Supplementary Information

for

Genome Remodeling in a Basal-like Breast Cancer Metastasis and Xenograft

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Excel spreadsheets can be downloaded from http://genome.wustl.edu/supplemental/BCA_nature_2010

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A. Supplementary Materials and Methods

Illumina library construction

We followed the procedure described by Mardis *et al*(*1*), modified for low input DNA amounts. Briefly, we started with 100ng of DNA from primary tumor, metastasis, xenograft, and the matched normal, in duplicate. After the DNA was fragmented, end repaired, and ligated with adaptors, we amplified the products and ran them on a polyacrylamide gel. We then excised gel slices between 100 bp and 400 bp at 50 bp increments, and eluted the DNA from each gel slice for making independent libraries. We prepared 4, 7, 4, and 16 libraries for primary tumor, metastasis, xenograft, and the matched normal, respectively. All libraries except for one normal library were used for subsequent sequencing.

- Normal: We used 15 of the 16 libraries (Library 11 had a single failed flowcell). Of those 15 libraries, Libraries 9 and 10 were fragment reads of length 75 bp.

- Primary tumor: 4 libraries were used.

- Brain metastasis: 7 libraries were used. Of those 7, Library 7 consisted of fragment reads of length 75 bp.

- Xenograft: 4 libraries were used.

We also made one library using normal male mouse spleen DNAs of NOD/SCID strain from the Jackson Laboratory. We combined 1ug genomic DNA from 4 samples to a final concentration of 100ng/ul. Then we prepared a single 1ug Illumina PE library from the pooled DNA (shearing the DNA with the wide range Covaris program). The final library DNA was size-fractionated to obtain a 200-500 bp library size range.

NOD/SCID has a spontaneous mutation congenic on a NOD/ShiLtJ background. Mice are homozygous for the *scid* mutation (*Prkdc*^{scid}, commonly referred to as *scid*). The mutation occurs in the gene that encodes the catalytic sub-unit of the DNA-activated protein kinase (*Prkdc*).

Illumina sequencing

After diluting the libraries to a 10nm concentration, we utilized the paired-end flow cell and cluster generation kits to produce flow cells with an average cluster density ranging between 170,000 to 220,000 clusters per tile. We employed the standard sequencing kits (Illumina Sequencing Kit v3) and performed 36-100 cycles of nucleotide incorporation. Following this first round of end sequencing, the flow cell was treated to remove the synthesized fragments, clusters were re-amplified, and the resulting fragments were linearized. We then annealed the read 2 sequencing primer, and initiated another round of sequencing by synthesis to complete the read pairs. The read length for the second sequencing round matched that of the first. Following each instrument run, we utilized the Illumina sequencing pipeline, version 1.3, to analyze the data and produced files containing high quality ("passed filter") reads with associated quality values.

Alignment, coverage analysis, and SNV/Indel calling

Illumina reads from metastasis, primary tumor, xenograft, and matched normal blood sample were aligned separately to the human NCBI Build 36 reference sequence using Maq(*2*). Genome-wide coverages were assessed by comparing SNVs detected by Maq with SNPs genotyped using Illumina 1M duo arrays for the primary tumor, the brain metastasis, and the matched normal. SNP array hybridization was not performed with xenograft DNA. Instead, we used the SNP array for the brain metastasis as a surrogate for monitoring the genome coverage of the xenograft. SNV positions detected by Maq were further filtered using Maq SNPfilter. Tumor indels detected by SAMtools(*3*) and supported by reads from at least two libraries were used for downstream somatic validation.

Comparison to dbSNP and other personal SNPs

We again followed the same procedure as described in Mardis *et al*(*1*). Predicted SNVs and Indels were compared to dbSNP 129. For SNVs, we require a position match for determining concordance between the variant and dbSNP 129. In addition, we compared (by position) predicted SNVs with SNPs found in the CEU and YRI trios as determined from the 1,000 Genomes project. CEU SNPs were predicted by Maq using alignment files downloaded from the

1,000 Genomes web portal. Maq was used to align the YRI trio reads generated by our center to human NCBI Build 36 and to predict SNPs.

Identification of Somatic SNVs and small Indels

SNVs: The Maq variant calling model, which takes into account basecall and mapping errors, was used to generate genotype likelihood files (GLF, exported with Maq glfgen) for primary tumor, metastasis, xenograft, and the matched normal. Using these files as inputs, we used a Bayesian calculation to determine a "Somatic" score. This score is a Phred-scaled probability that the tumor and normal genotypes were different at a position by error (e.g. when comparing primary tumor to the matched normal, metastasis to the matched normal, or xenograft to the matched normal). We simplified this calculation by assuming that the tumor and normal genotypes and data were independent. The prior probability is estimated based upon a population frequency of heterozygous variants of 0.001. We also computed the probability of different genotypes in metastasis and primary tumor to identify metastasis-specific SNVs. Variants where the Somatic score is greater than 40 and the average mapping qualities of reads supporting the variant in the tumor are greater than or equal to 70 are considered to be high-quality somatic variants, while the rest are designated as low-quality somatic variants. The high-quality cutoffs were determined by analysis of validation data from other in-house genomes. Manual review using IGV (http://www.broadinstitute.org/igv/) was performed on low-quality variants found in primary tumor, brain metastasis, and xenograft to eliminate false positives.

Indels: Indels were detected using a modified SAMtools indel-calling algorithm, tuned to detect differences between tumor and normal samples. Three filters were applied to this list: 1. remove any indel calls without multiple libraries supporting the call; 2. remove any indel calls with any normal support; and 3. remove all 1-bp indels without at least 10% of their total read coverage supporting the variant call. All remaining sites were annotated to identify coding and splice site indels. Reviewers examined each of these sites manually in whole genome data to select sites for experimental validation. Using available paired-end data, we can detect insertions up to 13 bp and deletions up to 30 bp .

Summary of mutation detection in the primary tumor, metastasis, and xenograft

We identified 4,121,595; 3,860,638; and 3,618,536 high quality SNVs in the primary tumor, metastasis, and xenograft, respectively. The process for selecting candidate somatic SNVs is shown in Supplementary Table 2. Briefly, we predicted 23,772 (3,372 high confidence (HC)), 28,308 (5,799 HC), and 23,558 (7,559 HC) putative somatic SNVs in the respective genomes. We further classified variants into four tiers according to genome annotations. Putative somatic SNVs that overlap with coding sequence, splice sites, and RNA genes were included as "tier 1". Based on confidence assignment and manual review, 67, 65, and 54 tier 1 SNV sites detected in the primary tumor, metastasis, and xenograft were selected for experimental validation (Supplementary Table 2a). In parallel, we predicted 45,946; 61,857; and 19,844 small indels in the respective samples as novel potential somatic mutations and successfully assembled 1,683; 2,026; and 827 putative somatic multi-base indels in their respective genomes. There were 48, 59, and 91 tier 1 indels that passed manual review in each respective sample, and these were selected for experimental validation (Supplementary Table 2b). Among the 28 predicted tier 1 HC SNVs and 48 indels in the primary tumor, 16 SNVs and 4 indels were validated as somatic sites (Supplementary Table 2a and 2b). In the metastasis, 46 HC SNVs and 59 indels were predicted, of which 33 and 7, respectively, were validated as somatic sites (Supplementary Table 2a and 2b). In the xenograft, 37 HC SNVs were validated and are present in primary tumor and/or the metastasis (Supplementary Table 2a and 2b).

