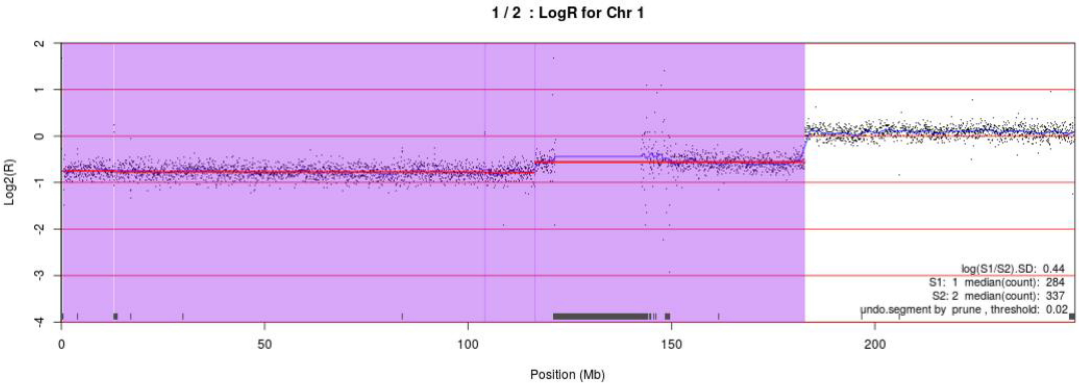
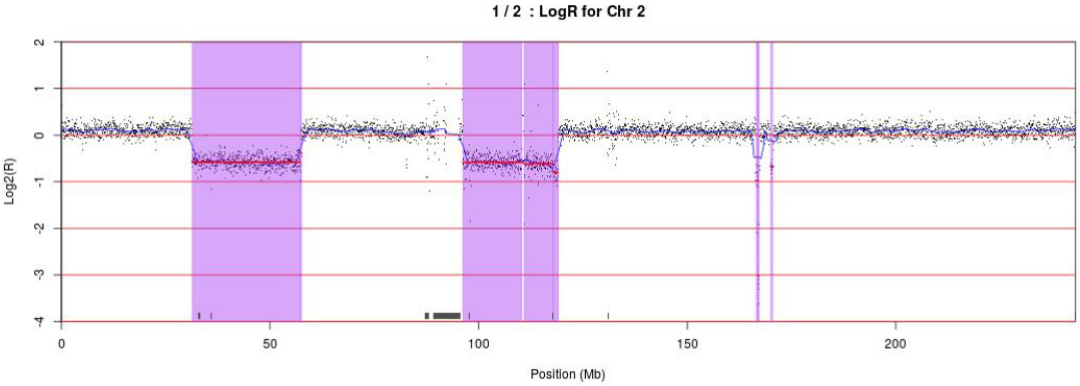
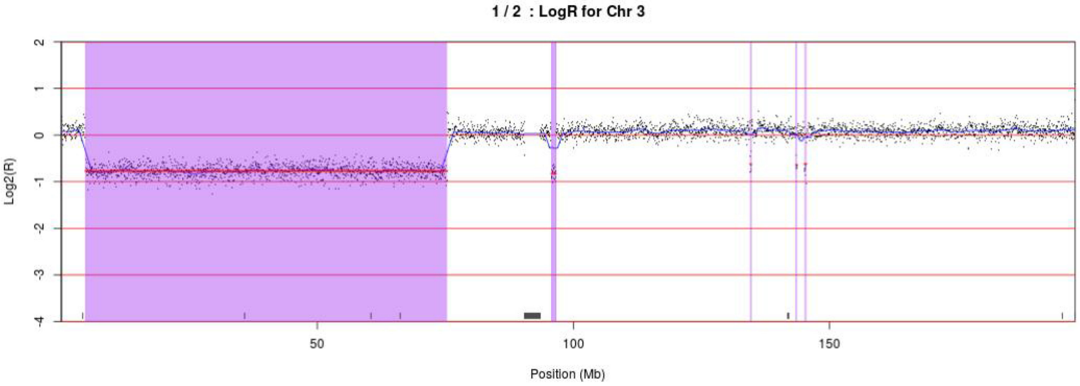
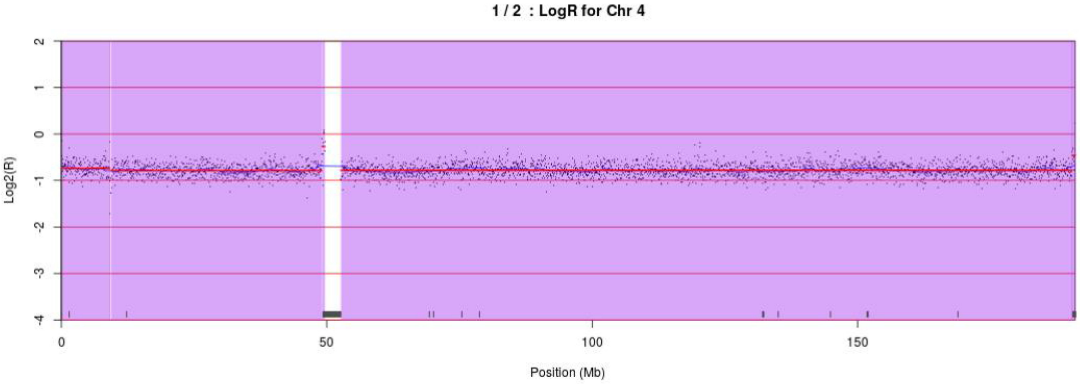
Large-scale copy number analysis reveals variations in genes not previously associated with malignant pleural mesothelioma

