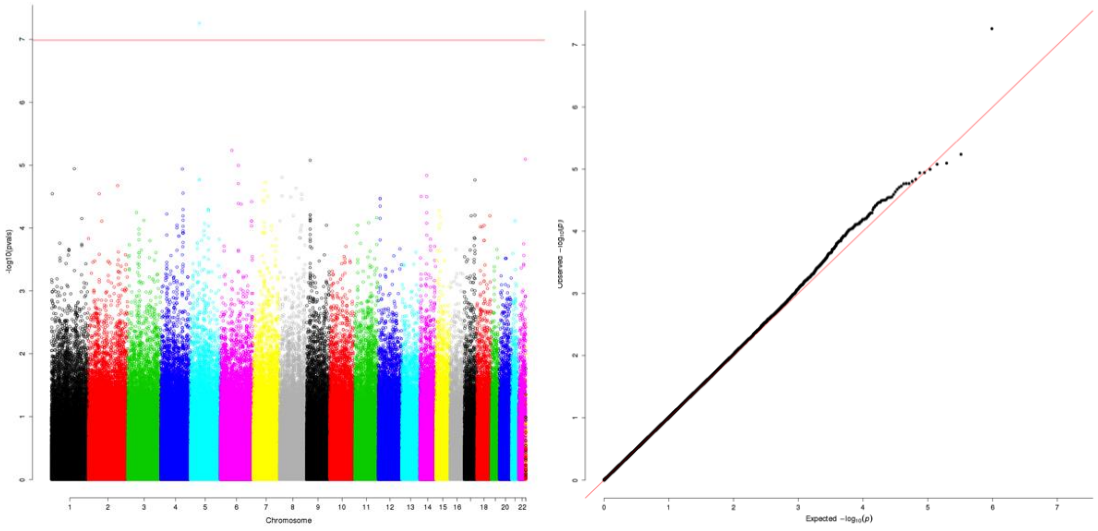

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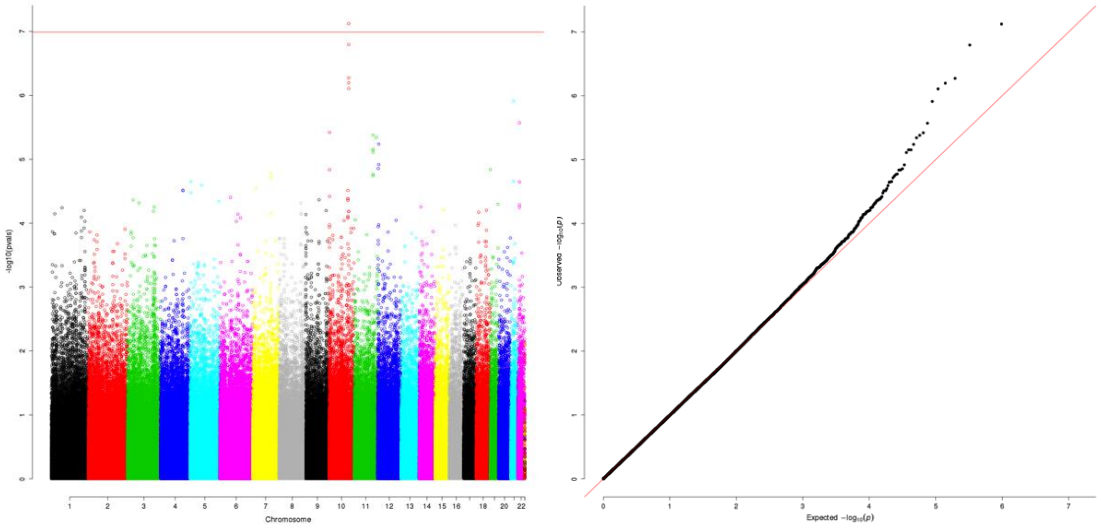

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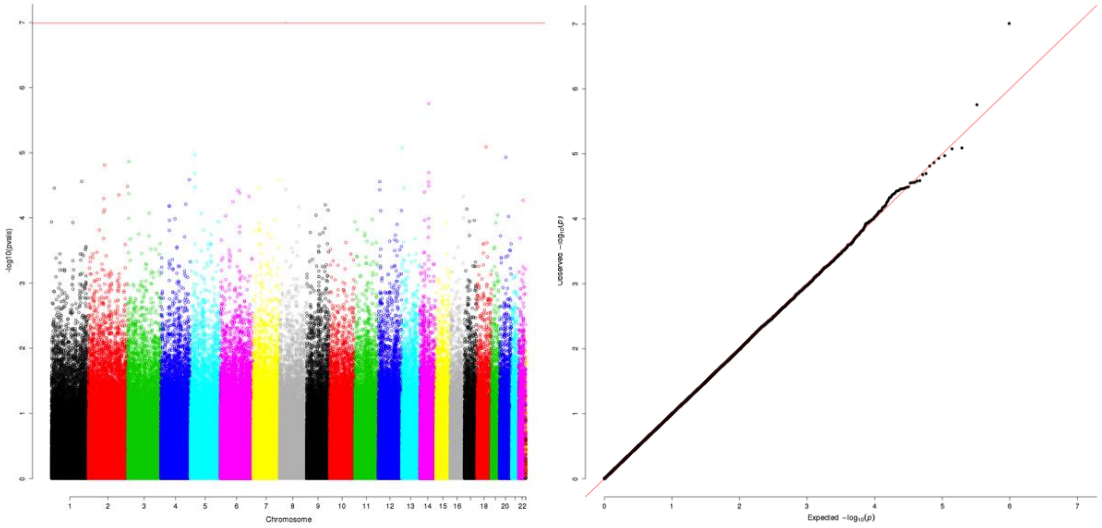

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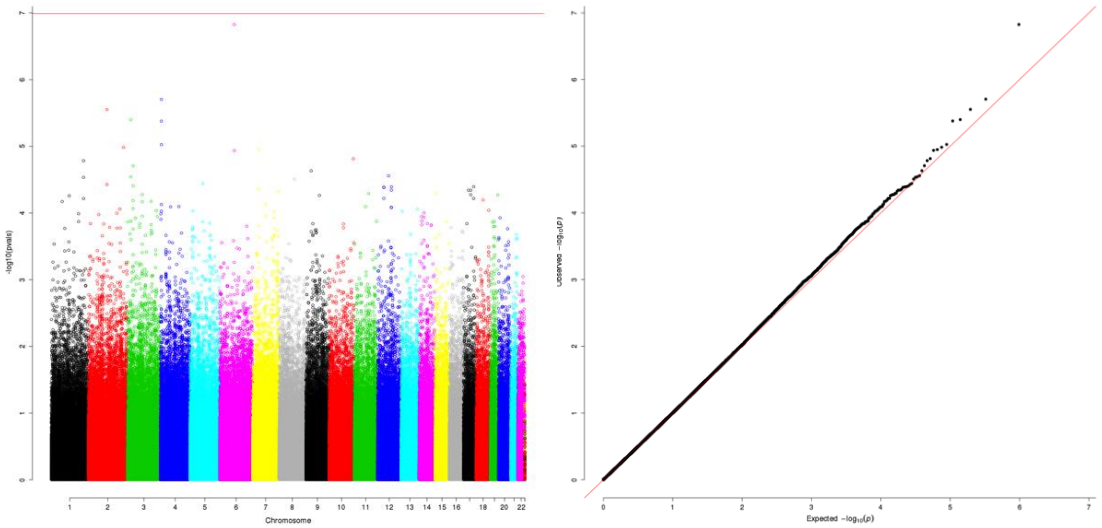

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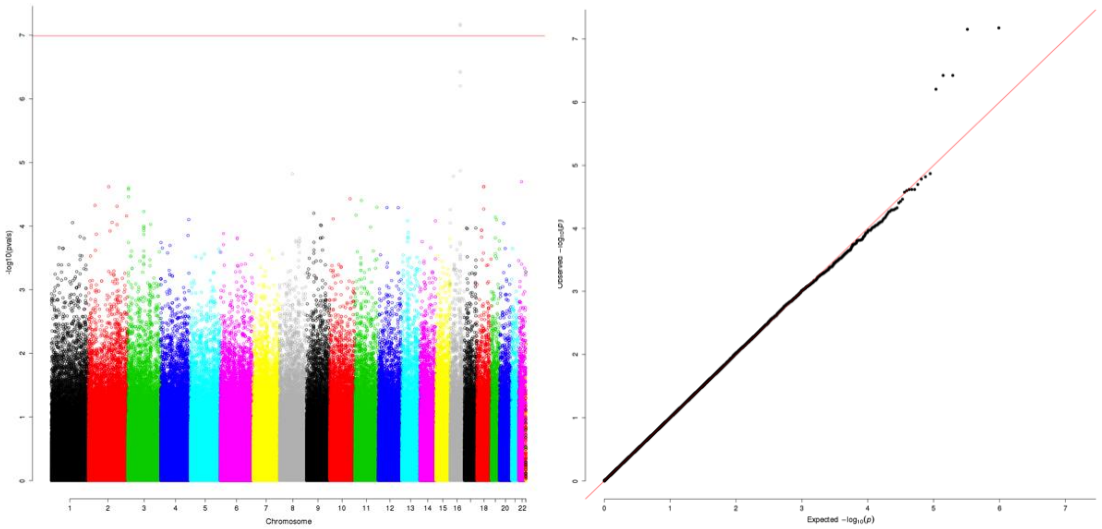