Identification of point mutations and small indels in primary tumor genome

We identified 4,967,429 SNVs in the primary tumor genome, of which 4,121,595 passed Maq SNPfilter. Of these, 3,540,263 were previously described in dbSNP 129 or found in CEU and YRI trios as determined from the 1,000 Genomes project (Supplementary Table 2a), indicating that they were inherited variants. Of the 581,332 potentially novel SNVs, 554,159 were also detected in the genome of normal cells from the same patient, suggesting that they are the patient's private inherited SNPs. After eliminating 2,007 LOH sites and 1,394 SNVs from Mitochondria and NT random contigs without annotation in the UCSC genome database (September 2008 download), we classified the remaining 25,166 potential novel somatic SNVs into four tiers, which are detailed in the "Tier annotation and SIFT annotation" section below. We identified 200 (28 high confidence (HC)) potential tier 1 mutations, 911 (185 HC) potential tier 2 mutations, 4,503 (920 HC) potential tier 3 mutations, and 18,158 (2,239 HC) potential tier 4

mutations. Of the 172 tier 1 variants that were called with low confidence, manual review was performed and 39 were selected for experimental validation (Supplementary Table 2a).

Indels were detected using a modified SAMtools indel-calling algorithm tuned to discover differences between tumor and normal samples. Of the 4,396,160 primary tumor indels detected by SAMtools, 631,536 are supported by reads from multiple primary tumor libraries. Among them, 60,399 are supported by reads from the normal, suggesting that they are germline indels. Since a 1-bp indel is often simply just a sequencing artifact, we required these cases to be additionally supported by greater than or equal to 10% of their total tumor coverage to reduce systematic noise. We identified 45,946 indels as novel potential somatic indels and further selected 116 that could potentially affect the coding or splice sites. Of the 116 putative somatic indels, 48 passed manual review and were subjected to experimental validation (Supplementary Table 2b).

Identification of point mutations and small indels in metastasis genome

In parallel, we identified 4,647,103 SNVs in the metastasis genome. Of the 3,860,638 that passed Maq SNPfilter, 3,321,746 were previously described, indicating that they were inherited variants. Of the 538,892 potentially novel SNVs, 487,182 were also detected in the normal genome. This leaves 51,710 as potentially novel somatic SNVs including 21,690 LOH sites, 28,308 sites that were further grouped into four tiers, and 1,712 MT and NT sites without tier assignment. Tier 1 includes 46 high confidence and 179 low confidence sites. Of the 179 variants that were called as low confidence, manual review (Supplementary Table 2a) was performed and 19 were selected for experimental validation.

Of the 4,684,771 metastasis indels detected by SAMtools, 713,933 are supported by reads from multiple libraries. Among them, 628,891 are supported by reads from the normal, suggesting that they are germline indels. After further filtering 1-bp indels with the same strategy used for primary tumor indel analysis, we identified 61,857 as novel potential somatic indels and further selected 125 that could potentially affect the coding or splice sites/regions for manual review. The 59 that passed manual review were subjected to experimental validation (Supplementary Table 2b).

Identification of point mutations and small indels in xenograft genome

We identified 4,489,151 SNVs in the xenograft genome, of which 3,618,536 passed Maq SNPfilter. Of these SNVs, 3,144,926 were previously described in dbSNP 129 or found in CEU and YRI trios as determined from the 1,000 Genomes project (Supplementary Table 2a), indicating that they were inherited variants. Of the 473,610 potentially novel SNVs, 3,171 were detected in NOD/SCID and 361,361 were also detected in the genome of normal cells from the same patient, suggesting that they are the patient's private inherited SNPs. After eliminating 83,763 LOH sites and another 1,757 SNVs from Mitochondria and NT random contigs which were without annotation in the UCSC genome database, we classified the remaining potential novel somatic SNVs into four tiers, which are detailed in the "Tier annotation and SIFT annotation" section below. We identified 328 (100 high confidence (HC)) potential tier 1 mutations, 1,475 (675 HC) potential tier 2 mutations, 4,832 (2,287 HC) potential tier 3 mutations, and 16,923 (4,497 HC) potential tier 4 mutations. Of the 100 HC tier 1 variants, manual review was performed and 54 were selected for experimental validation (Supplementary Table 2a).

Of the 3,604,771 xenograft indels detected by SAMtools, 438,603 are supported by reads from multiple primary tumor libraries. Among them, 418,678 are supported by reads from the normal, suggesting that they are germline indels. After removing those 1-bp indels supported by less than 10% of their total tumor read coverage, we identified 19,844 indels as novel potential somatic and further selected 128 that could affect coding or splice sites. Of the 128 putative somatic indels, 91 passed manual review and we successfully designed primers for 90 sites that were then subjected to experimental validation (Supplementary Table 2b).

Comparison of brain metastasis and primary tumor genomes

In order to identify mutations that are unique to or enriched in metastasis, we compared the metastasis genome with the primary tumor genome. We predicted 18 high confidence tier 1 SNV sites and 203 low confidence tier 1 SNV sites, of which 48 passed manual review (Supplementary Table 2c). In addition, we predicted 70 tier 1 indels, of which 56 passed manual review (Supplementary Table 2d).

Manual review guidelines for candidate selection and validation review:

Illumina data

Manual review and validation selection of low quality putative somatic SNVs and all putative somatic Insertions and Deletions.

1. The variant should be supported by at least 10% of high quality, unique reads in the tumor sample, with a minimum of two reads supporting a variant in the tumor sample and no high quality reads supporting the variant in the normal sample.
2. Variant supporting, high quality reads should not contain more than two high quality basepair mismatches.
3. Variant supporting reads or read pairs should map uniquely in the human genome.
4. Unique reads are identified and duplicate reads removed based on identical start positions of both reads if mapped.
5. Variants supported by extremely high levels of localized coverage are discarded.
6. Variants occurring only in reads containing simple repeat sequences are discarded as amplification artifacts.
7. Variants with excessive levels of support on only the positive or negative strand are discarded.
8. Indels occurring in homopolymers larger than 6 bp are reported as PCR amplification artifacts.