SUPPLEMENTARY MATERIALS

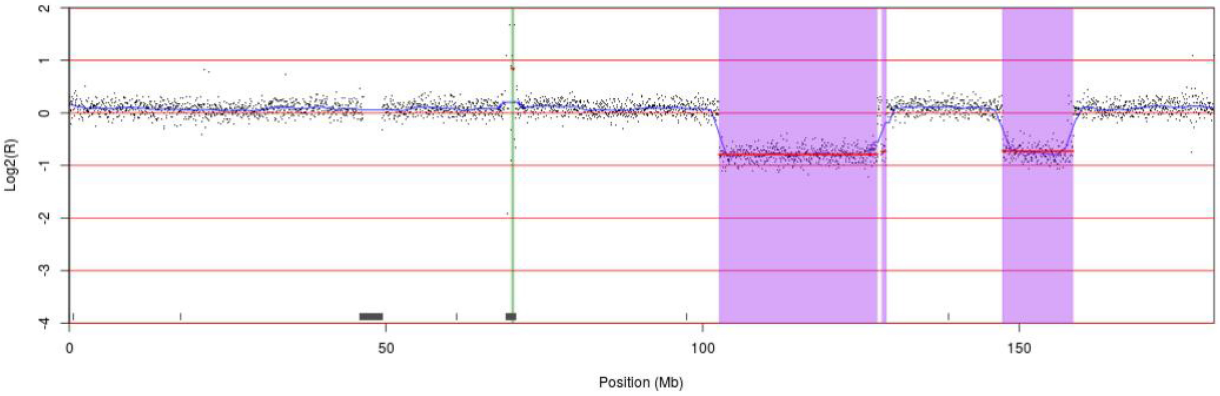

1 / 2 : LogR for Chr 1


1 / 2 : LogR for Chr 2

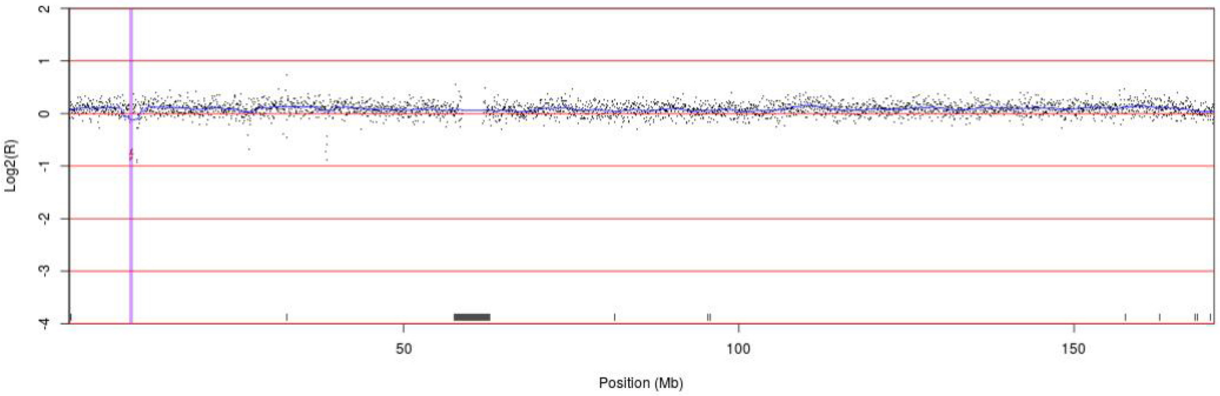

1 / 2 : LogR for Chr 3


1 / 2 : LogR for Chr 4

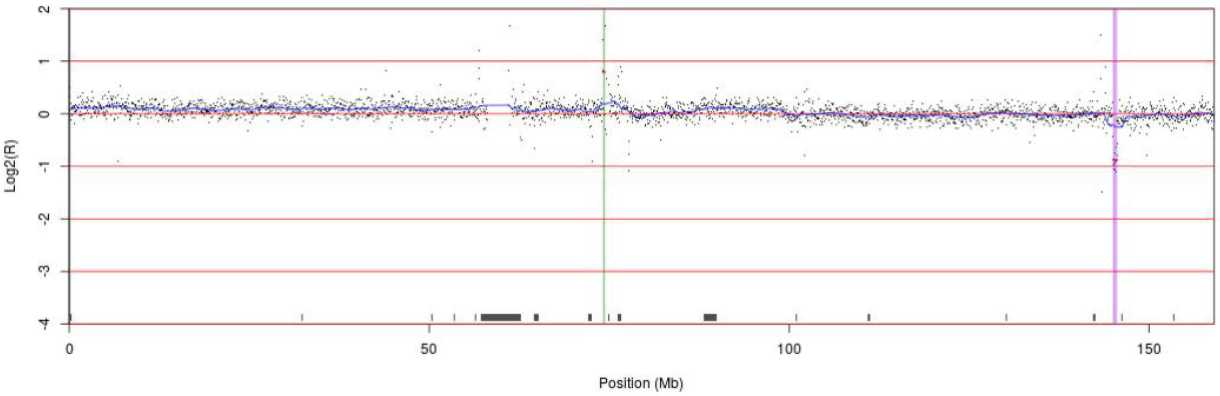
1 / 2 : LogR for Chr 5



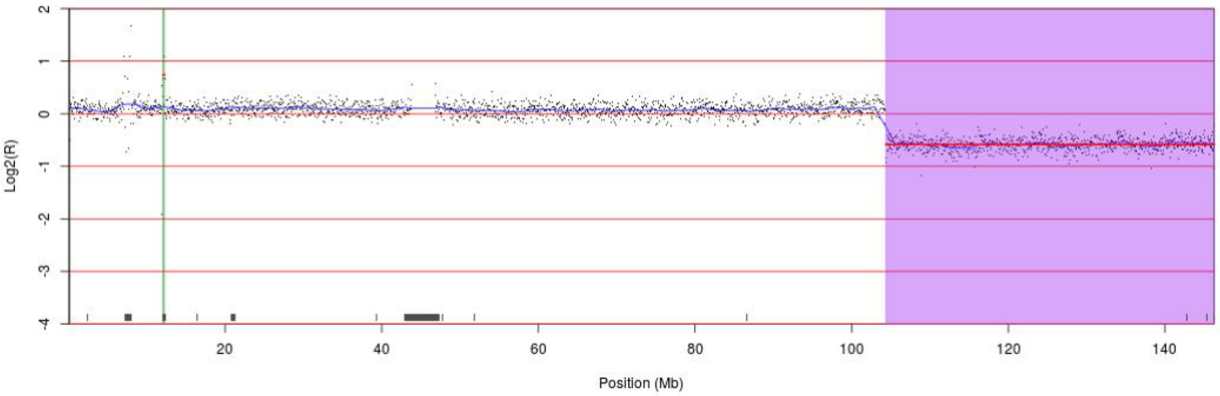
1 / 2 : LogR for Chr 6

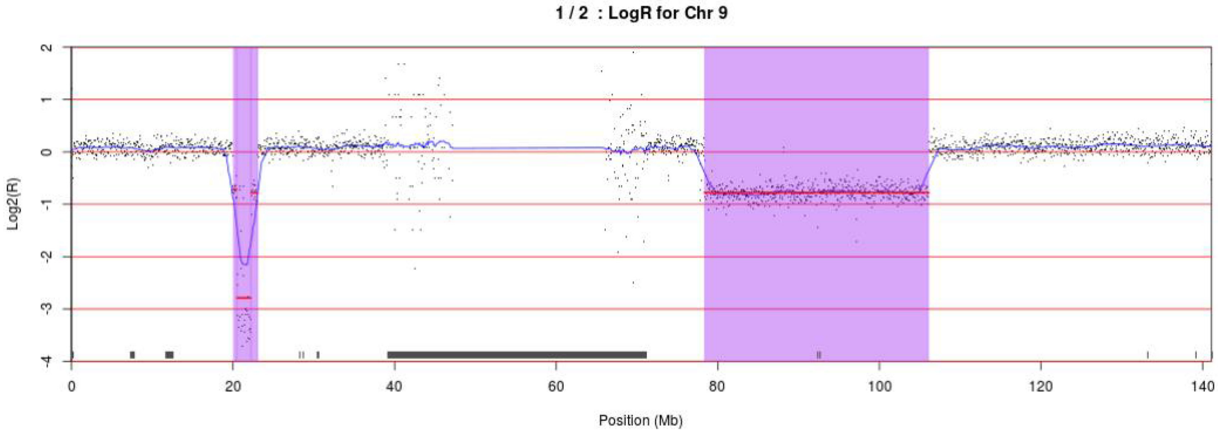


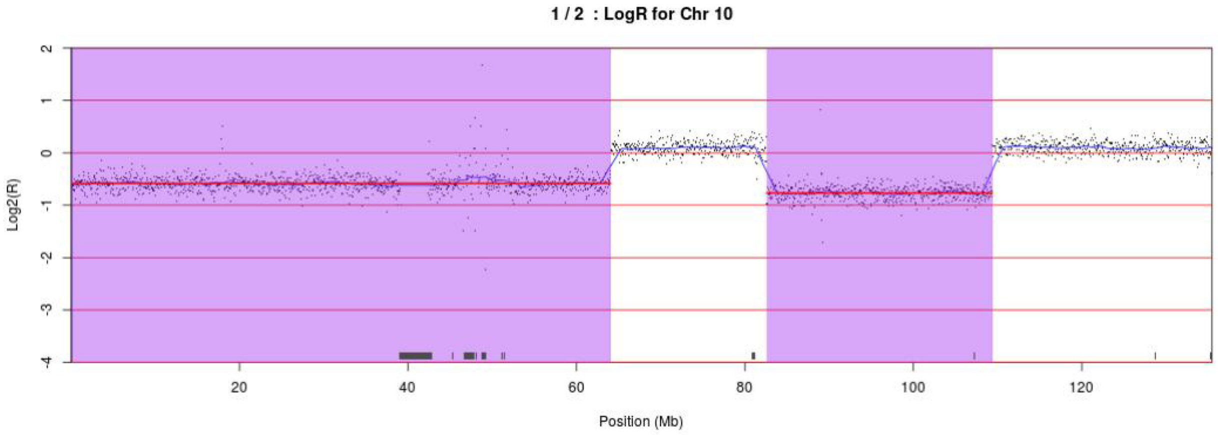
1 / 2 : LogR for Chr 7

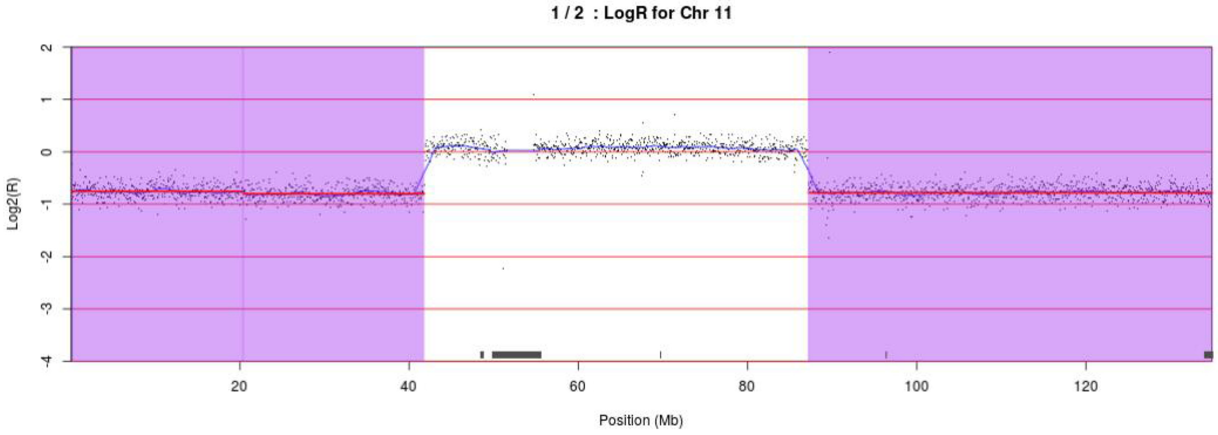


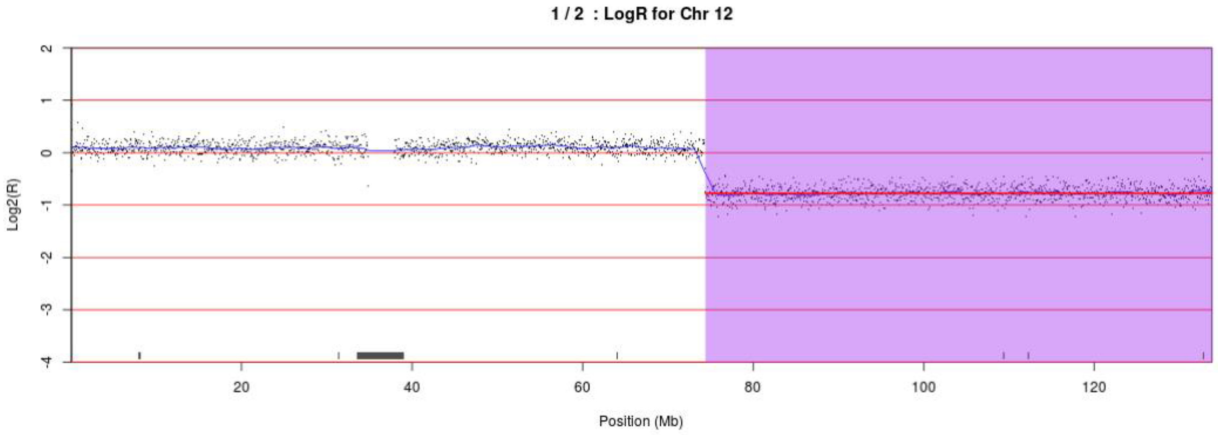
1 / 2 : LogR for Chr 8

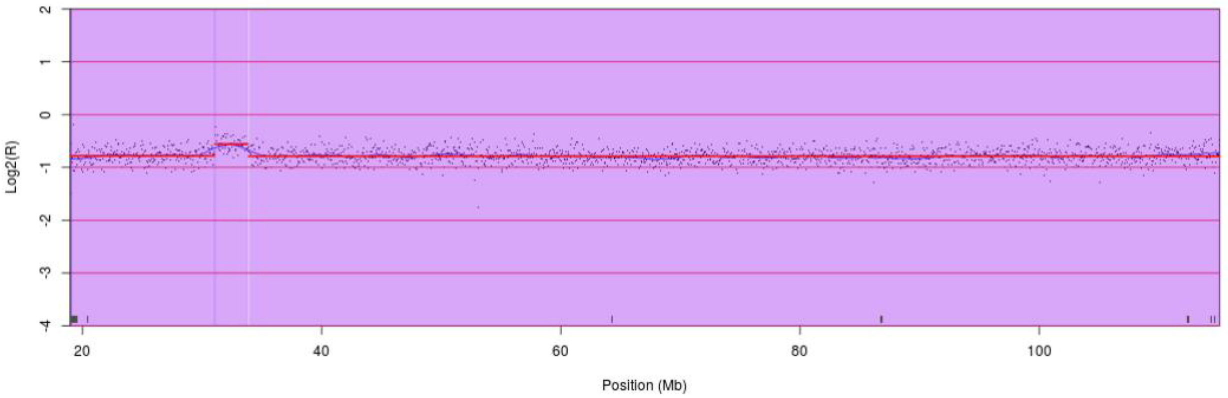


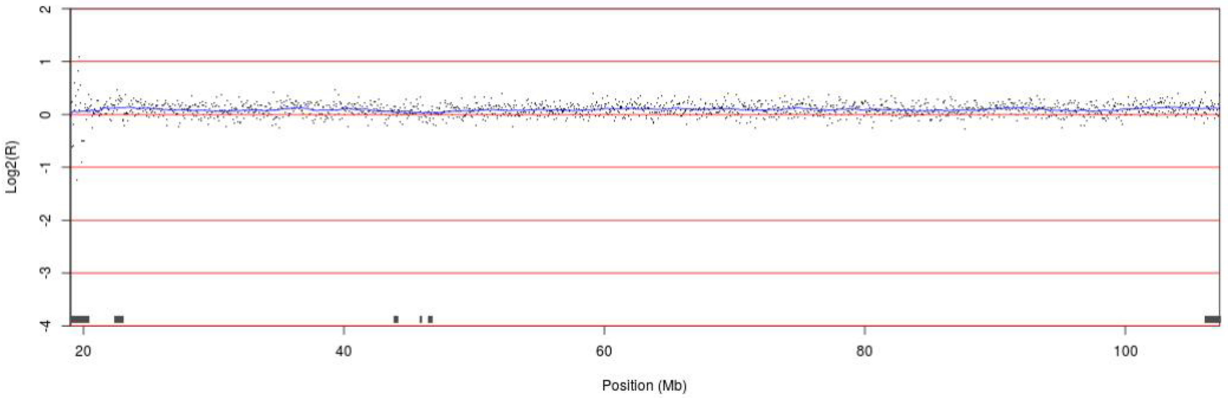

1 / 2 : LogR for Chr 9

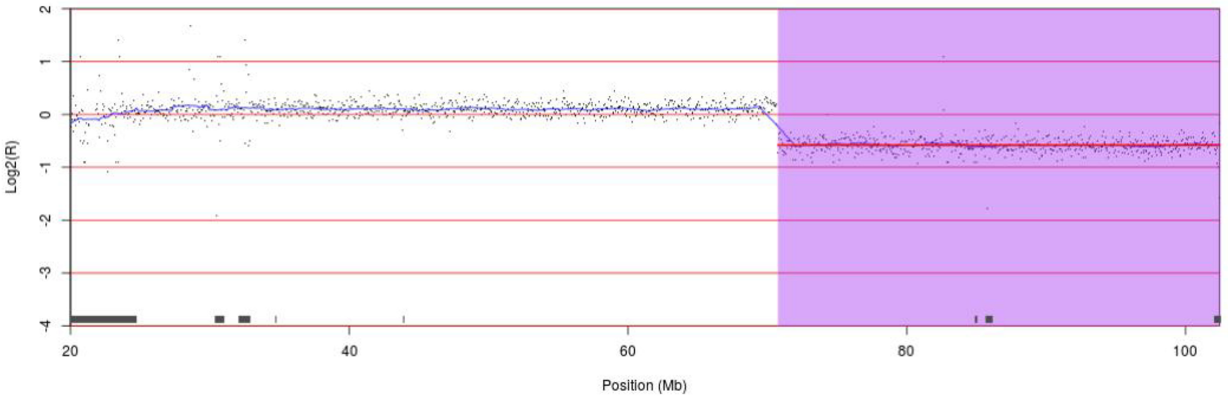

1 / 2 : LogR for Chr 10