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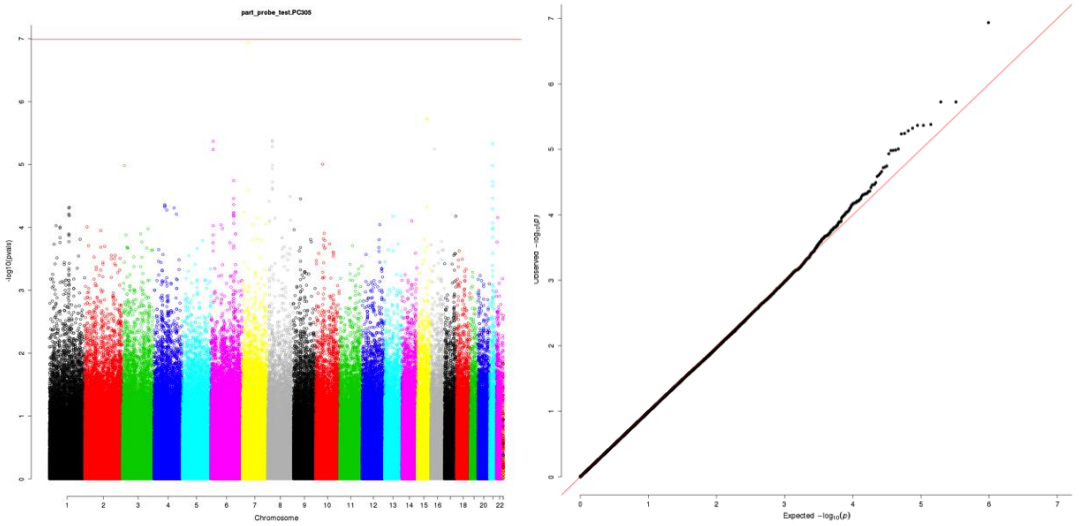

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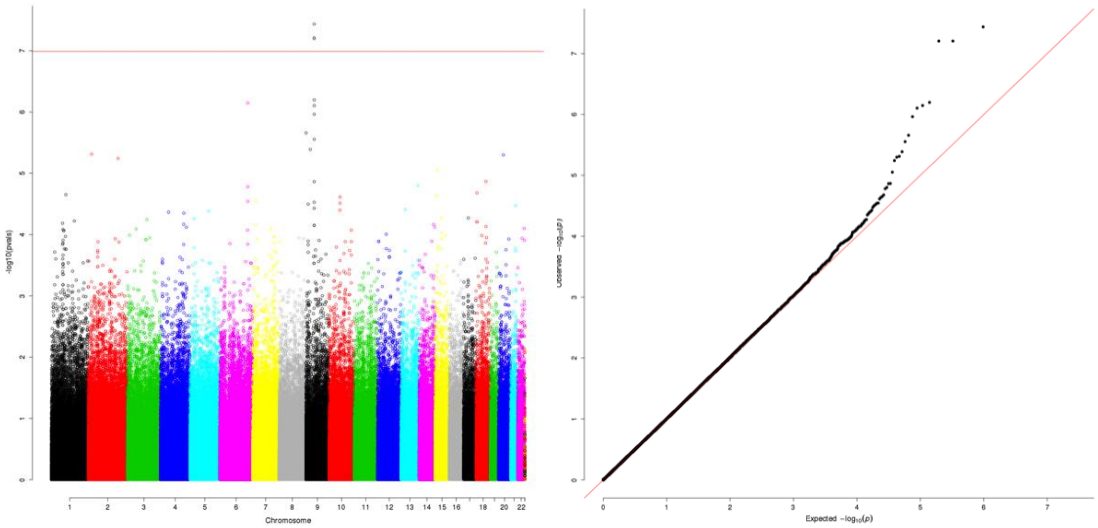

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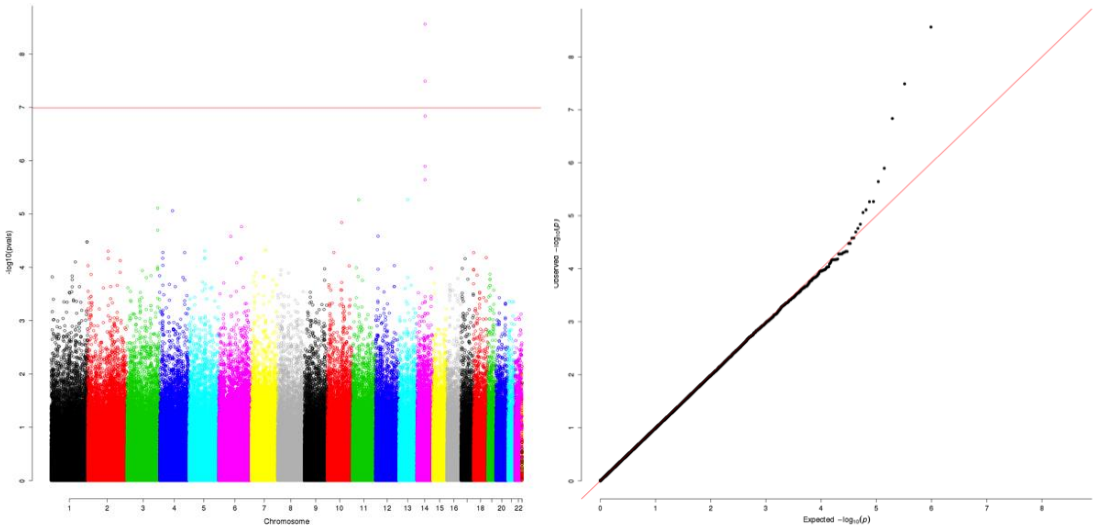
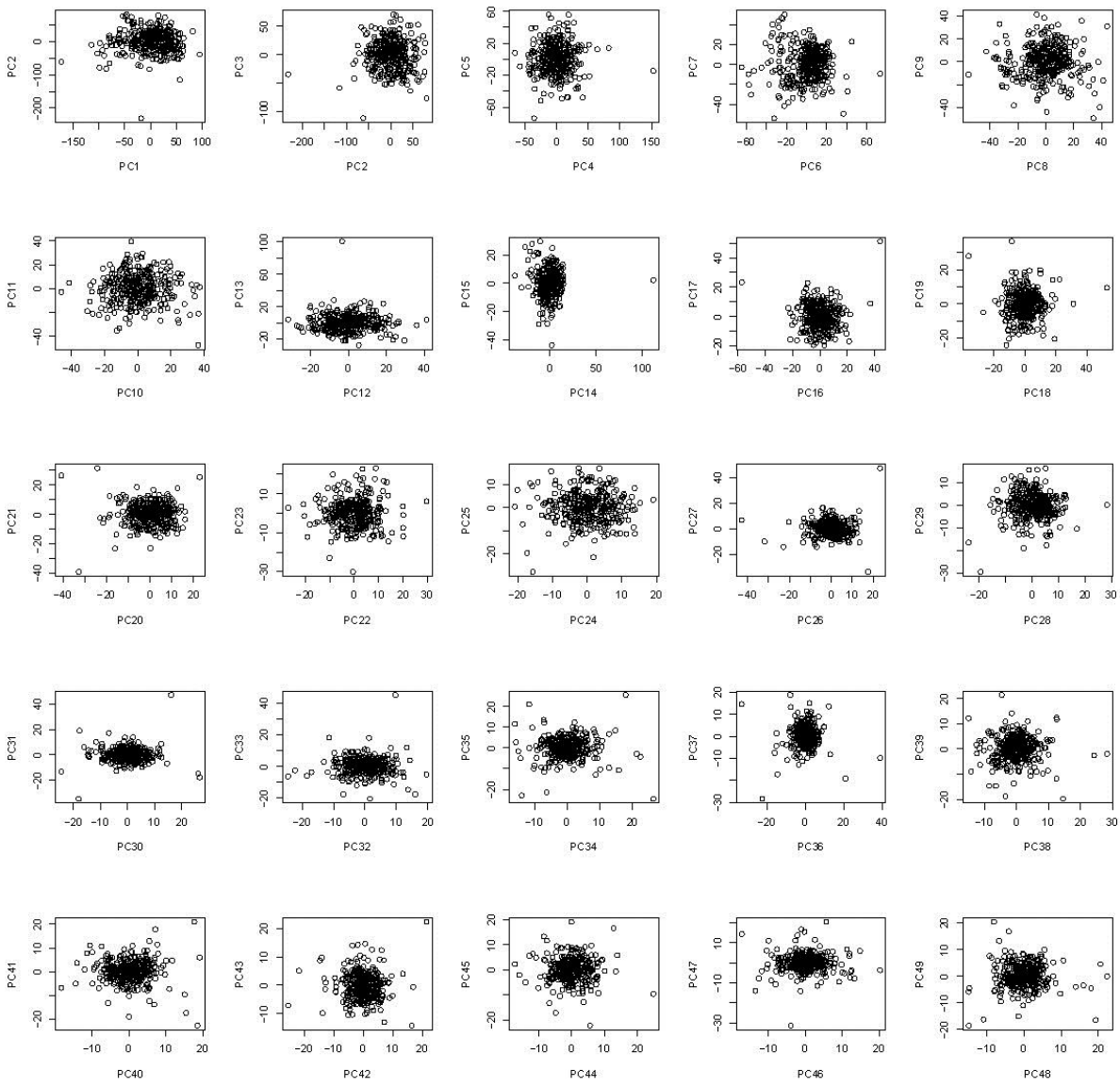


Figure S5 Manhattan and QQ plots. Manhattan and QQ plots for each PC with a significant SNP associated in Table S1. The significance