3730/Sanger sequencing validation with genomic PCR products

1. 3730 scf formatted trace files are basecalled by Phred and aligned to a sequence representative of the PCR product derived from NCBI Build 36.
2. Variants are considered validated when supported by high quality sequence from at least one PCR product with little to no background at base positions surrounding the variant site for SNVs, and little or no background preceding the breakpoint for heterozygous indels.
3. If coverage is available for both strands and the variant is only supported by a single strand the variant is discarded as a sequencing or capillary migration artifact

4. If high background signals occur in the reads supporting the variant, the variant is considered ambiguous and the validation experiment is repeated.
5. If more than two novel variants occur within a single read the sequence is realigned to the genome to exclude the possibility of paralog amplification.
6. If reads from multiple samples derived from different individuals support an identical somatic mutation, the validation is repeated to exclude the possibility of contamination.

Tier annotation and SIFT annotation

Transcripts from Ensembl build (46) and GenBank download (August 27th, 2007) were used for SNV and indel annotation in primary tumor and brain metastasis during the discovery phase. Transcripts from Ensembl build (54) and GenBank download (May 21st, 2009) were used for SNV and indel annotation in xenograft and also the final annotation for Table 1. Variants were classified into the following four tiers as described in Mardis *et al*(*1*).

Tier 1: Coding synonymous, nonsynonymous, splice site, and RNA variants

Tier 2: Conserved variants (cutoff: conservation score greater than or equal to 500 based on either the phastConsElements28way table or the phastConsElements17way table from the UCSC genome browser, and variants in regulatory regions annotated by UCSC annotation (Regulatory annotations included are targetScanS, ORegAnno, tfbsConsSites, vistaEnhancers, eponine, firstEF, L1 TAF1 Valid, Poly(A), switchDbTss, encodeUViennaRnaz, laminB1, cpgIslandExt)

Tier 3: Variants in non-repeat masked regions

Tier 4: The remaining SNVs

SIFT(3), which searches against the human SWALL database, was used to evaluate the potential impact on protein function for the eight validated missense mutations.

Validation of putative somatic SNVs and Indels by ABI 3730 and deep Illumina and/or 454 read counts

We combined tier 1 sites identified in primary tumor and brain metastasis and obtained deep read count data for the unique set including 156 substitutions (64 HC and 92 LC) and 140 indels. We attempted to design three independent primer pairs per site whenever possible and ensured all primers did not include SNP sites detected in this patient's genome. All primer pairs were used

for PCR amplification of DNA samples from peripheral blood, primary tumor, brain metastasis, and xenograft. PCR products from each sample were pooled and then prepared for Illumina sequencing. We also PCR amplified and sequenced 140 indels using the ABI 3730 platform. The combined analysis of Illumina and 3730 data initially yielded 46 somatic sites including 39 SNVs and 7 indels.

We then combined these 46 sites with the 251 putative tier 1 somatic sites (160 SNVs and 91 indels) detected in the xenograft to generate a unique set of 168 SNVs and 92 indels for ABI 3730 validation and Roche/454 deep read count analysis using all 4 samples. We were unable to design primers for one indel from a highly repetitive region. Four germline sites were included as controls. All validation reads were mapped to the NCBI build36 reference sequence, and to a modified reference where the putative variants were present, to obtain the number of reads supporting the variant and reference alleles in each sample.

3730 validation

We designed PCR primers that were tailed with universal forward and reverse primers, to produce optimal size amplicons ranging from 200 to 300 bp. Larger or smaller amplicons were picked if optimal size amplicons were otherwise not feasible. DNA samples from primary tumor, metastasis, xenograft, and the matched normal were used for PCR amplification and then the individual PCR product was sequenced on ABI 3730 using universal primers. Manual review was performed using amplicon-based assembly in Consed to determine the somatic status for each site.

Illumina and 454 deep read count

We prepared the pooled PCR products from validation reactions for Illumina and/or 454 sequencing in order to generate deep sampling of read counts for tier 1 SNV and indel sites. We ensured all primers did not span any SNP sites detected in this patient's genome.

Illumina: PCR products were concatenated and fragmented using the Covaris sonicator. Illumina adaptors were ligated to the resulting fragments, and we subsequently size-selected a 250-300 bp insert size for sequencing. We obtained 75 bp Illumina fragment reads, which were

then analyzed through the manufacturer's primary pipeline. For SNVs, these reads were aligned to the NCBI Build 36 reference sequence using Maq. Read counts of the reference and variant bases piling up at putative somatic positions were then tallied to validate these sites using a mapping quality threshold (>= q30) to remove noise resulting from poor alignments. For indels, a set of 100 bp contigs was created, one contig containing the mutated putative sequence, the other the reference sequence. The contig length forces all reads aligning to the contig to cross the putative indel site. Maq was again used to perform this alignment. Average coverage of these contigs was used as an approximation for site counts, with a high quality mapping cutoff used as in the SNV analysis.

The detailed procedure for pooling and concatenation and amplicon size are listed as the following:

The 3 designed amplicons (primer pairs) for each site as described in the text were split into 3 different groups: Set1, Set2, and Set3. This resulted in 12 different pools:
Primary Tumor
primer set1 -> pool #1
primer set2 -> pool #2
primer set3 -> pool #3

Normal
primer set1 -> pool #4
primer set2 -> pool #5
primer set3 -> pool #6

Metastasis
primer set1 -> pool #7
primer set2 -> pool #8
primer set3 -> pool #9

Xenograft

primer set1 -> pool #10
primer set2 -> pool #11
primer set3 -> pool #12

All 12 pools were concatenated and run on 1 lane Illumina for a total of 12 lanes (75 bp fragments).

AMPLICON SIZES:
all "set1" pools -> 79 - 1115 bp
all "set2" pools -> 62 - 1175 bp
all "set3" pools -> 63 - 1233 bp

Each pool was concatenated with the following methods:

1) End repair the amplicon pools using the Lucigen DNA Terminator End Repair Kit:

y ul purified, amplicon DNA (1-5ug)
x ul H_2O
10 ul 5X DNA Terminator End Repair Buffer
2 ul DNA Terminator End Repair Enzymes
50 ul final volume

Incubate at room temperature for 30 minutes.

2) Perform a QIAGEN minelute column clean-up, according to the manufacturer's instructions, with the following exception - elute 2X with 15uL of EB buffer (30uL total recovery).

3) Run a 1.2% Lonza Flashgel to verify DNA recovery (1uL of each sample).

4) Set up ligation reactions with a control using the New England BioLabs Quick Ligase Kit.