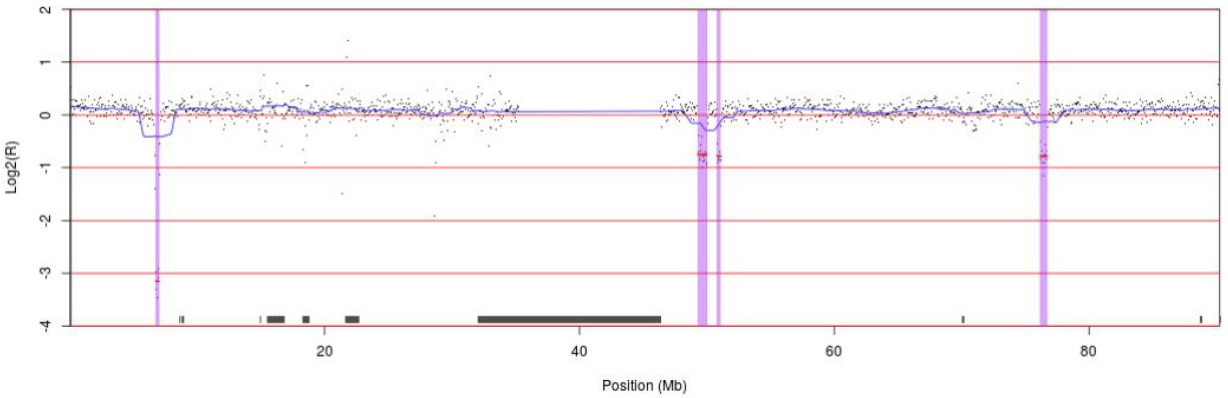

1 / 2 : LogR for Chr 11

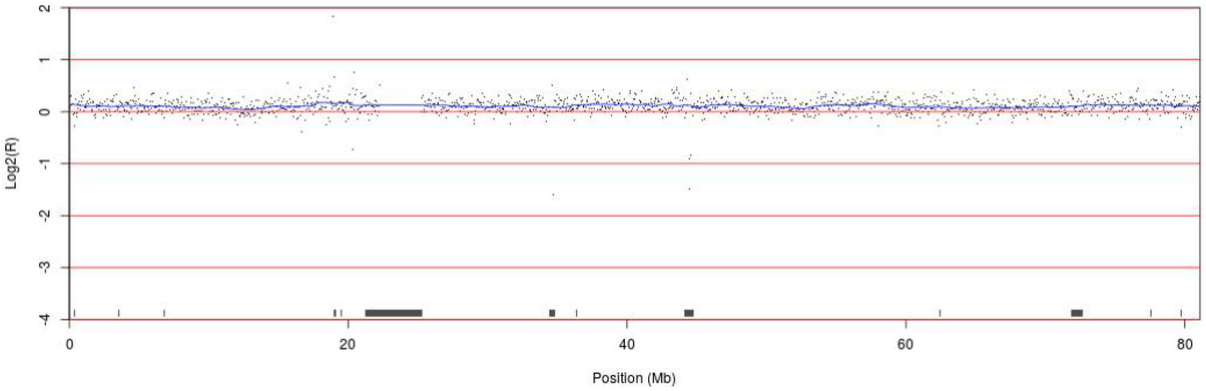

1 / 2 : LogR for Chr 12

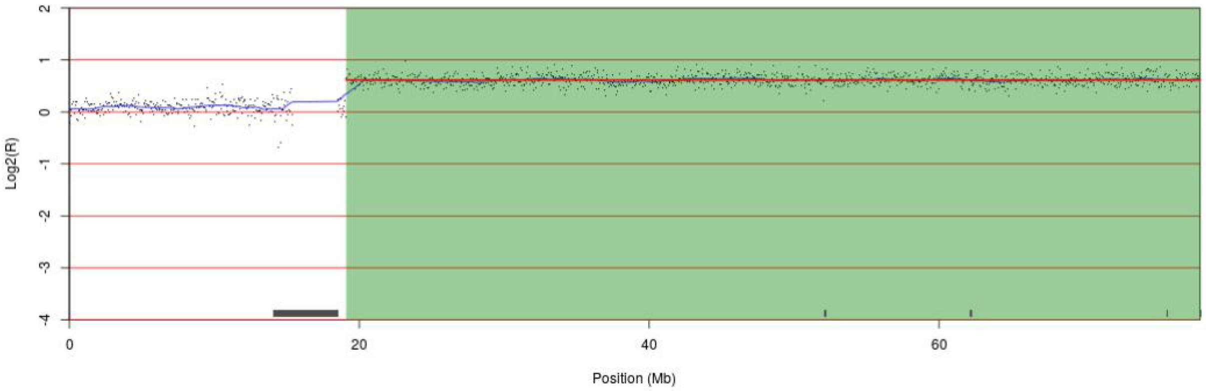

1 / 2 : LogR for Chr 13

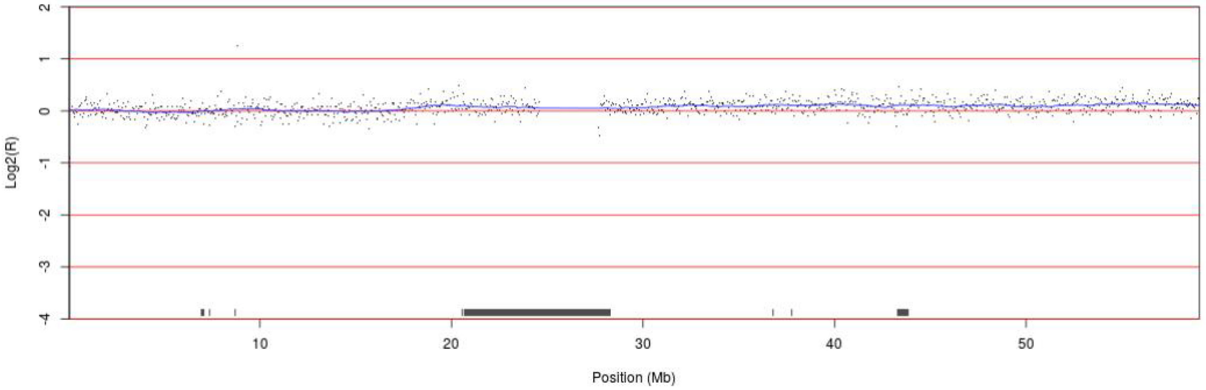

1 / 2 : LogR for Chr 14

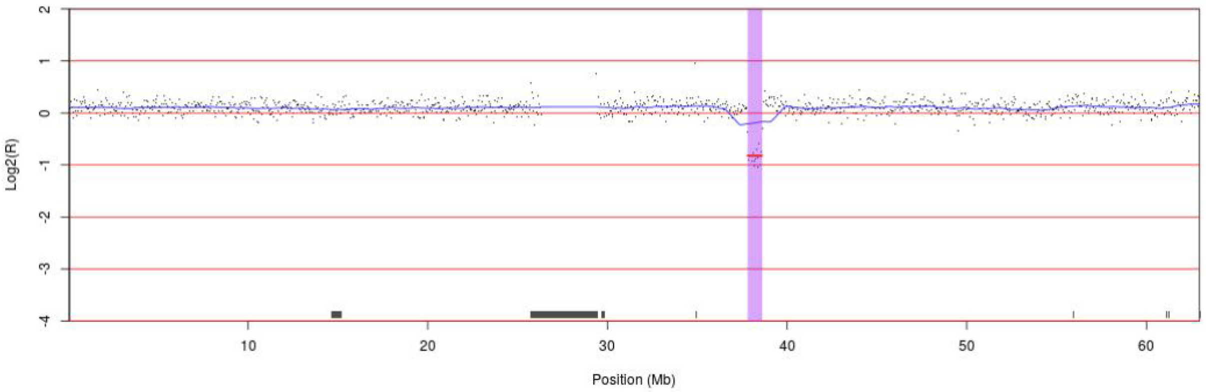

1 / 2 : LogR for Chr 15

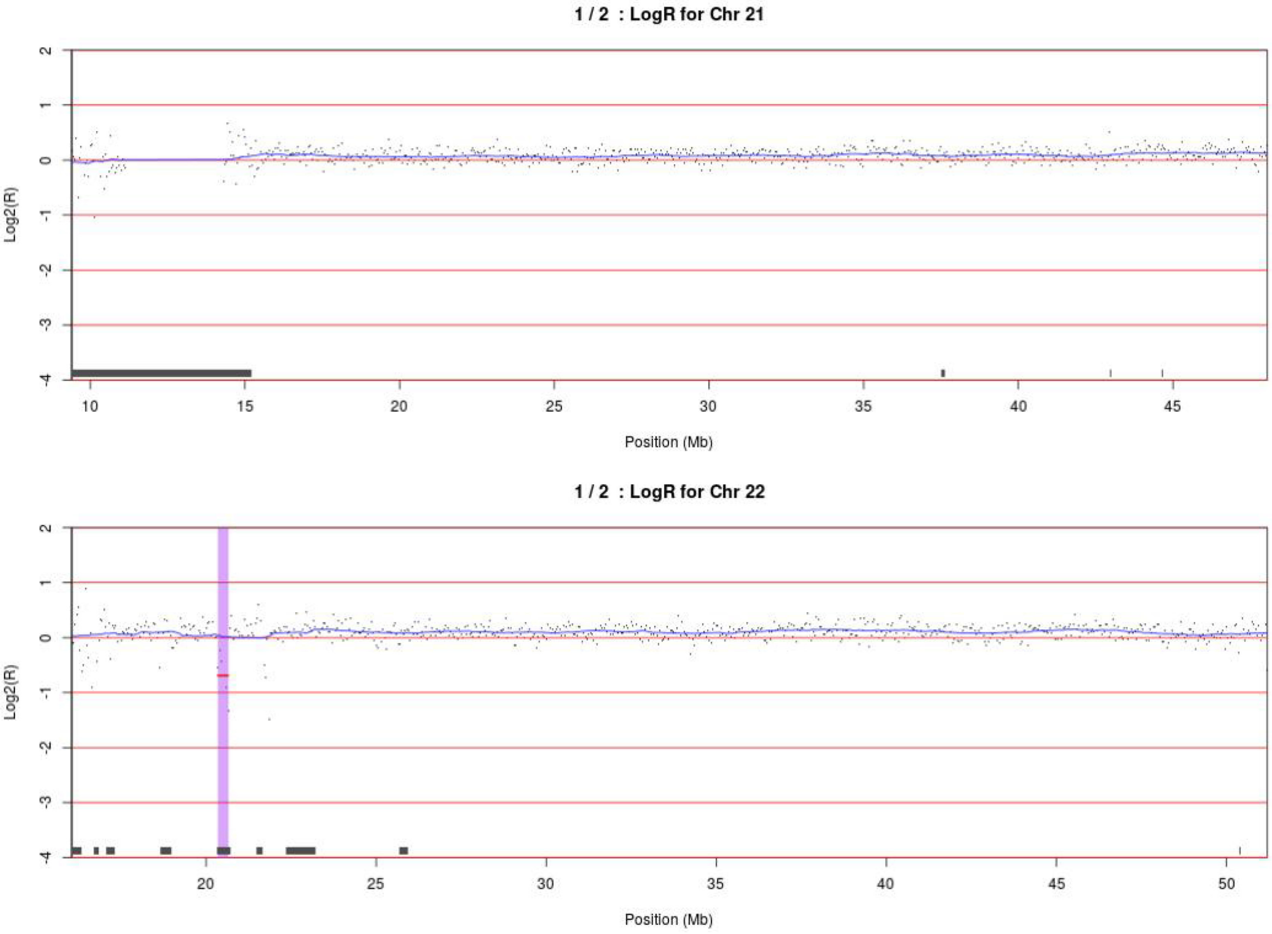

1 / 2 : LogR for Chr 16


1 / 2 : LogR for Chr 17


1 / 2 : LogR for Chr 18


1 / 2 : LogR for Chr 19

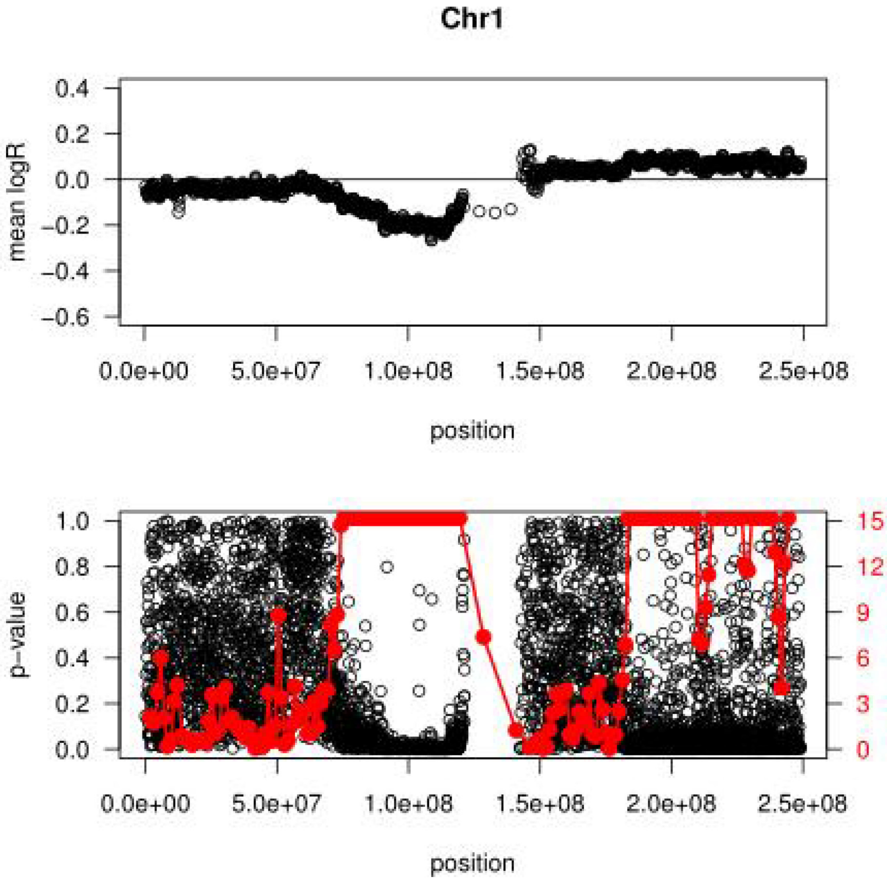

1 / 2 : LogR for Chr 20

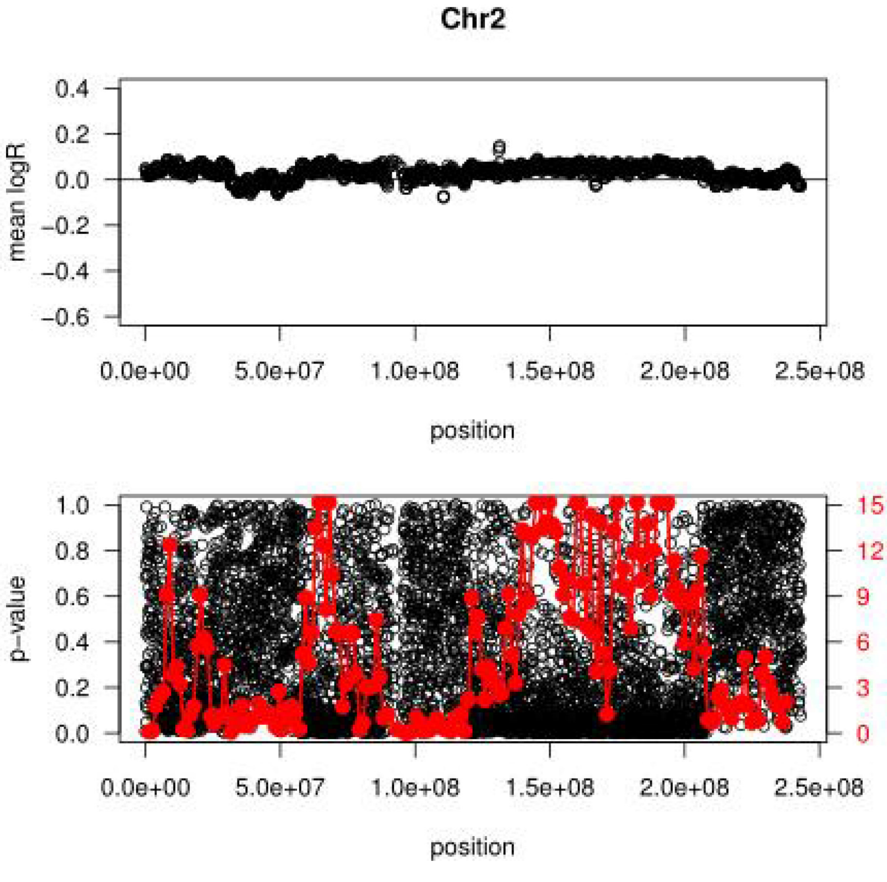


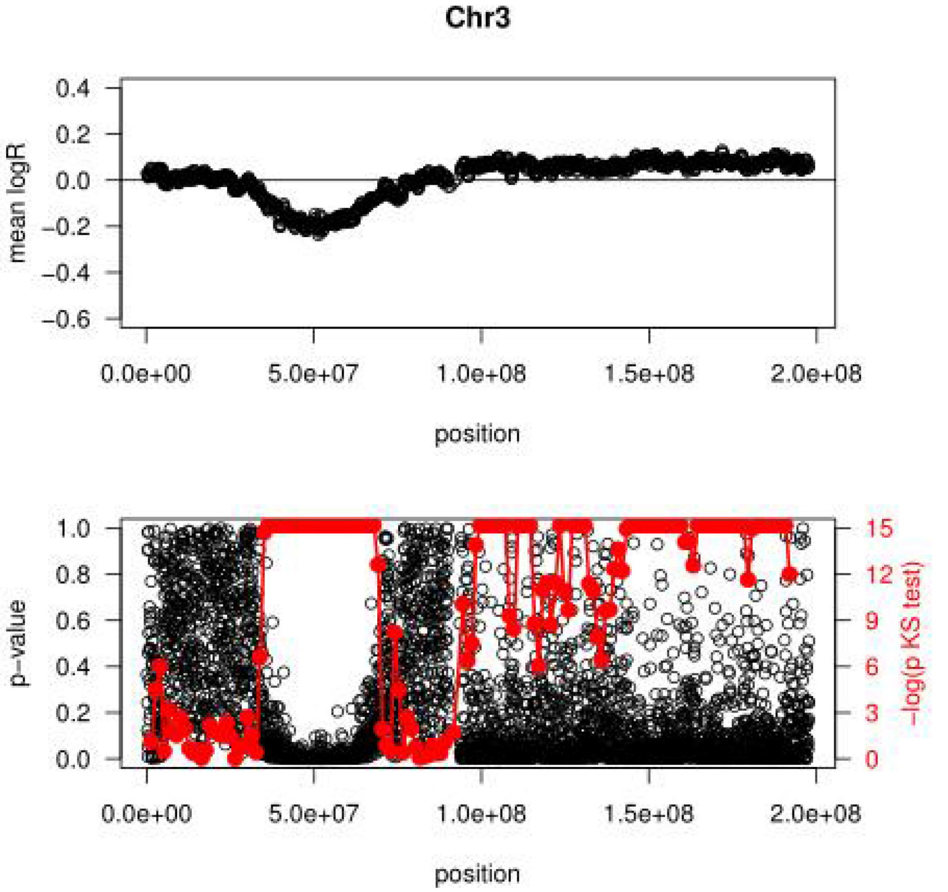
1 / 2 : LogR for Chr 21

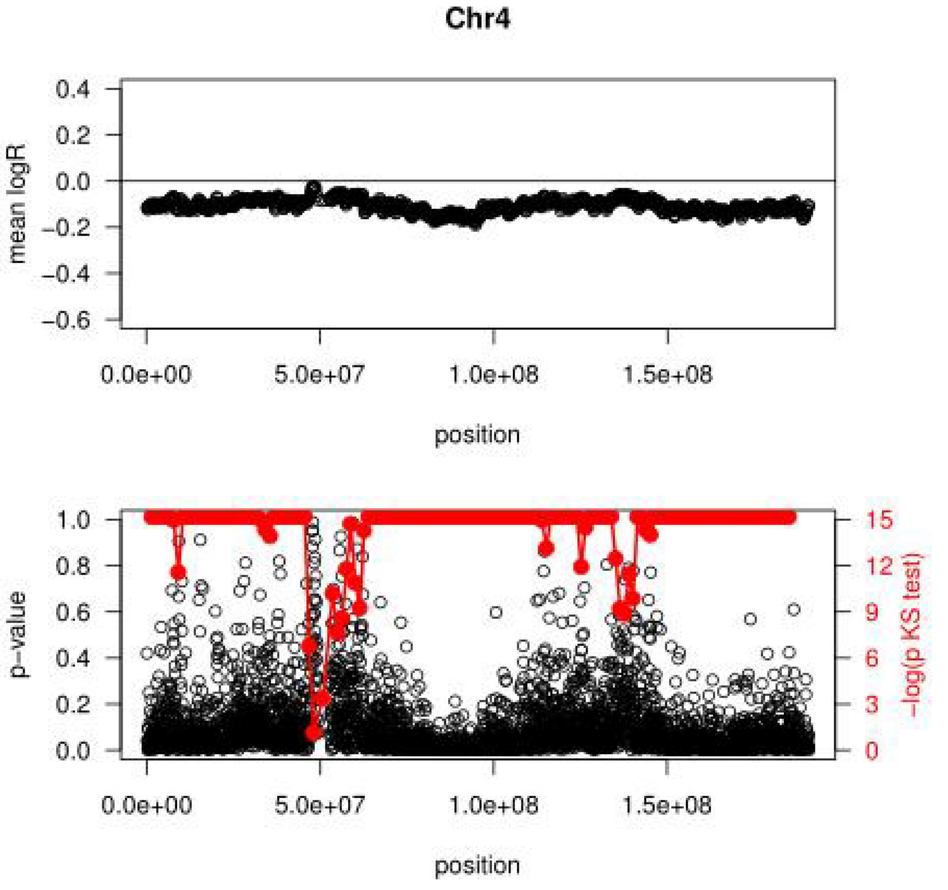
1 / 2 : LogR for Chr 22