value cut-off is drawn as a red line drawn on the Manhattan plots and is based on the Bonferroni correction for each PC. The QQ plot shows the expected p-values vs. the observed p-values in the study and the lambda value gives a numerical estimation of any inflation in the statistics.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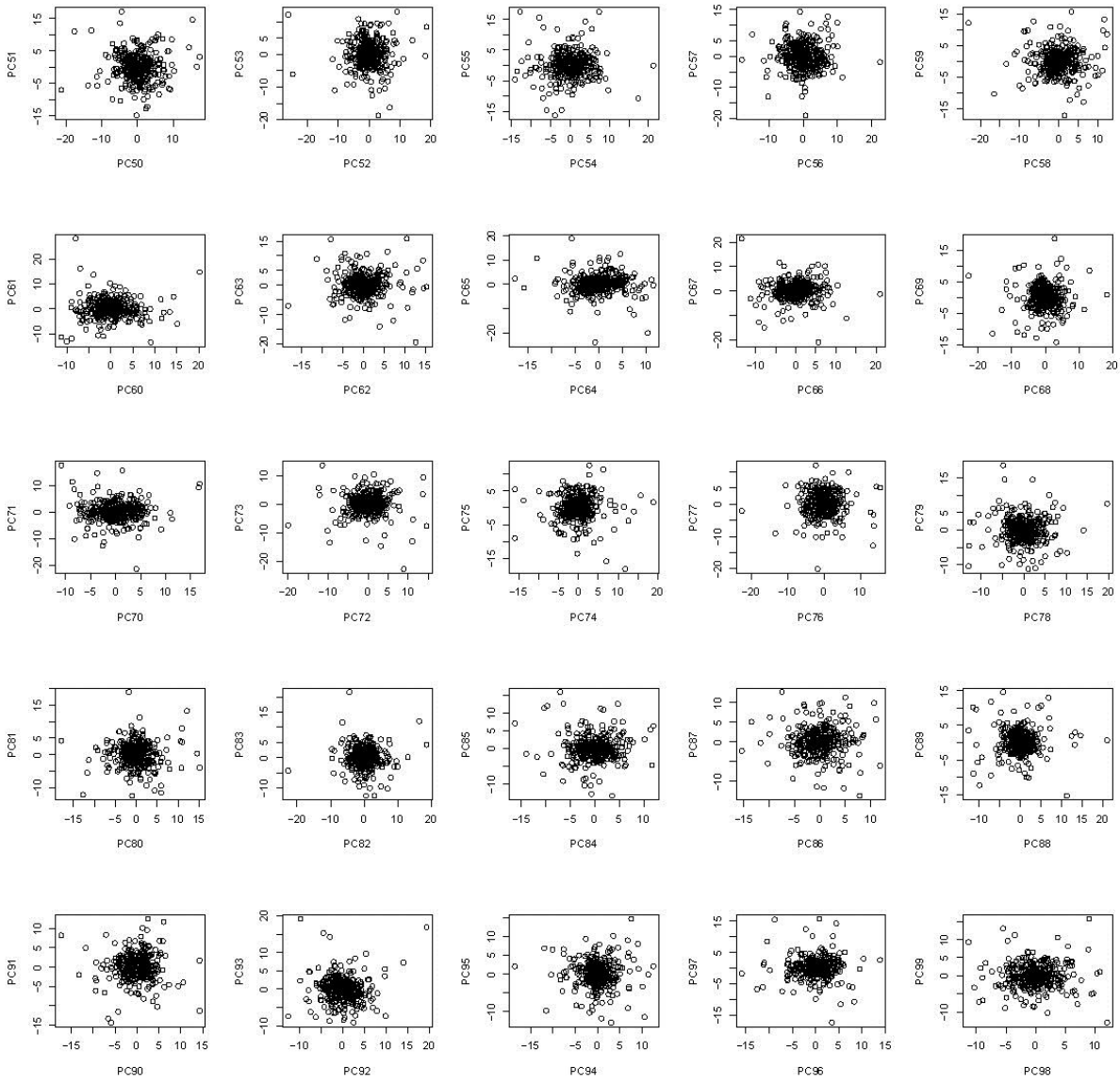
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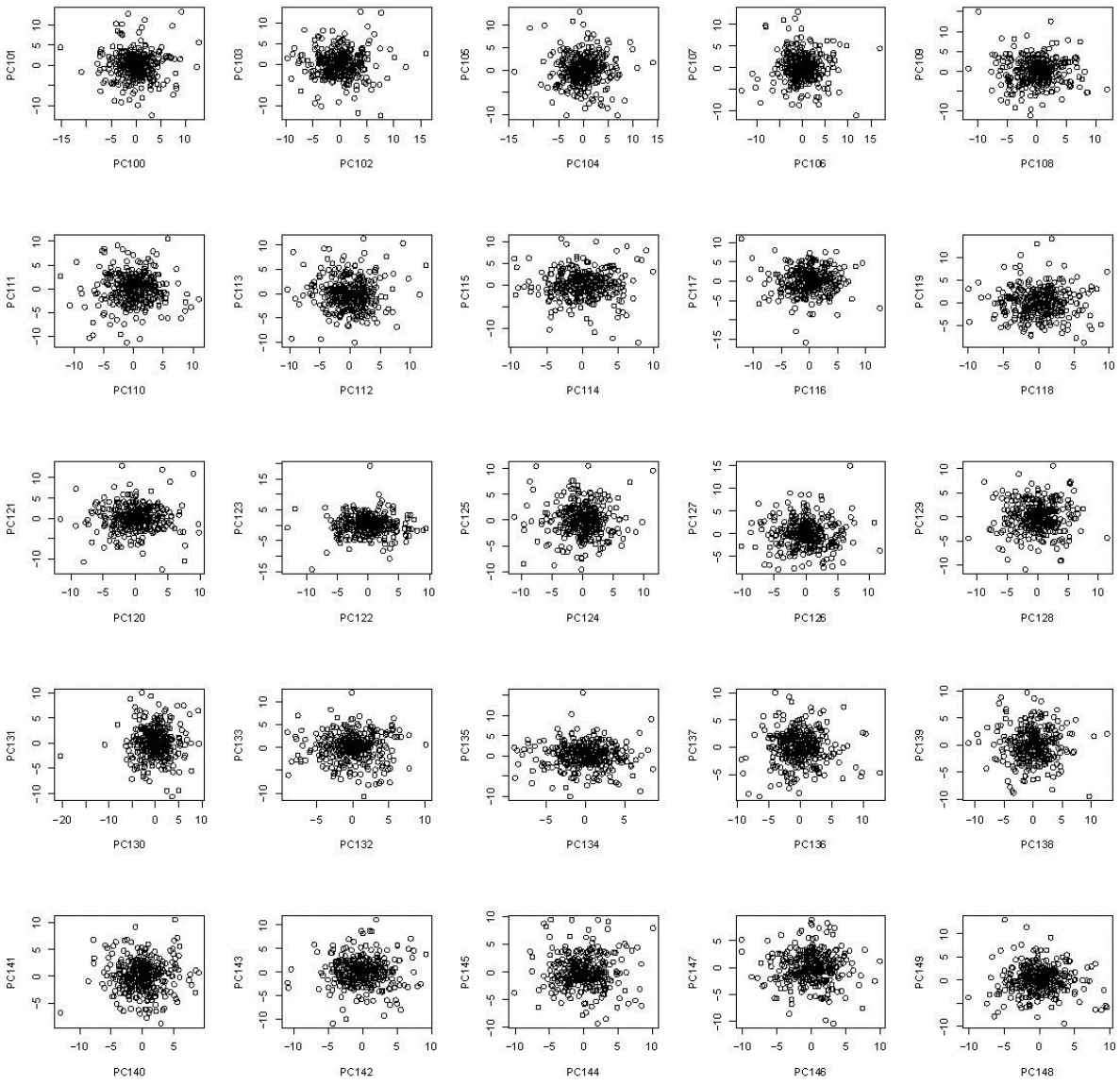