Sample cocktail:

50 ul 2X Quick Ligase Buffer
18 ul 40% PEG-8000
25 ul DNA
5 ul H_2O
2 ul T4 DNA Quick Ligase _
100 ul final volume

no ligase control cocktail:

50 ul 2X Quick Ligase Buffer
18 ul 40% PEG-8000
3 ul DNA
29 ul H_2O
0 ul T4 DNA Quick Ligase
100 ul final volume

Incubate at room temperature for 30 minutes.

5) Run a 2.2% Lonza FlashGel to confirm concatenation (5uL of each ligation).

6) Precipitate concatenated products prior to fragmentation on the Covaris. The excess glycerol in the amplification reaction will inhibit fragmentation.

Add 2.5x ice cold EtOH to volume of sample.
Add 0.1x 3M NaOAC to volume of sample.
Spin 15 minutes at 15,000 rpm.
Dump supernatent.
Wash with 500ul of ice cold 70% EtOH.
Spin 10 minutes at 15,000 rpm.

Air dry.

Another round of Illumina pooling experiment was conducted for 9 sites without sufficient read counts. Only primer pair 1 was used the second pooling experiment.

454: PCR products from the first primer pair for each site were pooled and then were subjected to 454 library construction followed by Titanium sequencing. Read sequences and quality scores were extracted with sffinfo (454 proprietary software), and then aligned to NCBI Build 36 using SSAHA2 with the SAM output option(4). Alignments were imported to BAM format using SAMtools. A SAMtools pileup file was generated, and read counts were determined by VarScan(5). We required a minimum base quality of 15, with at least 20 reads aligned, to report the allele frequencies. Variant frequencies were corrected based on tumor pathology as described above for Illumina reads.

Significance testing of allele frequency enrichment across tissue types.

To minimize the potential bias introduced by an individual sequencing platform, we generated read count data for 50 point mutations and indels using both Illumina and 454 technologies. We produced Illumina read counts using three independent primer pairs (designated as primer pairs 1, 2, and 3) for 41 out of 50 somatic sites, finding high concordance (correlation coefficients of 0.82775, 0.87437 and 0.94234 for primary tumor, metastasis, and xenograft, respectively) of mutant allele frequencies derived from the read counts of the three primer pairs. Furthermore, we generated read count data from primer pair 1 in duplicate (two Illumina lanes: 1A and 1B) for all four samples (normal, primary tumor, metastasis, and xenograft) and found strong cross-lane consistency (Normal 1A vs 1B, Tumor 1A vs 1B, Met 1A vs 1B, Xeno 1A vs 1B) as demonstrated by the high correlation (coefficients range from 0.997 to 0.999) of coverage depth per site across lanes of the same sample. Finally, we used primer pair 1 to generate Illumina read counts for the 9 sites without sufficient counts from the first round of validation.

In order to determine enrichment in a tissue, we developed a significance test that takes into account the different platforms, experiments and primer pairs that we generated. In this test, a t-value for each variant was calculated as t=D/SD (where D is the mean difference of variant

frequency between two tested tissue groups, and SD is the standard deviation of variant frequency within tissue groups), and then p-values were calculated based on the t-distribution. Prior to the test, tumor read counts were adjusted based on the observed read counts of the normal tissue at that site and the pathology estimate of tumor cellularity of the tumor in question. Briefly, we assumed that, for an amplicon, the pathology estimate is accurate and the distribution of alleles contributed by the normal is identical to what was observed from the direct sequencing of the normal tissue. Therefore, if pathology predicted that 30% of cells in the tumor are normal, we calculate the contribution of the normal tissue to the tumor reference allele count as: $(T_V + T_R) \bullet 0.3 \bullet \left(\frac{N_V}{N_V + N_R} \right)$, where T_V and T_R are the tumor variant and reference allele counts, respectively, and N_V and N_R are the respective normal variant and reference allele counts.

Measurement of expression levels and potential splicing effects of a subset of identified somatic mutations using RT-PCR followed by 3730 sequencing and 454 read counts

Based on transcript sequences surrounding the validated mutations with 200 base pairs of repeat-masked flanking sequence, we designed primers using Primer3 v0.4.0 (see below for citation) and successfully performed RT-PCR for 24 mutations using metastasis and xenograft RNAs. Due to the lack of RNA, RT-PCR was not performed for the primary tumor. For some of the mutations, we expanded the repeat-masked sequence to find suitable primers. Primer pairs were subsequently checked for uniqueness by BLAST to the entire CCDS transcriptome. The detailed RT-PCR experimental procedure is described in Mardis *et al*(*1*).

We were able to successfully amplify the mutant allele in the following genes and sequence using the ABI 3730: *GUK1*, *IGFBP3, SLC44A1, SHE, DYNC2H1, CHST7, FAM107B, NALCN, PPPDE1, PTPRJ, ZRSR2, MAP3K8, DDX11*, *TADA2L, TP53, RBM47, GTF3C3, IRAK2, JAK2, CHRNA9, KIAA0467,* and *WWTR1*.

We obtained sufficient 454 read counts for 11 mutations in both metastasis and xenograft. They are *GUK1*, *SLC44A1, PPDE1, DEPE3*, *MAP3K8, TADA2L, TP53, GTF3C3, JAK2, CHRNA9,* and *KIAA0467.* We have observed greater than 1% mutant allele frequency in 10 of them (not in *KIAA0467)*. We have found notable expression differences in the mutant allele in *CHRNA9*

between brain metastasis (3%) and primary xenograft passage 1 (17%) used for whole genome sequencing (Supplementary Table 16).

Screening for recurrent somatic mutations in additional breast primary tumor and metastasis samples

PCR-based 3730 sequencing was performed on 115 additional primary tumors (62 with matched normal) and 65 metastatic tumors (0 with matched normal) for validated point mutations and small indels. The breakdown of the samples is described below.

Primary Tumor:

* Basal
2 matched
32 unmatched
* Her2
3 matched
* Her2-E
9 unmatched
* Luminal B
49 matched
2 unmatched (these are potentially 2 pairs but the "matched" normal has a discrepant Participant ID)
7 unmatched
* Luminal A
6 unmatched
* Normal
2 unmatched
* Unknown
0

Total = 112 (54 matched [for CHGB screening, 55 matched were used]; 58 unmatched)

Metastatic tumor:

* 53 unmatched
* 14 unmatched (from 7 individuals)
* 6 unmatched (potentially from 3 individuals)

Total = 73 (0 matched)

Screening for recurrently mutated genes in additional breast tumors

We screened the coding exons for 9 genes (*MAP3K8, GUK1, NRG1, IRAK2, JAK2, PTPRJ, WWTR1, CSMD1,* and *NRK*) in 116 breast tumors to identify additional mutations. Matched normals were sequenced to determine somatic status. Significantly mutated gene test was performed as described previously(6). The background mutation rate ($1x10^{-06}$) used in this analysis was based on a previous report(7).