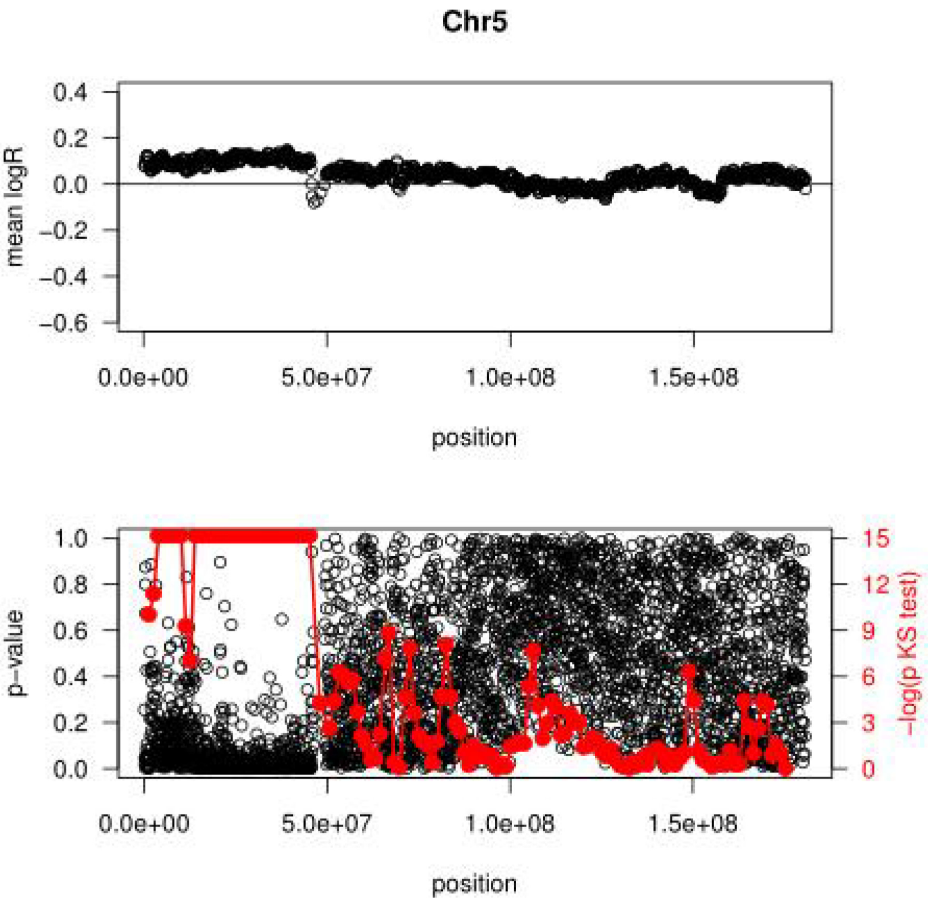
Supplementary Figure 1: Copy number profile of a representative tumor/normal sample pair. Log_2-ratios were plotted against chromosome position.

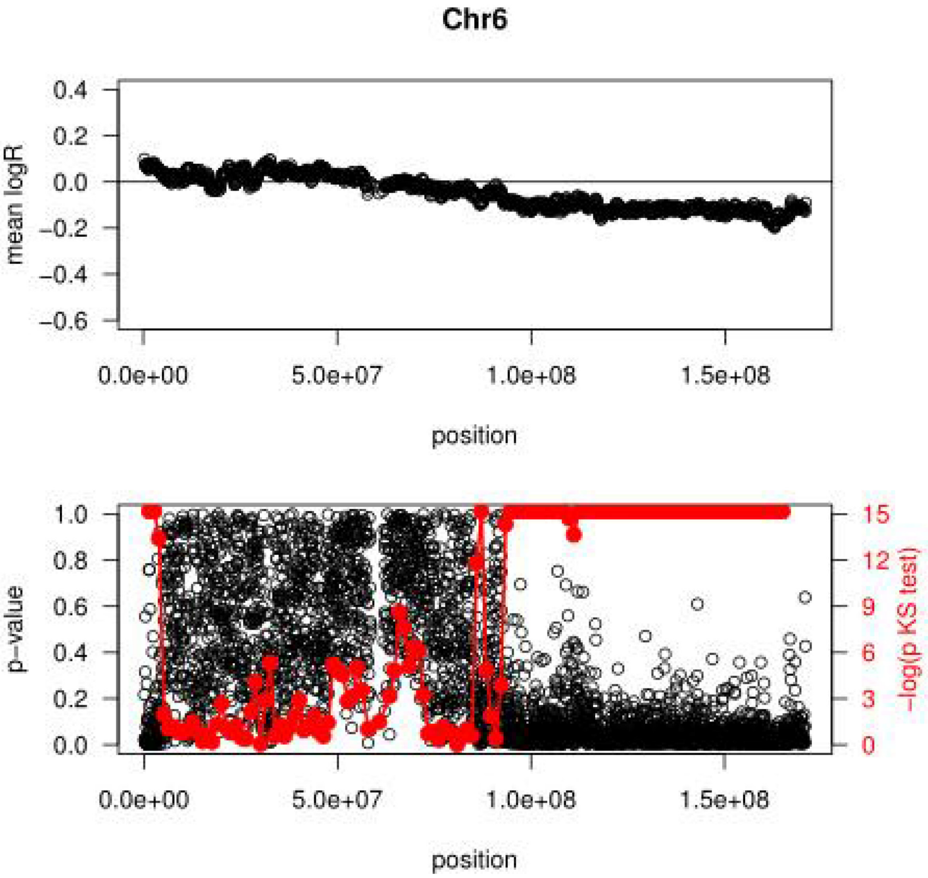

Chr1
mean logR
0.4
0.2
0.0
−0.2
−0.4
−0.6
0.0e+00
5.0e+07
1.0e+08
1.5e+08
2.0e+08
2.5e+08
position
p−value
1.0
0.8
0.6
0.4
0.2
0.0
−log(p KS test)
15
12
9
6
3
0
0.0e+00
5.0e+07
1.0e+08
1.5e+08
2.0e+08
2.5e+08
position

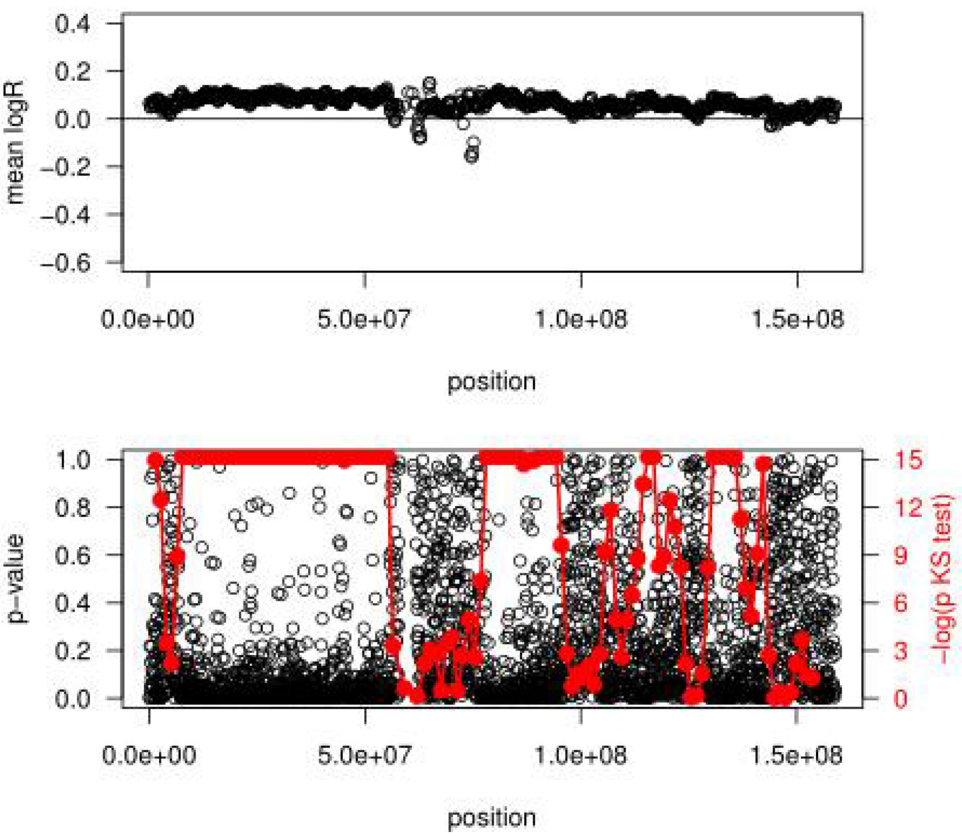

Chr2
mean logR
0.4
0.2
0.0
−0.2
−0.4
−0.6
0.0e+00
5.0e+07
1.0e+08
1.5e+08
2.0e+08
2.5e+08
position
p−value
1.0
0.8
0.6
0.4
0.2
0.0
−log(p KS test)
15
12
9
6
3
0
0.0e+00
5.0e+07
1.0e+08
1.5e+08
2.0e+08
2.5e+08
position