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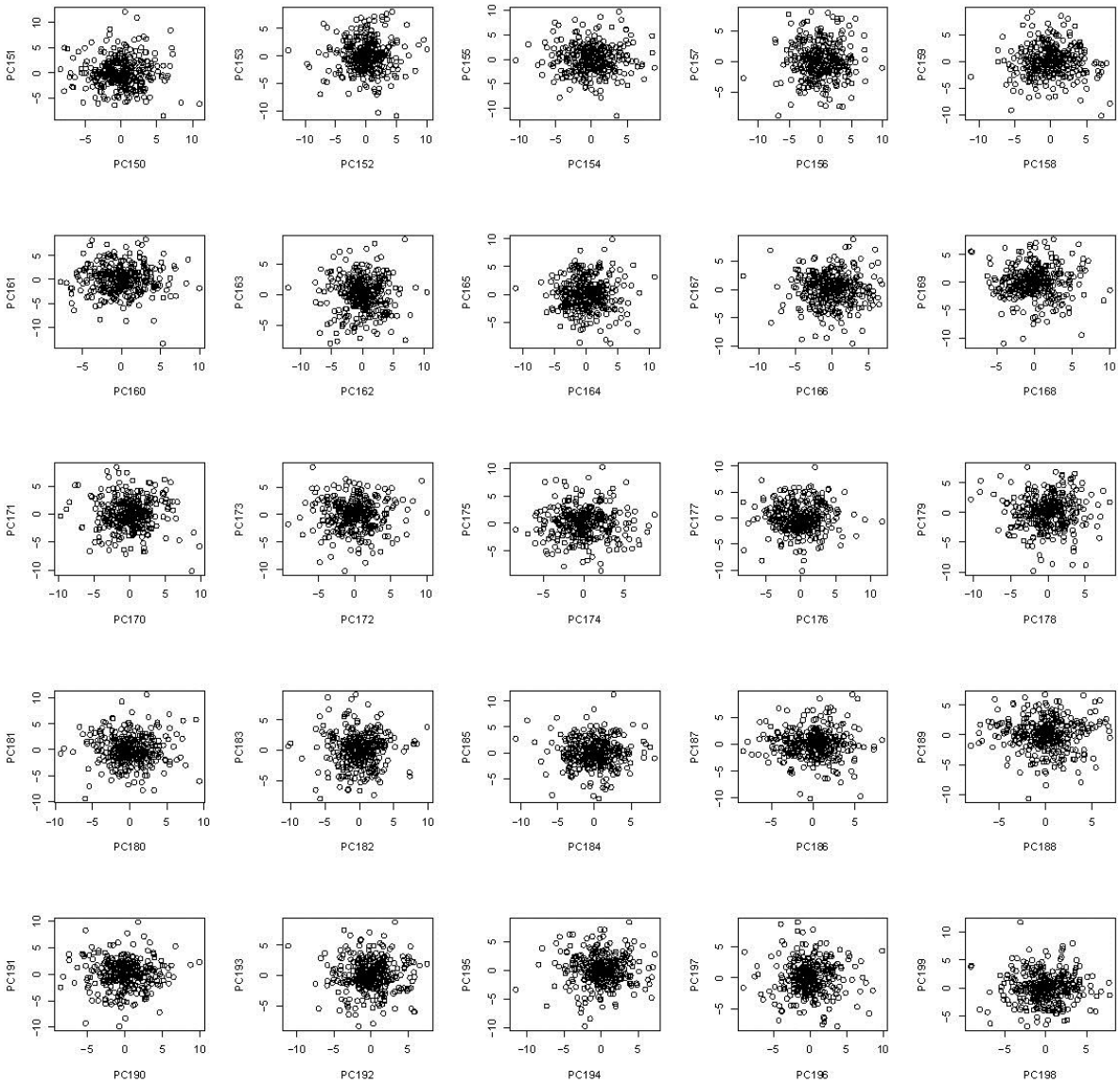
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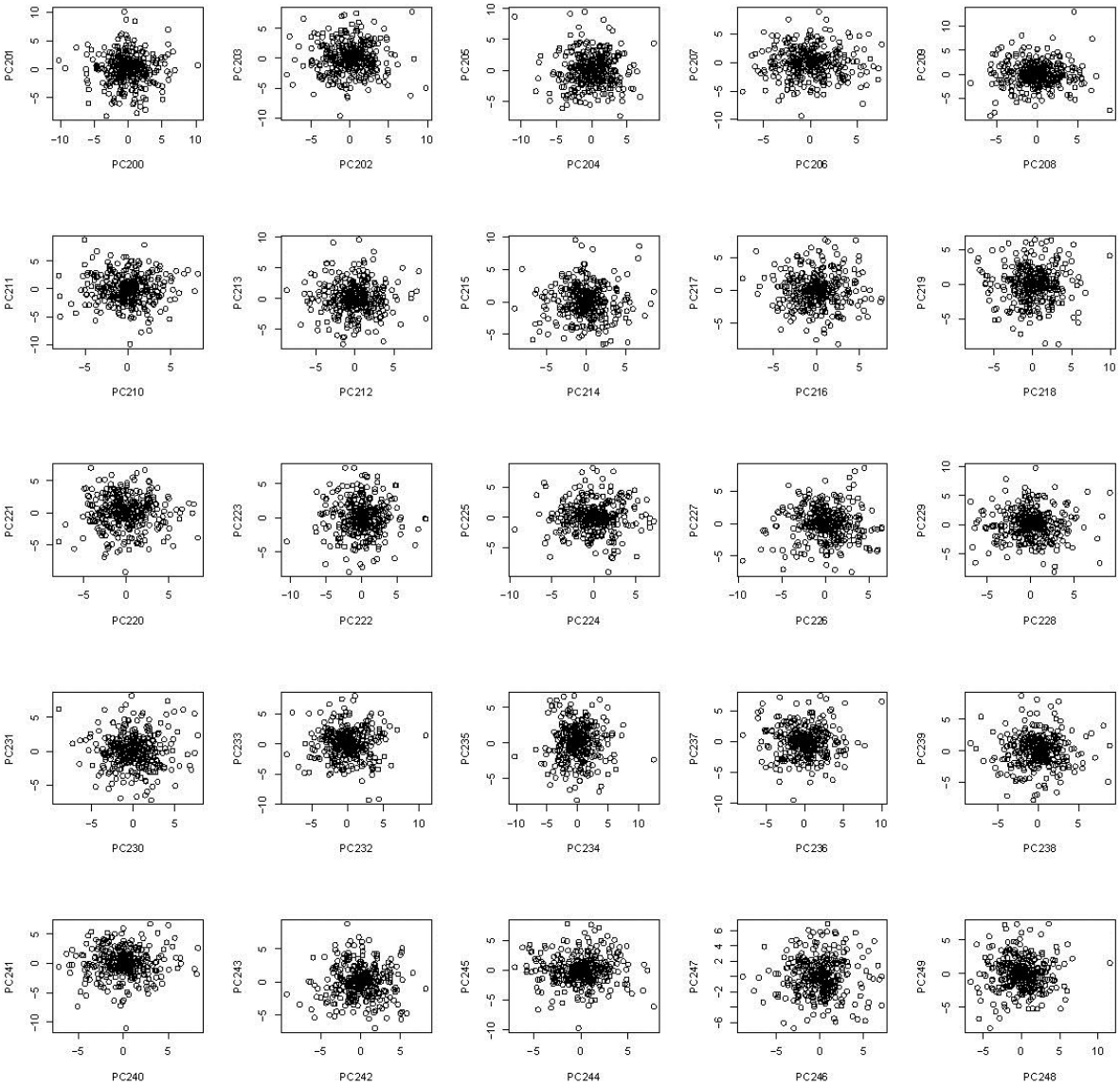
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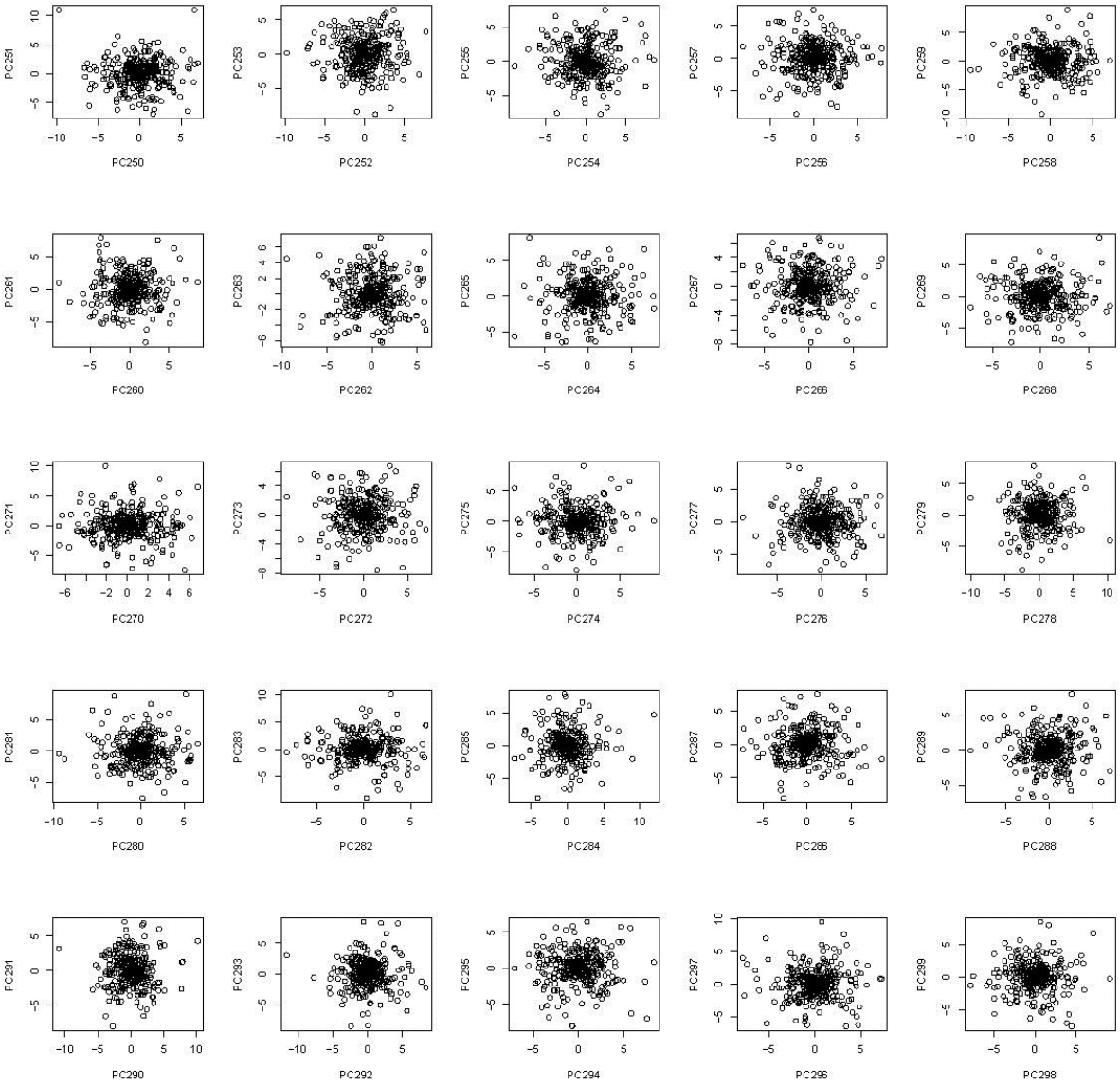
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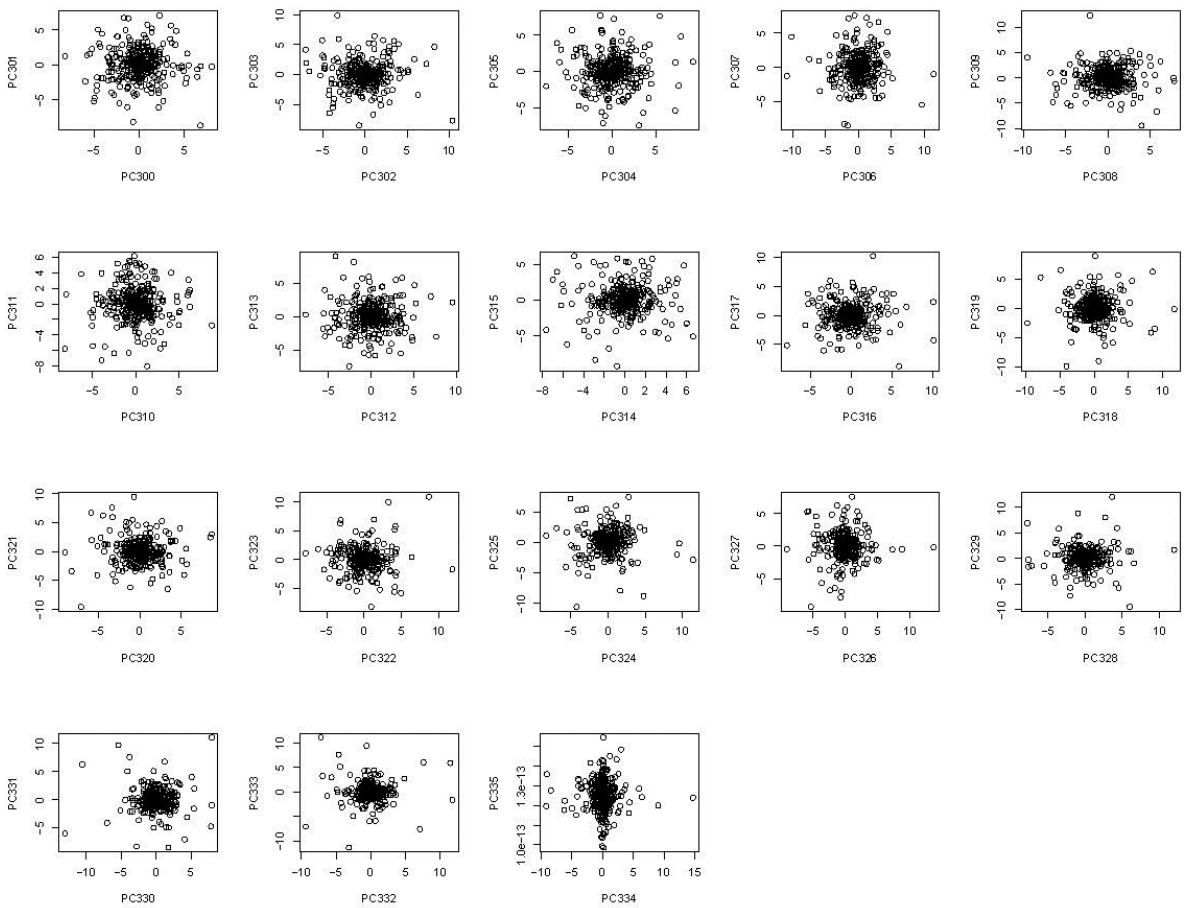