Subtype classification of 116 tumor samples:

2 are normal subtype (pathology status = malignant)
5 are basal subtype
4 are Her2 subtype
42 are Luminal A subtype
63 are Luminal B subtype

Recurrent Screening

To indentify recurrent functional somatic mutations in the nine genes where validated somatic mutations were identified in the original sample quartet, a panel of 116 additional tumor samples were selected. The panel consisted the following sample subtypes: 63 luminal B, 42 luminal A subtype samples, 5 basal subtype, 4 Her2 subtype, and 2 normal subtype. A total of 271 primer pairs were designed to target all coding exons from Ensembl database release 45 and the corresponding version of GenBank from CSMD1*, GUK1, IRAK2, JAK2, MAP3K8, NRG1, NRK,*

PTPRJ, and *WWTR1*. All 116 new tumor samples in addition to the original quartet were individually amplified with PCR using the standard Amplitaq Gold protocol and subsequently sequenced with Big Dye Terminators on the ABI 3730xl capillary sequencer. Nine Consed gene-based assemblies were created using crossmatch alignments of Phred basecalled scf files. The aligned and assembled data were processed with PolyScan and PolyPhred to identify novel, potentially somatic SNVs and Indels that would result in translational changes affecting the amino acid sequence of the protein according to Ensembl and GenBank transcript annotation. (Annotation types: missense, nonsense, frameshift, in-frame, splice site, non-start, non-stop/readthrough). Known germline variants from dbSNP130 were filtered and remaining putative variants were reamplified and resequenced using both the tumor and matched normal DNA in order to validate the variants and determine somatic status.

Array CGH Methodology

Agilent's aCGH platform uses a two-color competitive hybridization process to measure genome-wide DNA variation between two samples. Genomic DNAs from both a tumor and germline reference sample treated by restriction digestion (AluI/RsaI), then fluorescently labeled with either a Cy5 dye (tumor) or a Cy3 dye (germline reference), and the resulting DNA is column purified using the Bioprime Total Genomic Labeling System from Invitrogen (18097-011). Both tumor and germline purified samples are co-hybridized to an Agilent Human Genome 244K CGH array and washed according to Agilent protocols. Fluorescent signals are then extracted for each array feature using an Agilent scanner and Feature Extraction software, v9.1. We obtained aCGH data for metastasis and xenograft.

Illumina Array

We followed Illumina protocols to use Illumina 1M duo arrays for peripheral blood, primary tumor, and metastasis.

Identification of genomic regions with copy number alterations in primary tumor, metastasis, and xenograft

Our in-house algorithm cnvHMM (unpublished) was used to identify copy number alterations genome-wide. The numbers of confidently mapped reads (mapping quality > 35) in 5kb non-

overlapping windows were extracted from both the tumor and the normal genomes. Copy number segments were obtained using a Hidden Markov Model (HMM) that models the distribution of read counts as functions of the underlying copy number and the purity of the DNA. The log likelihood ratio score (likelihood of being a copy number altered segment/likelihood of being a copy number neural segment, LLR) was calculated for each copy number segment of each sample. The likelihood is estimated by HMM and is the product of emission probabilities and transition probabilities. It summarizes both the observed read counts and the length of the segments. An LLR score of 10 was used as the cutoff for selecting regions with copy number alterations.

Correlation Analysis of Copy Number Estimations from array CGH, Illumina SNP array, and whole genome sequencing

Copy number data computed from Illumina SNP array, array CGH and whole genome sequencing have different chromosome coordinate systems. To merge these datasets, we mapped aCGH and Illumina data onto the windows used in the analysis of whole genome sequencing data. Since coordinate ranges for probes used in aCGH are much smaller than the 10kb windows used in the depth analysis of the whole genome sequencing data, the start positions of the aCGH probes have been used for mapping. A Pearson correlation test was used in this analysis.

Structural variations (SVs) prediction using BreakDancer and de novo assembly of SVs

We performed SV detection using paired-end sequence data obtained from tumor and normal samples using BreakDancer(8). Multiple libraries were constructed from the genomic DNA of tumor and normal cells with insert sizes ranging from 117 bp to 387 bp. Empirical insert size distributions were obtained from the mapping results. All libraries had unimodal insert size distributions, although the standard deviation (SD) varied across libraries. In this experiment, all anomalous read pairs (ARPs) were required to have a Maq mapping quality greater than 35 with a separation distance exceeding 4 SD, or be in an unexpected orientation. SVs receiving minimal confidence scores (60 for deletions, and 90 for insertions, inversions, and translocations) and supported only by the tumor reads were selected for downstream analysis.

We performed de novo assembly for all predicted deletions, insertions, and inversions using an in-house assembler Tigra (unpublished) and for translocations using Phrap (http://www.phrap.org/). We used SAMtools to extract all Maq-mapped reads within 500-1,000 bp of each predicted breakpoint. Unmapped reads with mates mapping to the SV region were also included. For Tigra assembly, we used a kmer size of 25 and a minimal coverage of 2 to help remove tips caused by potential sequencing errors. Tigra confidence scores were defined as the N50 size of the local assembly/size of the region from where the reads were extracted. For Phrap assembly, the Illumina quality values were converted to Phred-like values as described online (http://maq.sourceforge.net/fastq.shtml). Assemblies were performed with Phrap version 1.080721 using the following parameters: -minscore 20 -vector_bound 0 -bandwidth 2 -max_group_size 0 -view -revise_greedy. All resulting contigs from both assemblers were compared to the SV region (+/- 500-1000 bp of breakpoints) from human NCBI Build 36 using cross_match.

Criteria for defining breakpoints and SV types using assembled contigs

1. Indel-containing contigs had two alignments in the same orientation and the alignment boundaries defined the indel breakpoints.
2. Overlapping alignments indicated direct repeats in the reference that were involved in the event.
3. Contigs with a single alignment to the reference were checked for smaller indels.
4. Contigs containing translocation breakpoints had alignments to both chromosomes.
5. Contigs spanning the entire inversion had three alignments, the middle of which is in the opposite orientation from the outer two.
6. If the inversion was larger than the contig size, only one inversion breakpoint was present. In this case, the contig had two alignments in the opposite orientation. A second contig defining the other inversion breakpoint was expected. The breakpoint positions on the reference indicated the inversion size.

Identify breakpoint reads by read remapping and assign tissue sources for SVs

For assembled and/or validated SVs, we used SAMtools to extract all Maq-mapped reads within 500-1,000 bp of each breakpoint and unmapped reads with mates mapping to the SV region.