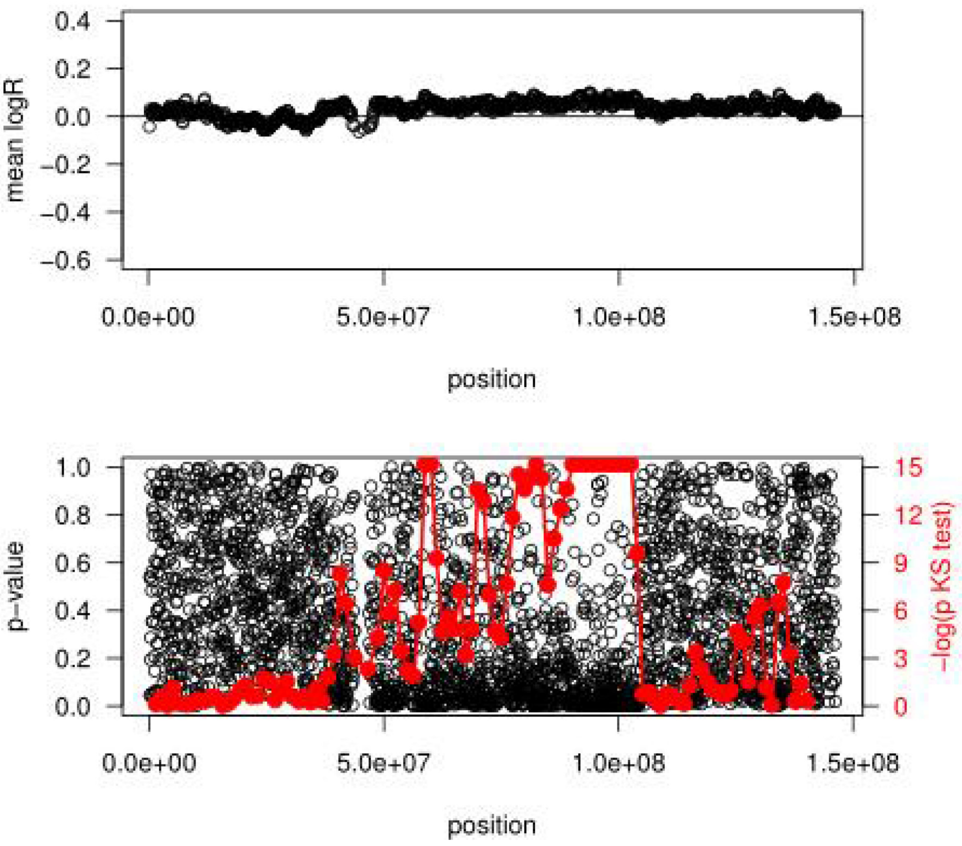

Chr3
mean logR
0.4
0.2
0.0
−0.2
−0.4
−0.6
0.0e+00
5.0e+07
1.0e+08
1.5e+08
2.0e+08
position
p−value
1.0
0.8
0.6
0.4
0.2
0.0
15
12
9
6
3
0
−log(p KS test)
0.0e+00
5.0e+07
1.0e+08
1.5e+08
2.0e+08
position


Chr4
mean logR
0.4
0.2
0.0
−0.2
−0.4
−0.6
0.0e+00
5.0e+07
1.0e+08
1.5e+08
position
p−value
1.0
0.8
0.6
0.4
0.2
0.0
15
12
9
6
3
0
−log(p KS test)
0.0e+00
5.0e+07
1.0e+08
1.5e+08
position

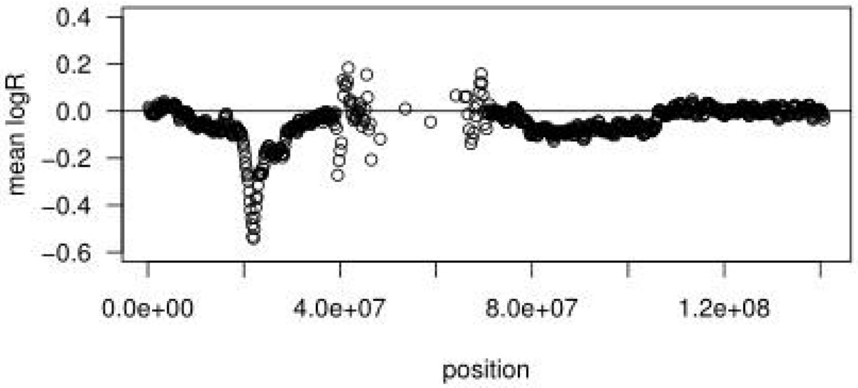

Chr5
mean logR
0.4
0.2
0.0
−0.2
−0.4
−0.6
0.0e+00
5.0e+07
1.0e+08
1.5e+08
position
p−value
1.0
0.8
0.6
0.4
0.2
0.0
−log(p KS test)
15
12
9
6
3
0
0.0e+00
5.0e+07
1.0e+08
1.5e+08
position

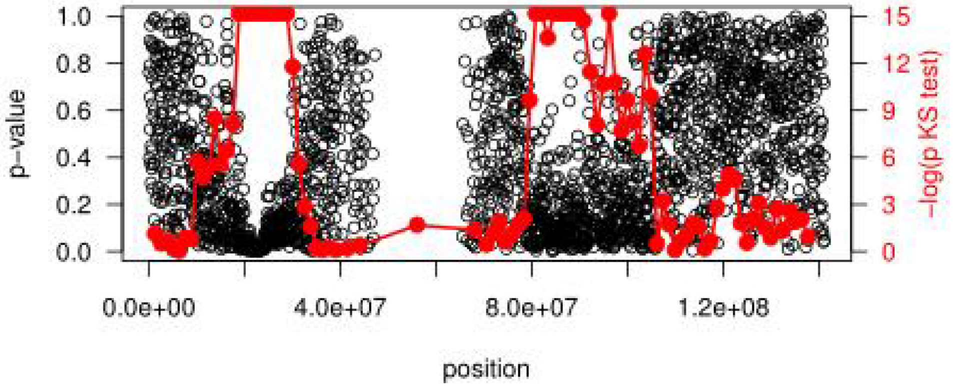

Chr6
mean logR
0.4
0.2
0.0
−0.2
−0.4
−0.6
0.0e+00
5.0e+07
1.0e+08
1.5e+08
position
p−value
1.0
0.8
0.6
0.4
0.2
0.0
−log(p KS test)
15
12
9
6
3
0
0.0e+00
5.0e+07
1.0e+08
1.5e+08
position


Chr7
mean logR
0.4
0.2
0.0
−0.2
−0.4
−0.6
0.0e+00
5.0e+07
1.0e+08
1.5e+08
position
p−value
1.0
0.8
0.6
0.4
0.2
0.0
15
12
9
6
3
0
−log(p KS test)
0.0e+00
5.0e+07
1.0e+08
1.5e+08
position

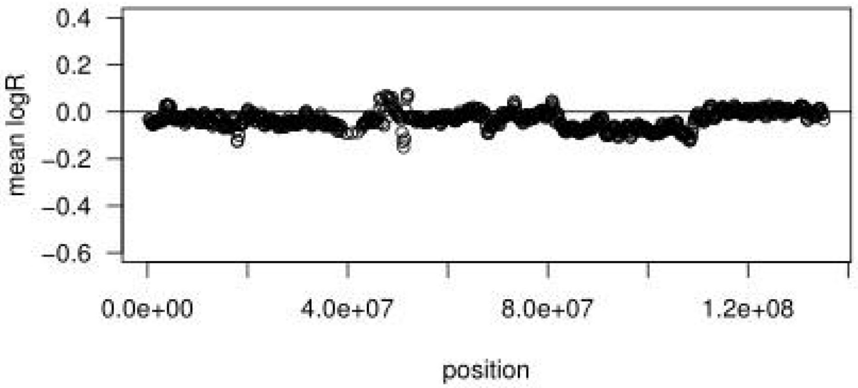

Chr8
mean logR
0.4
0.2
0.0
−0.2
−0.4
−0.6
0.0e+00
5.0e+07
1.0e+08
1.5e+08
position
p−value
1.0
0.8
0.6
0.4
0.2
0.0
15
12
9
6
3
0
−log(p KS test)
0.0e+00
5.0e+07
1.0e+08
1.5e+08
position

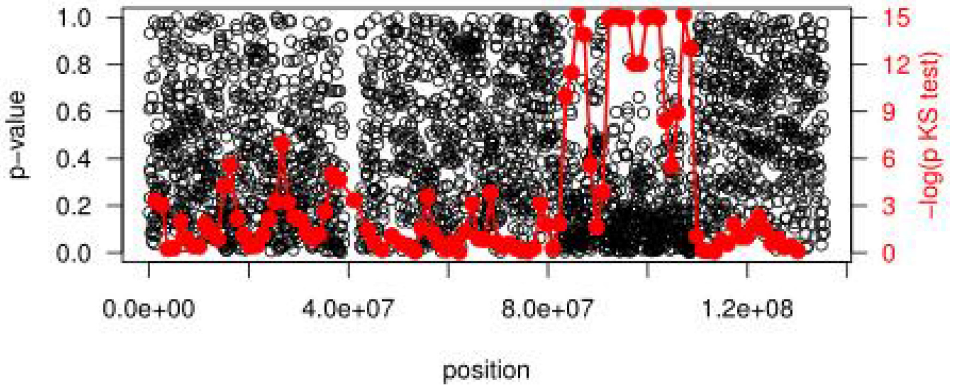
Chr9

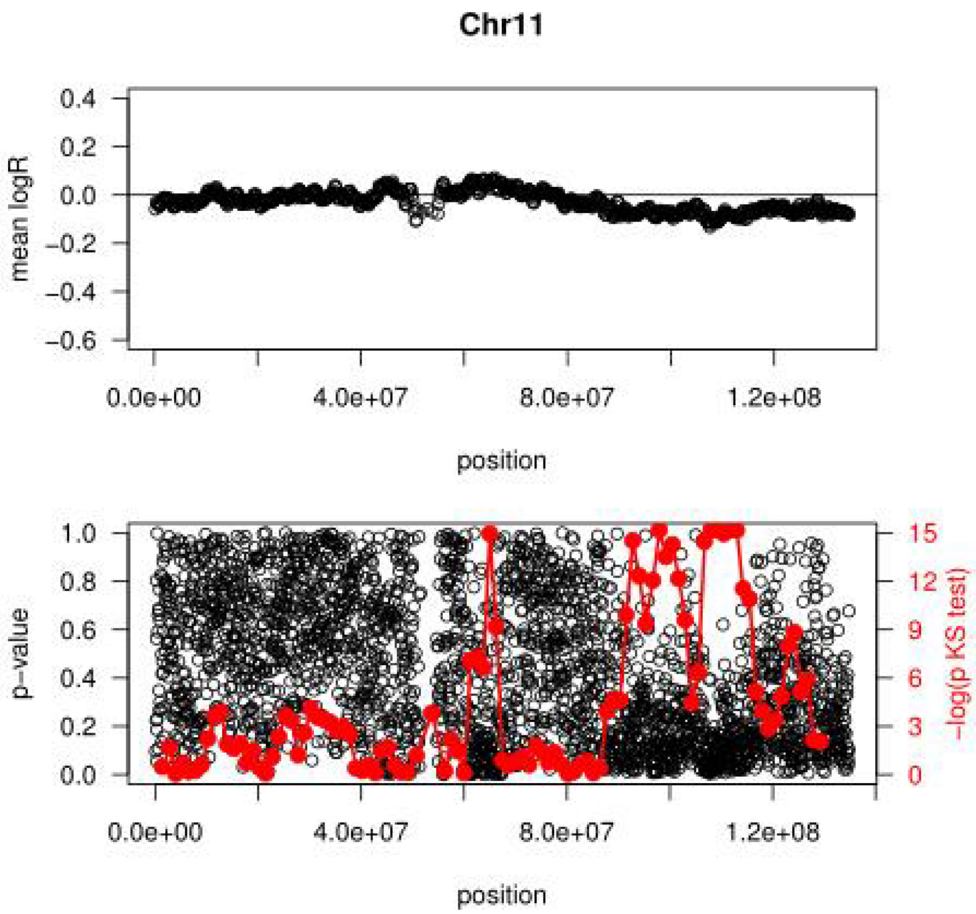

mean logR
0.4
0.2
0.0
−0.2
−0.4
−0.6
0.0e+00
4.0e+07
8.0e+07
1.2e+08
position


p−value
1.0
0.8
0.6
0.4
0.2
0.0
−log(p KS test)
15
12
9
6
3
0
0.0e+00
4.0e+07
8.0e+07
1.2e+08
position

Chr10

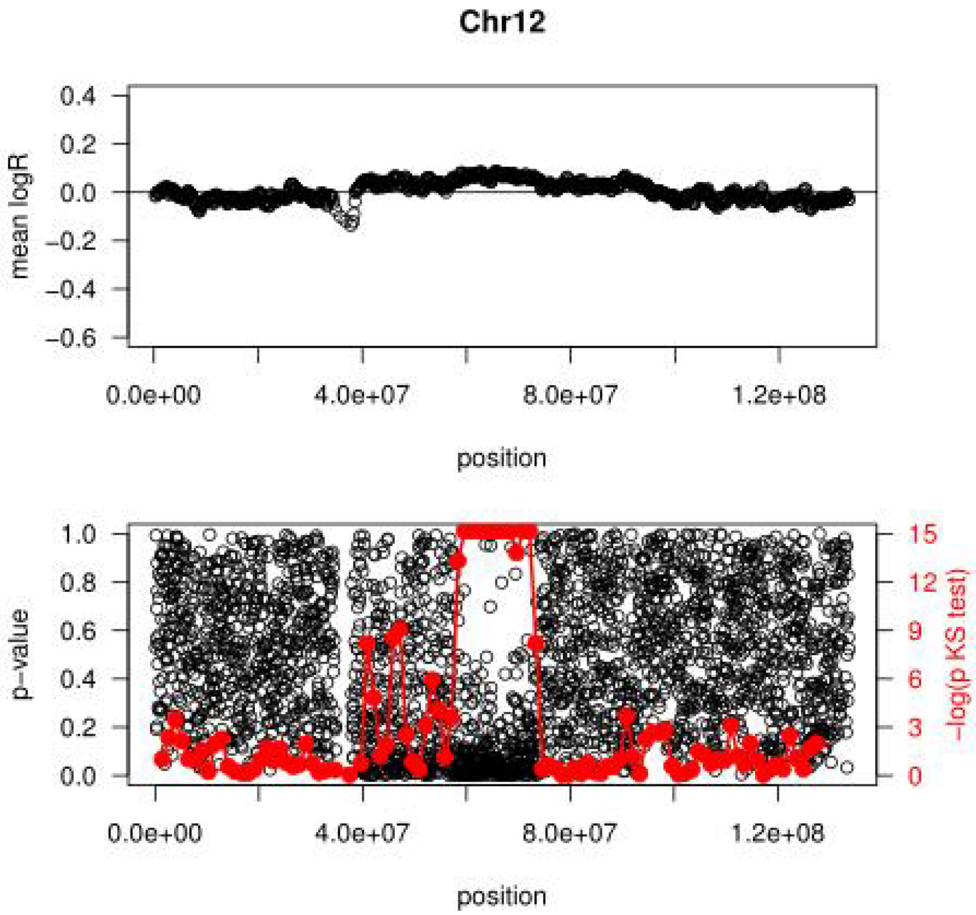

mean logR
0.4
0.2
0.0
−0.2
−0.4
−0.6
0.0e+00
4.0e+07
8.0e+07
1.2e+08
position


p−value
1.0
0.8
0.6
0.4
0.2
0.0
−log(p KS test)
15
12
9
6
3
0
0.0e+00
4.0e+07
8.0e+07
1.2e+08
position