Figure S1 Scores plots of PCs against their adjacent vectors. Demonstrates a homogenous population with no clear substructure or independent clustering of groups of individuals.

Table S2 Pathway analysis for the first 50 PCs Pathway analysis for PC1-50 was performed using DAVID Bioinformatics Resources 6.7, Functional Annotation Tool. PC – principal component, Term – name of KEGG pathway, Count – count of probes in each hit, % – percentage of all probes submitted for that PC that are present within the pathway, P – the p-value that is calculated using a modified Fischer's exact test for enrichment, FDR – correction of p-values and using the Benjamini-Hochberg FDR method.

PC	Term	Count	%	P	FDR
1	Ribosome	8	7.9	1.00E-06	4.50E-05
3	Fc gamma R-mediated phagocytosis	14	2.7	4.30E-05	5.40E-03
7	Porphyrin metabolism	7	1.5	1.60E-04	2.00E-02
8	Proteasome	12	2.6	2.70E-07	4.00E-05
	Oxidative phosphorylation	18	3.9	1.20E-06	8.70E-05
	Huntington's disease	21	4.6	1.90E-06	9.00E-05
	Parkinson's disease	15	3.3	8.50E-05	3.10E-03
	Alzheimer's disease	15	3.3	1.10E-03	3.00E-02
12	Hematopoietic cell lineage	13	2.5	1.40E-05	2.00E-03
	B cell receptor signaling pathway	10	1.9	5.60E-04	3.80E-02
	Antigen processing and presentation	10	1.9	1.20E-03	5.30E-02
	Graft-versus-host disease	7	1.3	1.30E-03	4.40E-02
	Non-small cell lung cancer	8	1.5	1.50E-03	4.00E-02
	Asthma	6	1.2	2.00E-03	4.40E-02
13	RNA degradation	11	2.3	1.30E-05	1.80E-03
	Oxidative phosphorylation	15	3.1	7.80E-05	5.60E-03
	Ribosome	11	2.3	5.00E-04	2.40E-02
18	Ribosome	14	2.9	9.40E-07	1.00E-04

24	B cell receptor signaling pathway	14	2.9	2.00E-07	2.70E-05
25	B cell receptor signaling pathway	11	2.2	1.10E-04	1.60E-02
26	Primary immunodeficiency	8	1.7	7.90E-05	1.20E-02
32	Oxidative phosphorylation	13	2.7	2.90E-04	3.70E-02