Then we mapped the reads to SV-containing contigs using cross_match. Reads crossing breakpoints of SV contigs were tallied. The number of reads spanning the breakpoints but supporting the reference allele was also recorded. In addition, we annotated the tissue source of the reads supporting the reference or SV allele for determining the source of SVs. Specifically, we obtained all reads that mapped within 500 bp of SV breakpoints and generated contigs using the NCBI Build 36 reference sequence +/- 500 bp of each SV breakpoint. Then, we aligned reads with a Maq alignment score of 30 or greater to assembled SV contigs and to reference sequence using cross_match (parameters: -discrep_lists -alignments -minmatch 10 –maxmatch 10 -minscore 15).

We filtered read to contig/reference hits as follows:

1. A read could not have >= 5 bp of unaligned bases on its ends.
2. cross_match score >= 20 was required.
3. If cross_match scores were between 20 to 30, no substitutions were allowed.
4. If cross_match score is > 30, 4% substitutions were allowed.
5. Reads supported the SV if the read crossed the breakpoint with at least 2 extra bases and the read did not align to the reference sequence.

Pairoscope-based manual review of translocations

We selected translocations supported by at least 5 read pairs and 2 libraries for further study. Translocations were manually reviewed using the "Pairoscope graph". Pairoscope is a software package that was developed to provide a means to visualize the read pairs in regions of a genome, along with the read depth and gene structure, that have been identified as containing a structural variant. Manual reviewers evaluated the read pair mapping patterns in normal, primary tumor, brain metastasis, and xenograft to eliminate false predictions.

Validation of SVs by PCR followed by ABI 3730 and 454 sequencing

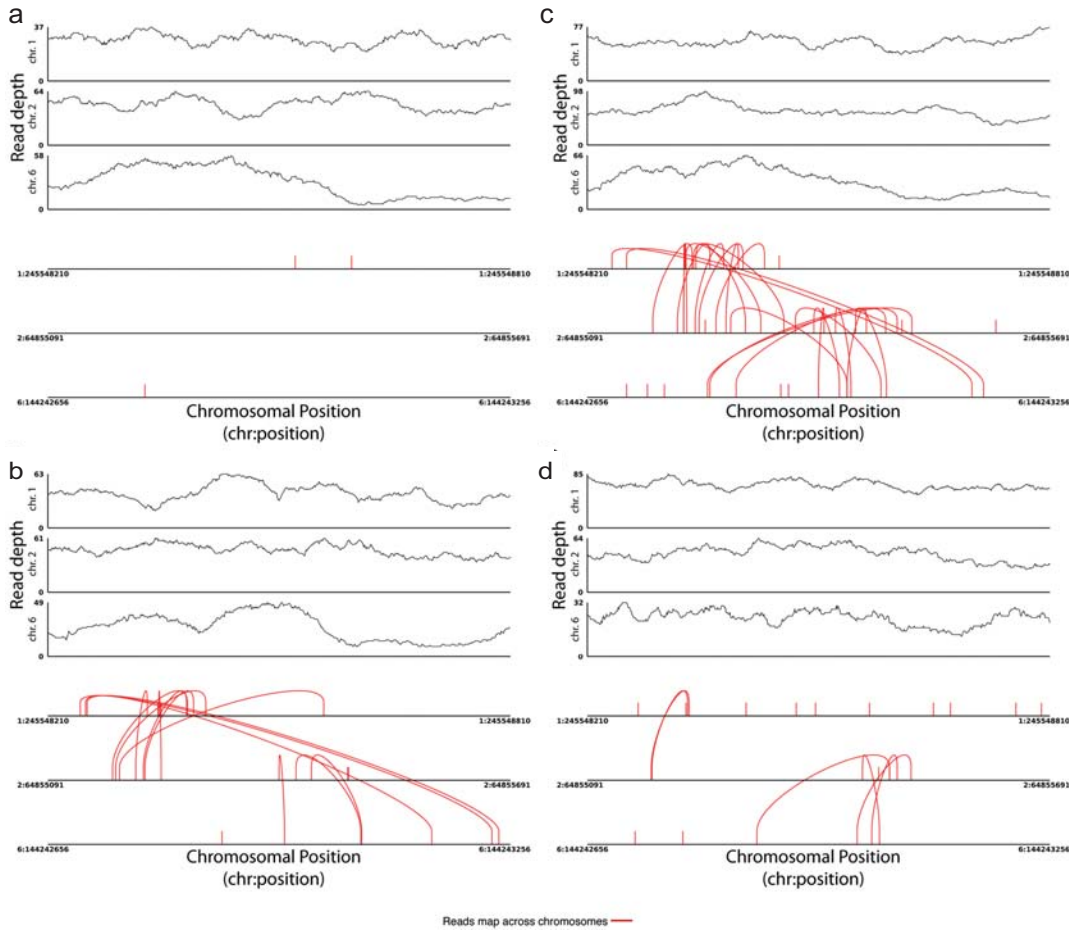
For small insertions, small inversions, and deletions of most sizes, PCR primers were designed approximately 100-200 bp outside the boundaries of the breakpoints defined by BreakDancer. For large inversions, a total of 4 primers were designed for 2 breakpoints and 2 independent PCR reactions targeting 2 breakpoints were performed. For translocations, a total of 4 primers that

reside 5’ and 3’ from the predicted breakpoints were designed for each prediction and all 6 possible combinations of the 4 primers were used for PCR amplification to determine the efficiency of the primers and the orientations of the translocation. SVs were considered validated if any single resulting read sequence spanned the predicted breakpoints. All PCR products were evaluated on a 2% agarose gel. Regardless of yield, all products were sequenced in both directions using Big Dye Terminator reactions and subsequently loaded on an ABI 3730 capillary sequencer. The resulting traces were assembled onto an SV-containing reference sequence extracted from the region surrounding the predicted SV site on NCBI Build 36 with an additional 500-1,000 bp of flanking 3' and 5' sequence. All resulting diploid trace data were manually reviewed and those traces showing unambiguous evidence of homozygous or heterozygous SVs were classified as either somatic or germline events, or were alternatively labeled as variants if the somatic status could not be determined due to lack of sequence data from the matched normal sample. In addition, all 3730 traces were aligned to NCBI Build 36 using cross_match for classifying SV events using the same standards as those used in manual review. Moreover, we pooled all PCR products from normal, primary tumor, brain metastasis, and xenograft independently and sequenced the four pools on the Roche 454 platform. The 454 reads were analyzed through the manufacturer’s primary pipeline, and aligned to the NCBI Build 36 reference sequence using cross_match. The alignments were interpreted as described in the “Criteria for defining breakpoints and SV types using assembled contigs” section above.