Chr11

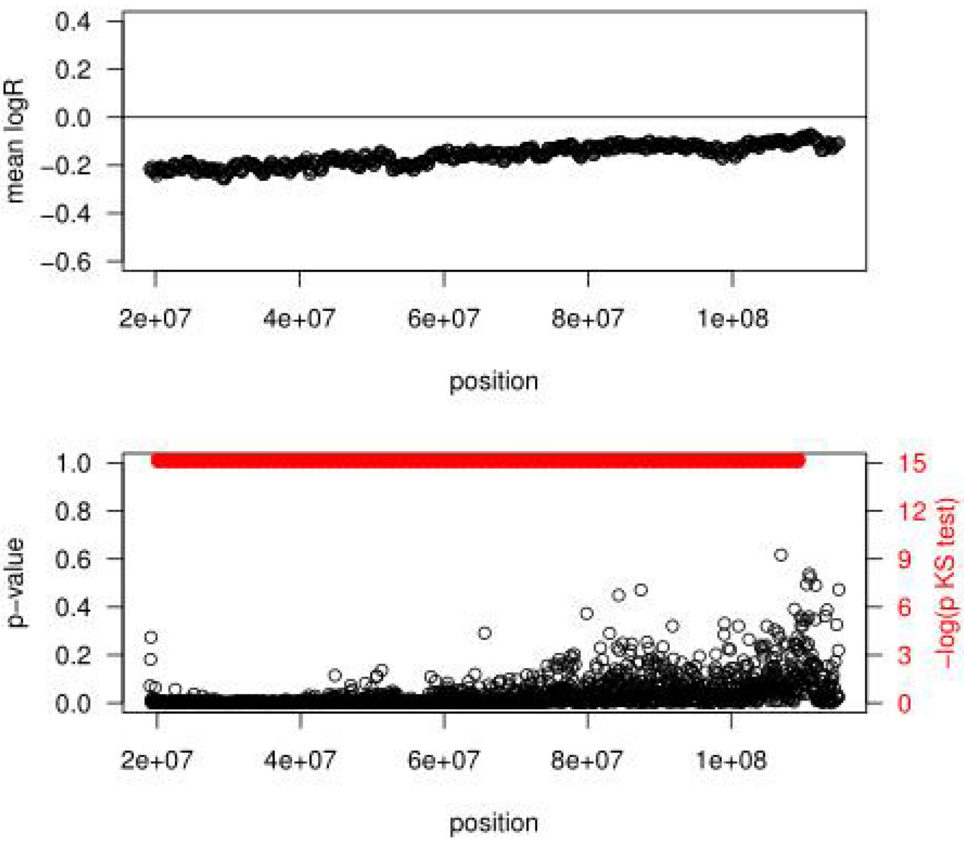
mean logR
0.4
0.2
0.0
−0.2
−0.4
−0.6
0.0e+00
4.0e+07
8.0e+07
1.2e+08
position
p−value
1.0
0.8
0.6
0.4
0.2
0.0
−log(p KS test)
15
12
9
6
3
0
0.0e+00
4.0e+07
8.0e+07
1.2e+08
position



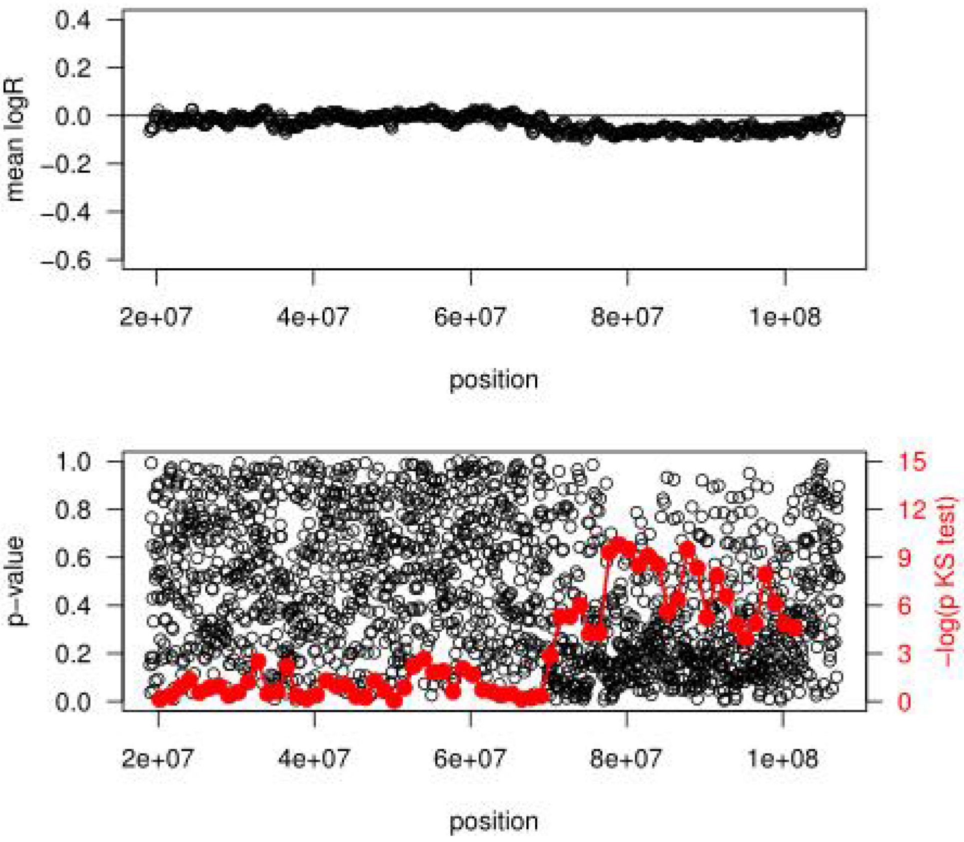
Chr12

mean logR
0.4
0.2
0.0
−0.2
−0.4
−0.6
0.0e+00
4.0e+07
8.0e+07
1.2e+08
position
p−value
1.0
0.8
0.6
0.4
0.2
0.0
−log(p KS test)
15
12
9
6
3
0
0.0e+00
4.0e+07
8.0e+07
1.2e+08
position

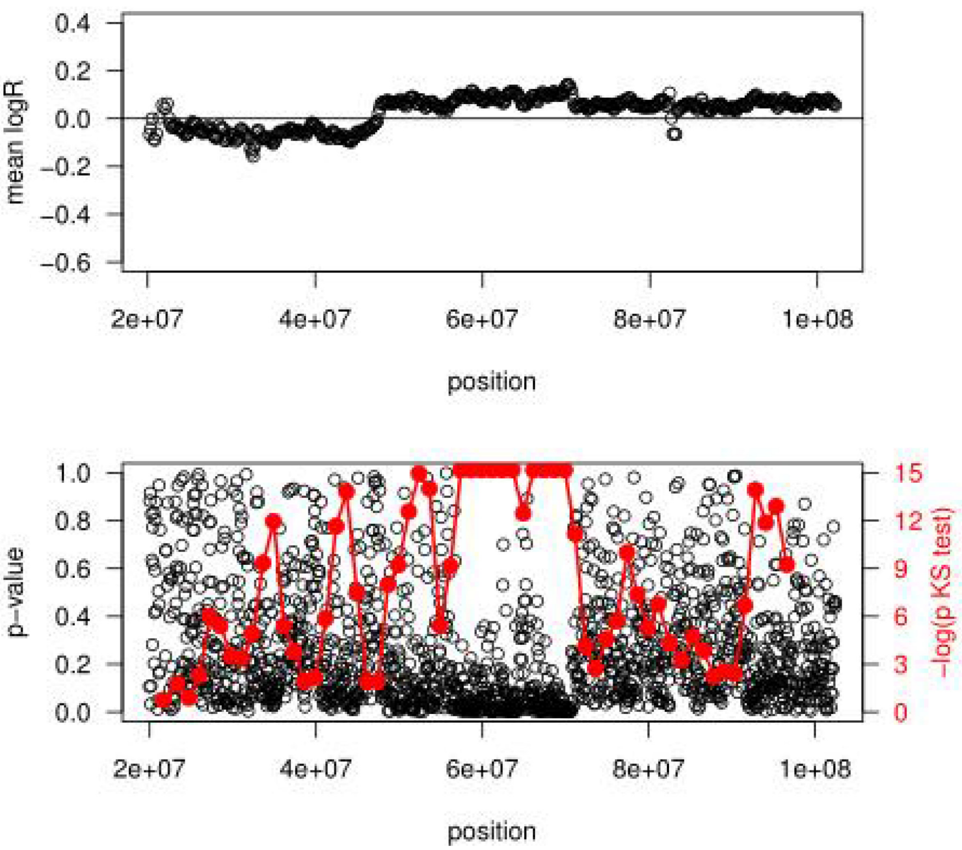
Chr13


mean logR
0.4
0.2
0.0
−0.2
−0.4
−0.6
2e+07
4e+07
6e+07
8e+07
1e+08
position
p−value
1.0
0.8
0.6
0.4
0.2
0.0
15
12
9
6
3
0
−log(p KS test)
2e+07
4e+07
6e+07
8e+07
1e+08
position

Chr14

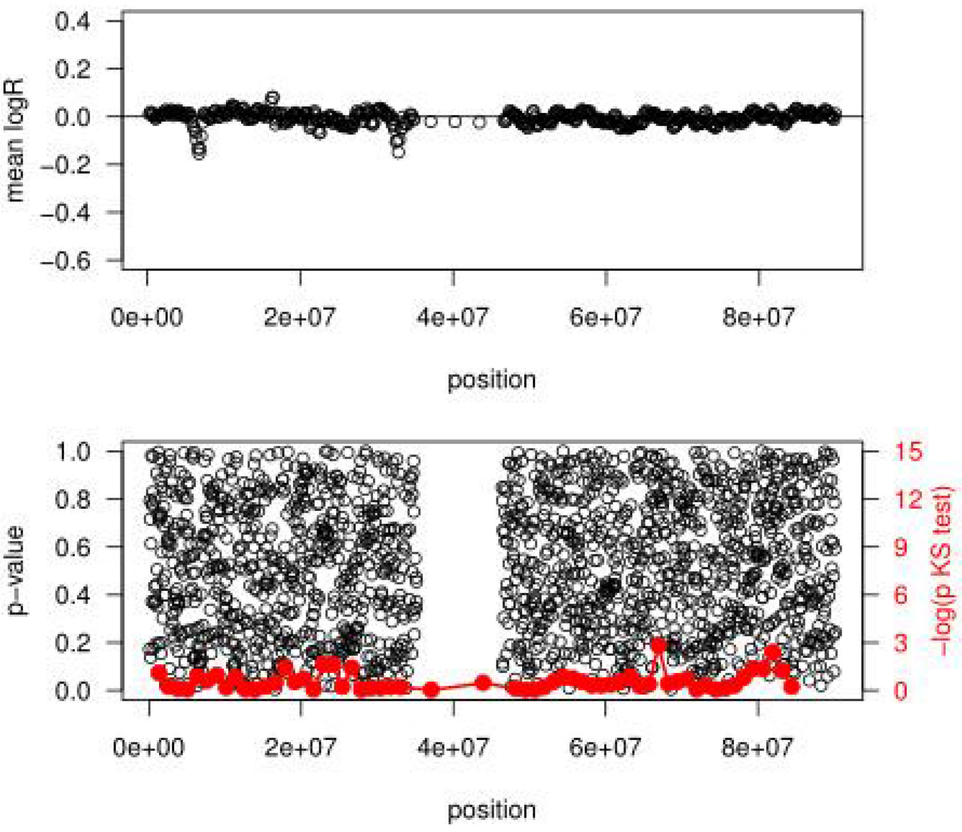

mean logR
0.4
0.2
0.0
−0.2
−0.4
−0.6
2e+07
4e+07
6e+07
8e+07
1e+08
position
p−value
1.0
0.8
0.6
0.4
0.2
0.0
15
12
9
6
3
0
−log(p KS test)
2e+07
4e+07
6e+07
8e+07
1e+08
position

Chr15

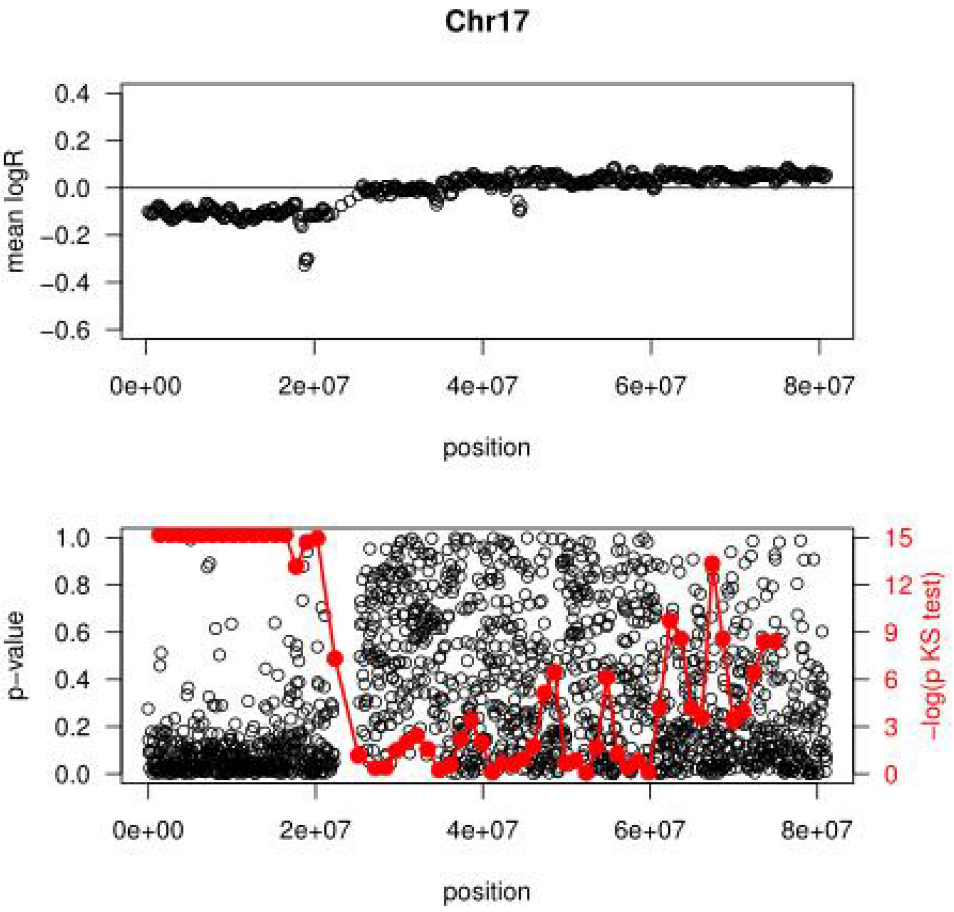


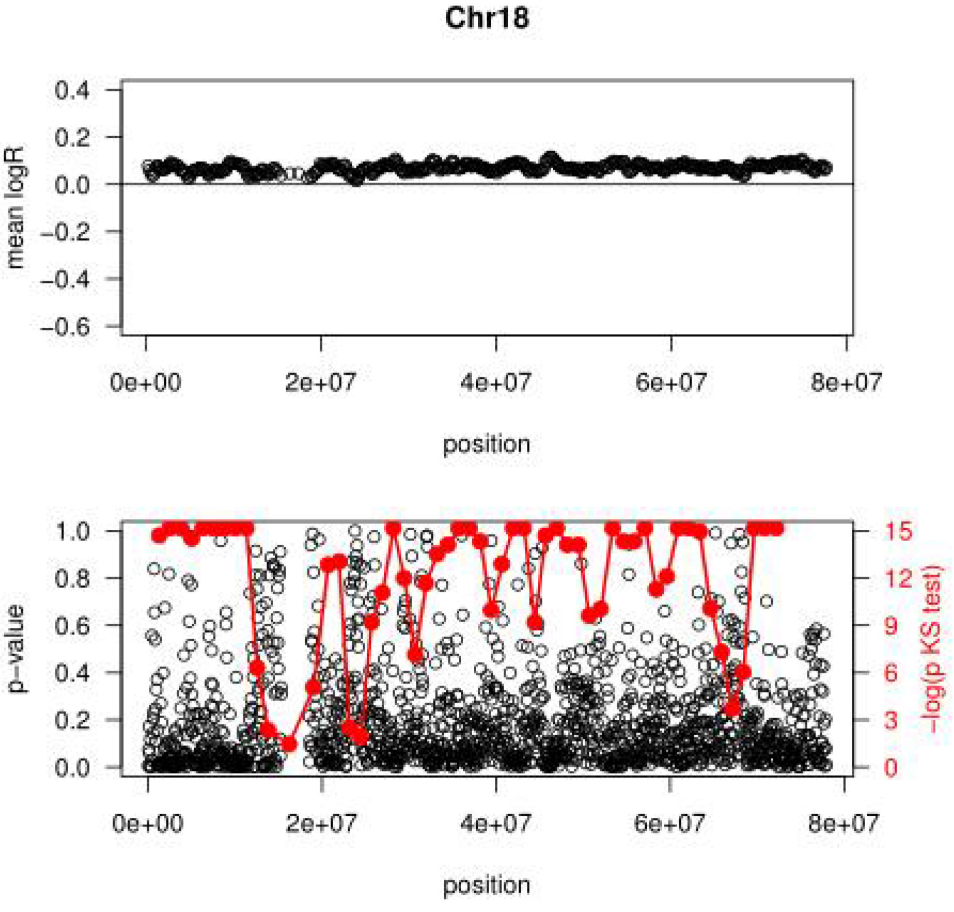
mean logR
0.4
0.2
0.0
−0.2
−0.4
−0.6
2e+07
4e+07
6e+07
8e+07
1e+08
position
p−value
1.0
0.8
0.6
0.4
0.2
0.0
15
12
9
6
3
0
−log(p KS test)
2e+07
4e+07
6e+07
8e+07
1e+08
position

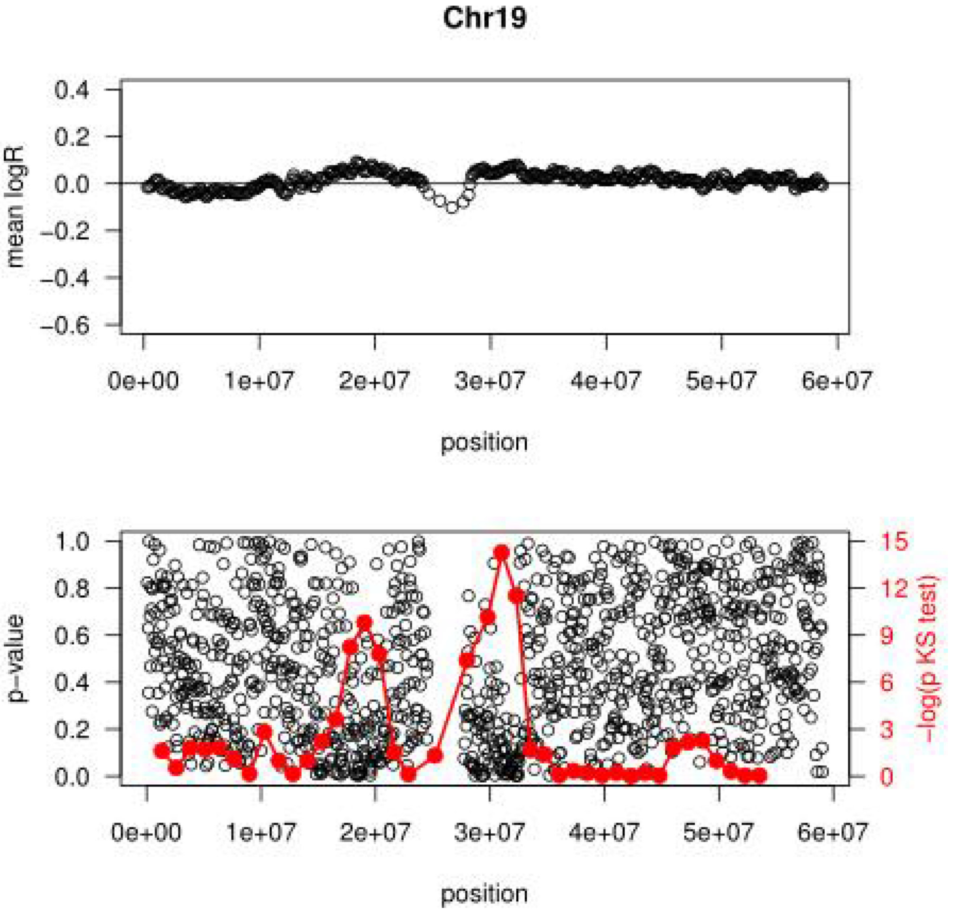
Chr16

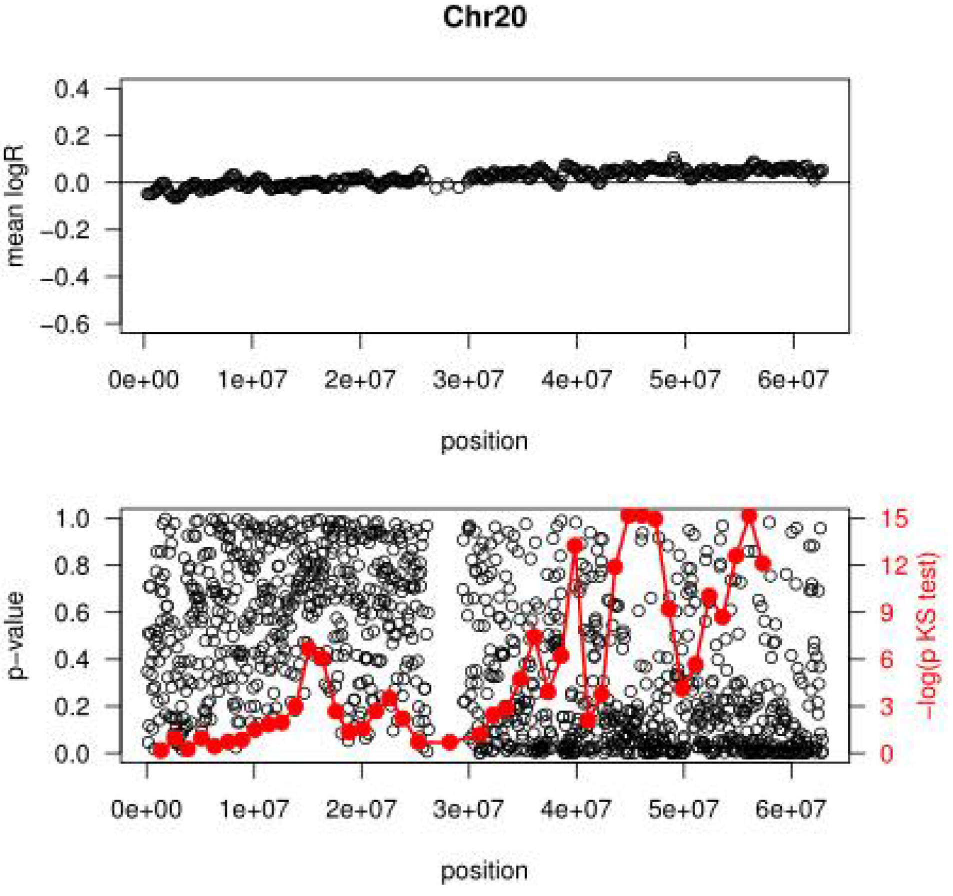


mean logR
0.4
0.2
0.0
−0.2
−0.4
−0.6
0e+00
2e+07
4e+07
6e+07
8e+07
position
p−value
1.0
0.8
0.6
0.4
0.2
0.0
15
12
9
6
3
0
−log(p KS test)
0e+00
2e+07
4e+07
6e+07
8e+07
position

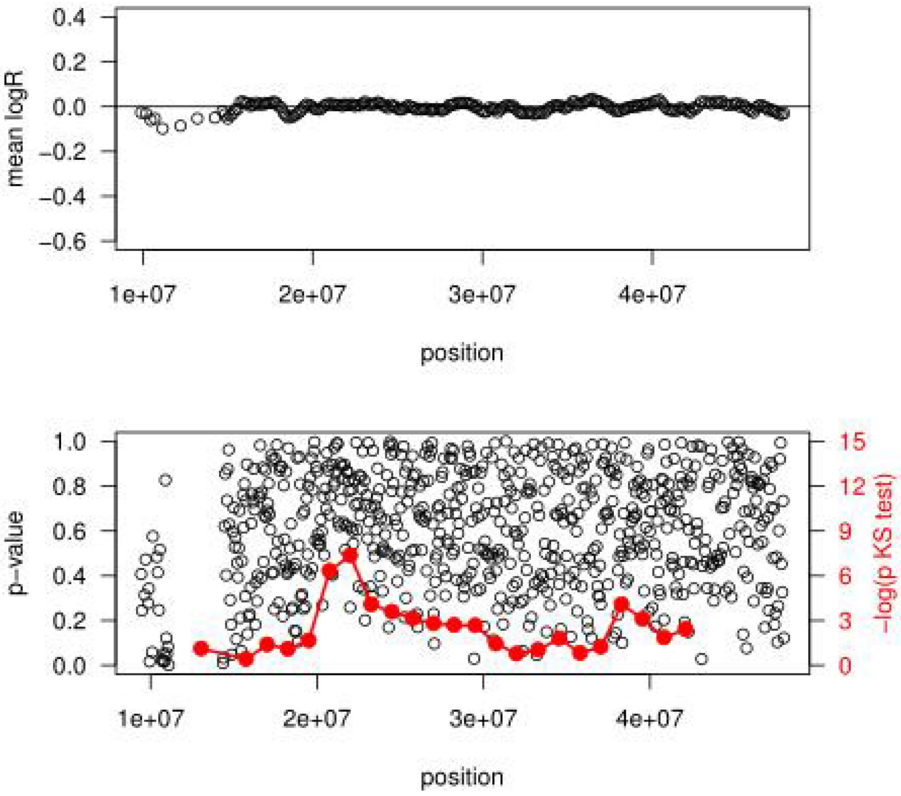

Chr17
mean logR
0.4
0.2
0.0
−0.2
−0.4
−0.6
0e+00
2e+07
4e+07
6e+07
8e+07
position
p−value
1.0
0.8
0.6
0.4
0.2
0.0
15
12
9
6
3
0
−log(p KS test)
0e+00
2e+07
4e+07
6e+07
8e+07
position


Chr18
mean logR
0.4
0.2
0.0
−0.2
−0.4
−0.6
0e+00
2e+07
4e+07
6e+07
8e+07
position
p−value
1.0
0.8
0.6
0.4
0.2
0.0
15
12
9
6
3
0
−log(p KS test)
0e+00
2e+07
4e+07
6e+07
8e+07
position