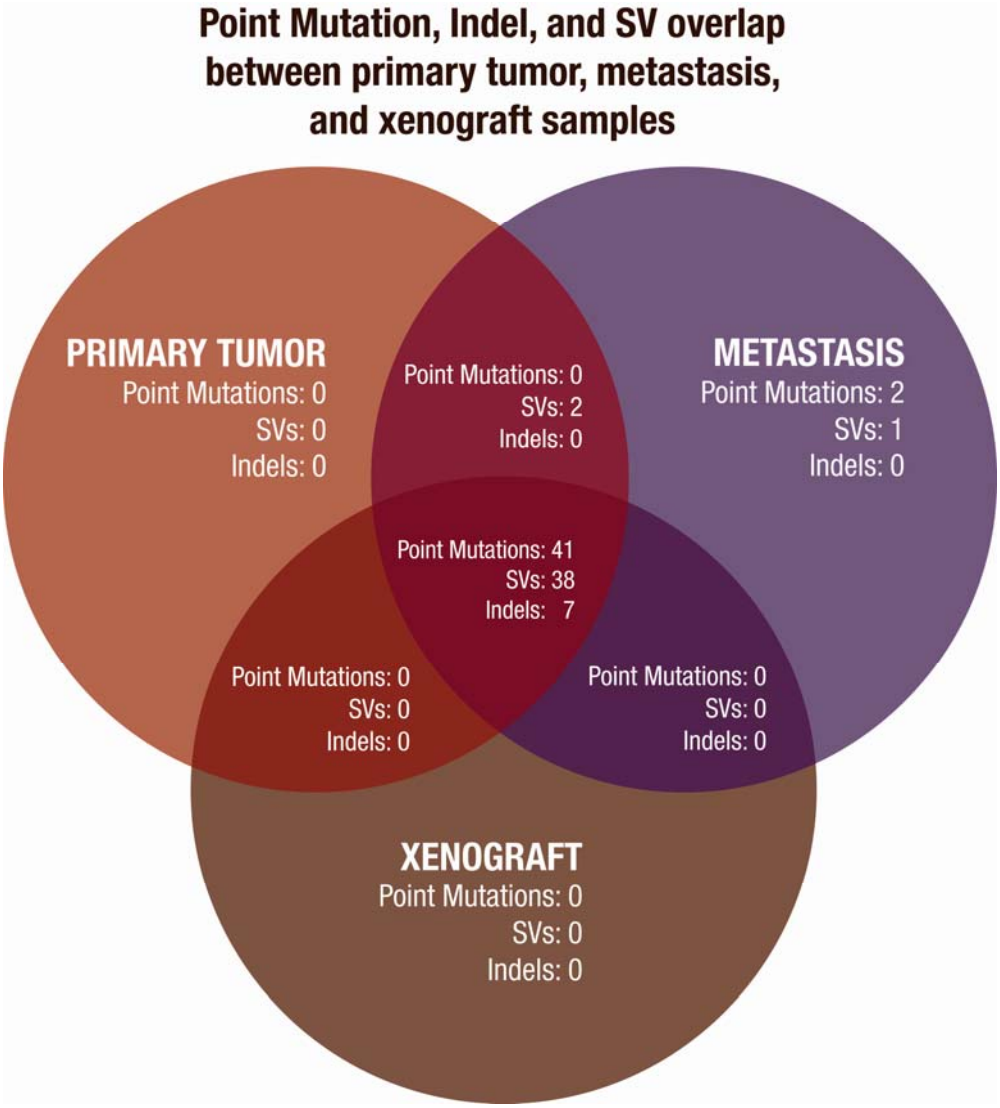
The overlap of point mutation, indel, and SV between primary tumor, metastasis, and xenograft is shown in Supplementary Figure 2.

B. Supplementary Figures

Supplementary Figure 1



Supplementary Figure 2



C. Supplementary Figure Legends

Supplementary Figure 1. Three linked translocations. A graph of read pairs in a 1,000 bp region containing 3 separate translocations for the normal (a), the primary tumor (b), the metastasis (c), and the xenograft (d). The top sections display the read depth at each base. The bottom sections show each read within the region whose mate mapped to a different chromosome as red bars, with matched pairs connected by arcs.

Supplementary Figure 2. The overlap of point mutation, indel, and SV between primary tumor, metastasis, and xenograft.

D. Supplementary Tables

Supplementary Table 1. Genomic Coverage

	Blood	Primary Tumor	Brain Metastasis	Xenograft
Bases Sequenced (Gbp)	130.7	124.9	111.8	149.2
SNVs detected	4,325,512	4,121,595	3,860,638	3,626,361
Concordance with dbSNP	78.54%	78.87%	79.00%	79.48%
Estimated Haploid Coverage	38.8X	29.0X	32.0X	23.8X
Known Heterozygote Coverage	98.27%	96.79%	96.17%	88.77%
Known Homozygote Coverage	99.28%	93.70%	97.15%	98.70%

Supplementary Table 2a. The process for selecting candidate somatic SNVs in primary tumor, brain metastasis, and xenograft. Identification of somatic mutations. Putative somatic variants were separated from germline variants as shown in the primary tumor, the brain metastasis and the mouse xenograft. Variants are listed as validated in each column if they were somatic in any of the three samples.

Category	Primary Tumor	Metastasis	Xenograft
Tumor SNVs detected	4,967,429	4,647,103	4,489,151
SNVs passing maq SNP filter	4,121,595	3,860,638	3,618,536
SNVs described previously	3,540,263	3,321,746	3,144,926
Novel SNVs	581,332	538,892	473,610
SNVs also detected in normal	554,159	487,182	361,361
SNVs called in NOD/Scid	—	—	3,171
Novel potential somatic SNVs	27,173	51,710	109,078
LOH SNVs	2,007	21,690	83,763
SNVs unable to be classified	1,394	1,712	1,757
Tier1 SNVs	200	225	328
Tier1 HC SNVs	28	46	100
Tier1 LC SNVs	172	179	228
Tier1 HC SNVs passing review	—	—	54
Tier1 LC SNVs passing review	39	19	—
Tier1 Validated HC SNVs	16	33	37
Tier1 Validated LC SNVs	6	3	0
Tier2 SNVs	911	1,059	1,475
Tier 2 HC SNVs	185	313	675
Tier3 SNVs	4,503	5,754	4,832
Tier3 HC SNVs	920	1,689	2,287
Tier4 SNVs	18,158	21,270	16,923
Tier4 HC SNVs	2,239	3,751	4,497

Supplementary Table 2b. The process for selecting candidate somatic Indels in primary tumor, brain metastasis, and xenograft. Putative somatic variants were separated from germline variants as shown in the primary tumor, the brain metastasis and the mouse xenograft. Variants are listed as validated in each column if they were somatic in any of the three samples.