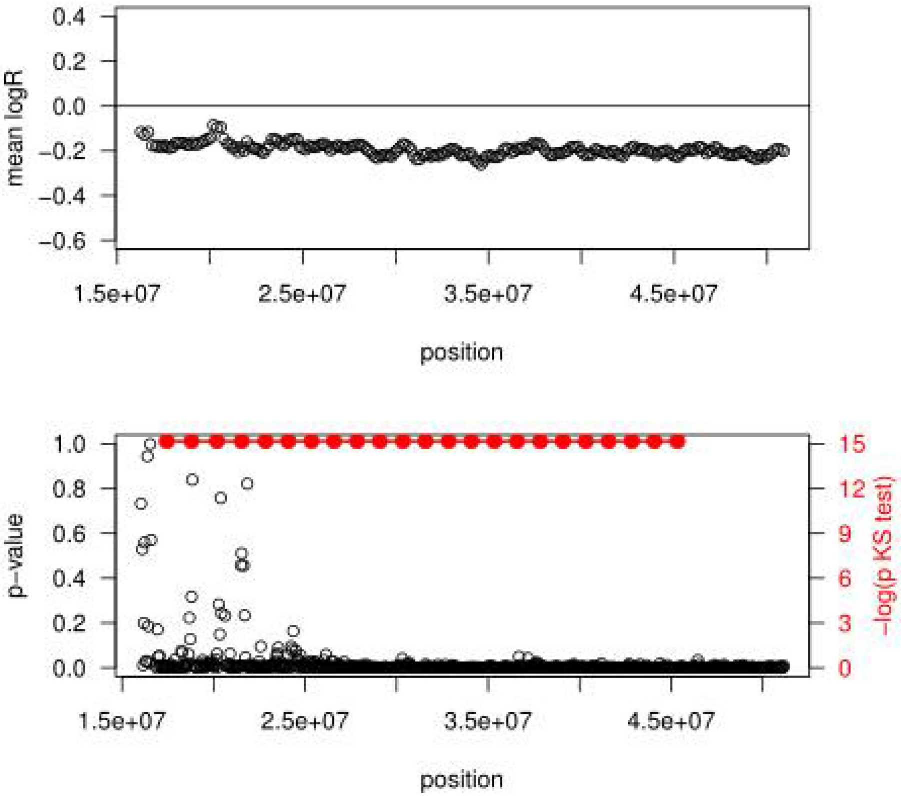

Chr19
mean logR
0.4
0.2
0.0
−0.2
−0.4
−0.6
0e+00
1e+07
2e+07
3e+07
4e+07
5e+07
6e+07
position
p−value
1.0
0.8
0.6
0.4
0.2
0.0
−log(p KS test)
15
12
9
6
3
0
0e+00
1e+07
2e+07
3e+07
4e+07
5e+07
6e+07
position


Chr20
mean logR
0.4
0.2
0.0
−0.2
−0.4
−0.6
0e+00
1e+07
2e+07
3e+07
4e+07
5e+07
6e+07
position
p−value
1.0
0.8
0.6
0.4
0.2
0.0
−log(p KS test)
15
12
9
6
3
0
0e+00
1e+07
2e+07
3e+07
4e+07
5e+07
6e+07
position

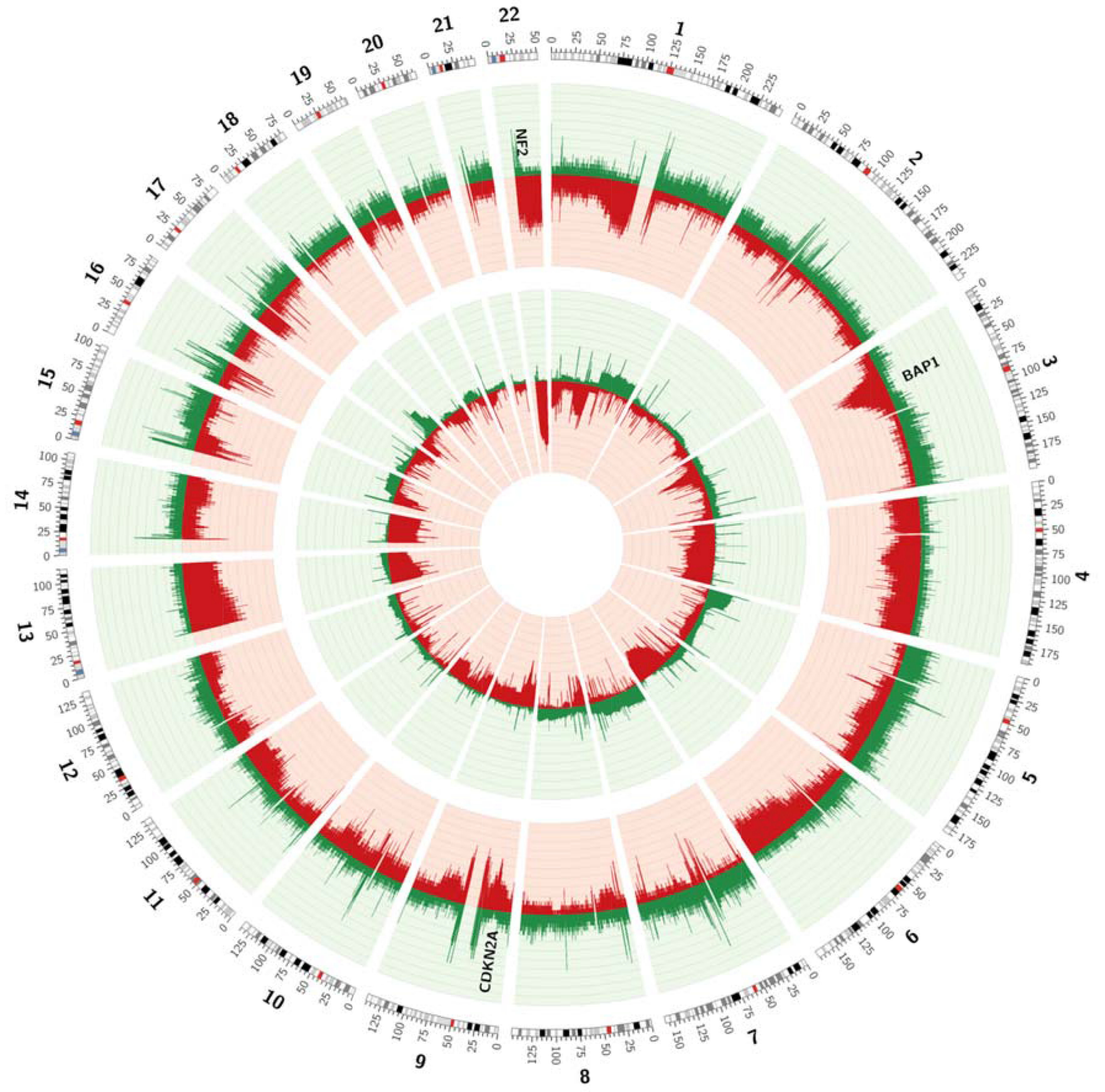
Chr21



Chr22



Supplementary Figure 2: Mean copy number profile over the 21 tumor/normal sample pairs. In the upper figures, the mean $\log_2$-ratio over the 21 sample pairs is plotted against chromosome position. In the lower figures, the black dots represent the *p*-values for the one-sample t-test for each 50 kb-bin. The red line represents the negative logarithm of the *p*-value of the Kolmogorov-Smirnov test.



Supplementary Figure 3: Circos plot of the copy number variations observed in low-pass whole genome data of 21 MPMs and array data of 85 MPMs. The outer layer represents the frequency of copy number loss (red) and gain (green) in every 50 kb-bin observed in the low-pass whole genome data. The inner layer represents the frequency of copy number loss (red) and gain (green) for every chromosome position observed in the array data from TCGA.

Supplementary Table 1: Associations between the presence of copy number loss in the 'Cancer census genes' most frequently lost in the TCGA-dataset and clinicopathological parameters

Gene name	***P*-value for association with gender**	***P*-value for association with age at diagnosis**	***P*-value for association with asbestos exposure**	***P*-value for association with histological diagnosis**	***P*-value for association with survival**
EP300	0.553[a]	0.266	0.749[a]	0.388	1[a]
PDGFB	0.803	0.423	0.749[a]	0.489	0.740[a]
MKL1	0.803	0.423	0.749[a]	0.489	0.740[a]
MYH9	0.803	0.423	0.749[a]	0.489	0.740[a]
APOBEC3B	0.620	0.401	0.529[a]	0.574	1[a]
ZNF278	0.702	0.586	0.826	0.283	0.524[a]
NF2	0.804	0.907	0.525[a]	0.328	0.344[a]
MN1	1	0.542	1	0.291	0.173[a]
CHEK2	0.817	0.749	0.773	0.291	0.322[a]
EWSR1	0.785	0.800	0.928	0.361	0.319[a]
BCR	0.955	0.682	0.677	0.240	0.512[a]
SMARCB1	1	0.553	0.872	0.271	0.340[a]
MAPK1	1	0.633	1	0.428	0.517[a]
CLTCL1	1	1	1	0.623	0.212[a]
SEPT5	1	1	1	0.623	0.212[a]
LZTR1	1	1	1	0.623	0.212[a]
CDKN2A	0.822	0.557	0.958	0.464	**0.010**
SETD2	0.644	0.623	0.141	0.549	0.514[a]
BAP1	1	0.855	0.217	0.945	0.513[a]
NCKIPSD	0.877	0.668	0.134	0.402	0.517[a]
PBRM1	0.835	0.649	0.322	0.945	1[a]

[a] To identify associations, a Pearson's Chi-squared test with Yates' continuity correction was performed. However, when more than 20% of the cells had an expected count below five, a Fisher's Exact test was used.

Supplementary Table 2: Associations between the presence of copy number gain in the 'Cancer census genes' most frequently gained in the TCGA-dataset and clinicopathological parameters

Gene name	*P*-value for association with gender	*P*-value for association with age at diagnosis	*P*-value for association with asbestos exposure	*P*-value for association with histological diagnosis	*P*-value for association with survival
TERT	0.532[a]	0.074	0.736[a]	0.666	1[a]
SDHA	0.528[a]	0.178	0.737[a]	0.778	1[a]
DROSHA	0.514[a]	0.298	0.492[a]	0.909	1[a]
IL7R	0.337[a]	0.469	0.719[a]	1	1[a]
LIFR	0.337[a]	0.469	0.719[a]	1	1[a]
FCGR2B	0.721[a]	0.533[a]	0.678[a]	1[a]	0.675[a]
CDC73	1[a]	1[a]	0.705[a]	0.489[a]	0.188[a]
PTPRC	0.729[a]	1	1[a]	0.721	0.110[a]
MDM4	0.493[a]	1	1[a]	0.764[a]	0.112[a]
ELK4	0.729[a]	1	1[a]	0.721	0.110[a]
SLC45A3	0.729[a]	1	1[a]	0.721	0.110[a]
HLF	1[a]	0.615	0.435[a]	0.336[a]	0.431[a]
MSI2	1[a]	0.557	0.429[a]	0.507[a]	0.408[a]
RNF43	1[a]	0.615	0.435[a]	0.336[a]	0.431[a]
CLTC	1[a]	0.615	0.435[a]	0.336[a]	0.431[a]
PPM1D	1[a]	0.615	0.435[a]	0.336[a]	0.431[a]
BRIP1	1[a]	0.585	0.435[a]	0.338[a]	0.436[a]
CD79B	1[a]	0.615	0.435[a]	0.336[a]	0.431[a]
DDX5	1[a]	0.615	0.435[a]	0.336[a]	0.431[a]
AXIN2	1[a]	0.615	0.435[a]	0.336[a]	0.431[a]
PRKAR1A	1[a]	0.615	0.435[a]	0.336[a]	0.431[a]

[a] To identify associations, a Pearson's Chi-squared test with Yates' continuity correction was performed. However, when more than 20% of the cells had an expected count below five, a Fisher's Exact test was used.

Supplementary Table 3: Associations between the presence of copy number loss in the 'Cancer census genes' most frequently lost in the LP-WGS-dataset and clinicopathological parameters

Gene name	*P*-value for association with gender[a]	*P*-value for association with age at diagnosis[a]	*P*-value for association with histological diagnosis[a]	*P*-value for association with survival[a]	*P*-value for association with neo-adjuvant treatment[a]
EP300	0.500	0.303	1	1	0.362
SETD2	0.533	0.303	1	0.530	1
PBRM1	1	0.303	1	0.530	1
ROS1	0.533	1	1	0.517	0.659
ZNF198	1	0.303	1	0.530	1
RB1	1	0.629	0.521	0.517	0.659
CHEK2	1	0.141	1	1	0.659
TRIM33	0.133	1	1	0.517	1
CACNA1D	1	0.629	1	0.517	1
FLT3	1	0.629	1	0.517	1
FOXO1	1	0.350	0.257	0.263	1
MKL1	1	0.629	1	0.517	1
EPS15	1	0.350	1	0.263	0.387
WHSC1	0.171	1	1	0.263	1
PTPN13	0.171	1	1	0.263	1
RAP1GDS1	0.171	1	1	0.263	1
FBXW7	0.171	1	1	0.228	0.670
FAT1	0.171	1	1	0.228	0.670
NFIB	0.171	0.650	1	0.228	1
MLLT3	0.171	1	0.553	0.263	1
BRCA2	1	1	0.553	0.263	0.670
LHFP	1	0.350	1	0.263	1
LCP1	1	1	1	1	1
MAPK1	1	0.350	0.553	0.263	0.670

[a] To identify associations, a Fisher's Exact test was performed, as for every association more than 20% of the cells had an expected count below five.

Supplementary Table 4: Associations between the presence of copy number gain in the 'Cancer census genes' most frequently gained in the LP-WGS-dataset and clinicopathological parameters

Gene name	*P*-value for association with gender[a]	*P*-value for association with age at diagnosis[a]	*P*-value for association with histological diagnosis[a]	*P*-value for association with survival[a]	*P*-value for association with neo-adjuvant treatment[a]
PMS2	0.533	0.629	0.247	1	1
FCGR2B	0.429	0.629	1	1	0.635
EIF4A2	1	0.629	1	1	0.149
TERT	1	1	0.128	0.530	1
HNRNPA2B1	1	0.582	1	0.530	0.311
EGFR	1	1	0.128	1	1
MET	1	0.582	0.128	1	1
RAD21	1	1	1	0.155	0.635
KLF6	0.429	1	0.549	1	0.635
NAB2	1	0.303	1	1	0.635
MLLT6	0.429	0.303	1	0.530	0.635
CIC	0.429	0.629	0.549	0.155	0.635
FAM131B	1	0.303	1	0.530	1
PLAG1	1	0.582	1	0.530	0.587
CHCHD7	1	0.582	1	1	0.311
RECQL4	0.352	0.303	0.489	1	0.311
NUTM2B	1	1	0.489	1	1
NUTM2A	1	1	1	1	1
ETNK1	1	1	1	0.422	1
DICER1	0.352	1	0.489	0.530	0.311
CD79B	0.352	0.582	0.489	1	1
PRKAR1A	0.352	0.582	0.489	1	0.311
ZNF521	1	1	1	1	1

[a] To identify associations, a Fisher's Exact test was performed, as for every association more than 20% of the cells had an expected count below five.