Category	Primary Tumor	Metastasis	Xenograft
Tumor indels detected	4,396,160	4,684,771	3,604,771
Indels with multiple library support	631,536	782,629	438,603
Indels detected in the normal	571,137	628,891	418,678
Novel indels	60,399	85,042	19,925
1 bp indels without 10% of total tumor coverage as support	14,453	23,185	81
Novel potential somatic indels	45,946	61,857	19,844
Tier 1 indels	98	106	128
Tier1 indels passing review	48	59	91
Tier1 Validated HC SNVs	4	7	0
Tier2 indels	1070	1,439	1,780
Tier 2 HC indels	57	75	126
Tier3 indels	6,973	9,482	5,613
Tier3 HC indels	457	500	281
Tier4 indels	40,512	59,560	12,238
Tier4 HC indels	1,161	1,446	409

Supplementary Table 2c. The process for selecting candidate metastasis specific somatic SNVs.

Category	Metastasis
Tumor SNVs detected	4,647,103
SNVs passing maq SNP filter	3,860,638
SNVs described previously	3,321,746
Novel SNVs	538,892
SNVs also detected in primary tumor	488,697
SNVs called in NOD/Scid	—
Novel potential metastasis-enriched SNVs	50,195
LOH SNVs	18,062
SNVs unable to be classified	1,467
Tier1 SNVs	221
Tier1 HC SNVs	18
Tier1 LC SNVs	203
Tier1 HC SNVs passing review	—
Tier1 LC SNVs passing review	48
Tier1 Validated HC SNVs	7
Tier1 Validated LC SNVs	2
Tier2 SNVs	1,244
Tier 2 HC SNVs	137
Tier3 SNVs	6,332
Tier3 HC SNVs	824
Tier4 SNVs	22,869
Tier4 HC SNVs	2,301

Supplementary Table 2d. The process for selecting candidate metastasis specific somatic Indels.

Category	Metastasis
Tumor indels detected	4,684,771
Indels with multiple library support	782,629
Indels detected in the primary tumor	681,071
Novel indels	101,198
1 bp indels without 10% of total tumor coverage as support	15,700
Novel potential metastasis-enriched indels	85,498
Tier 1 indels	155
Tier1 indels passing review	63
Tier1 Validated HC SNVs	3
Tier2 indels	1768
Tier 2 HC indels	21
Tier3 indels	11,845
Tier3 HC indels	112
Tier4 indels	61,054
Tier4 HC indels	534

Supplementary Table 3a. Illumina and 454 deep read count and corrected readcount for 50 somatic sites in excel spreadsheet.

Supplementary Table 3b. Summary of 50 somatic point mutations and small indels identified in the primary tumor, brain metastasis, and xenograft in excel spreadsheet.

Supplementary Table 4. Recurrent screening identified 4 *CSMD1* and 1 *JAK2* mutations.

Chromosome	Genomic position	NCBI build	Gene	Reference allele	Variant allele
8	3193010	36	CSMD1	G	A
8	2996427	36	CSMD1	C	G
8	2842969	36	CSMD1	A	G
8	2783657	36	CSMD1	C	T
9	5116757	36	JAK2	G	C

Supplementary Table 5. Summary of regions with significant copy number alterations in primary tumor.

Chromosome	Start position	End position	Size	Number of markers	HMM state	Copy Number	LLR score
1	0	790000	790000	62	0	0.21	40.36
1	1250000	1660000	410000	42	0	0.63	14.96
1	12760000	13650000	890000	72	0	0.16	47.57
1	83370000	83720000	350000	36	0	0.47	17.58
1	103570000	104090000	520000	41	0	0.48	20.4
1	108560000	108830000	270000	28	0	0.48	13.6
1	115710000	115920000	210000	22	0	0.25	13.62
1	120340000	120730000	390000	34	0	0.36	19.3
1	141600000	142710000	1110000	82	0	0.35	44.7
1	142730000	143220000	490000	32	0	0.16	21.88
1	143270000	143620000	350000	19	0	0.27	11.71
1	144470000	144870000	400000	35	0	0.16	23.88
1	145880000	146160000	280000	29	0	0.04	21.59
1	146310000	147220000	910000	74	0	0.39	41.89
1	147520000	148100000	580000	53	0	0.51	26.71
1	241120000	241430000	310000	32	0	0.85	10
2	86920000	88070000	1150000	116	0	0.2	74.87
2	89060000	89370000	310000	32	0	0.44	15.96
2	89590000	89950000	360000	37	0	0.57	15.89
2	91200000	91620000	420000	43	0	0.45	20.67
2	95440000	96080000	640000	65	0	0.84	17.19
2	97040000	97610000	570000	56	0	0.47	26.85
2	109820000	110170000	350000	36	0	0.02	27.05
2	110520000	111100000	580000	43	0	0.04	31.9
2	111730000	112080000	350000	36	0	0.27	21.73
2	113860000	114130000	270000	28	0	0.36	15.41
2	130870000	131180000	310000	32	0	0.09	22.63
2	132240000	132680000	440000	45	0	0.58	18.25
2	242170000	242350000	180000	19	0	0.04	14.1
3	46320000	46460000	140000	15	0	0.09	10.61
3	68010000	68140000	130000	14	0	0.05	10.28
3	76320000	76480000	160000	17	0	0.08	12.25
3	121760000	121900000	140000	15	0	0.09	10.69
4	8960000	9360000	400000	41	0	0.51	12.64
4	68910000	69620000	710000	61	0	0.21	39.44
4	132800000	133120000	320000	33	0	0.78	10.75
5	12840000	13250000	410000	42	0	0.11	29.72
5	20730000	20970000	240000	25	0	0.62	10.61
5	34110000	34430000	320000	33	0	0.54	15.35

5	68860000	71160000	2300000	231	0	0.14	155.7
5	175260000	175480000	220000	23	0	0.29	13.15
5	176980000	177410000	430000	44	0	0.41	22.2
5	180190000	180330000	140000	15	0	0.09	10.64
6	9100000	9350000	250000	20	0	0.03	14.91
6	26790000	27070000	280000	29	0	0.6	12.27
6	57800000	58820000	1020000	97	0	0.89	22.68
6	115340000	115680000	340000	35	0	0.03	26.21
6	157510000	157980000	470000	42	0	0.01	31.71
6	167690000	168030000	340000	32	0	0.21	19.66
7	56780000	57190000	410000	36	0	0.37	19.45
7	61110000	61240000	130000	14	0	0.07	10.1
7	62330000	62730000	400000	41	0	0.34	23.09
7	64600000	64880000	280000	29	0	0.65	10.96
7	72050000	72350000	300000	31	0	0.12	21.3
7	73790000	74980000	1190000	94	0	0.14	63.32
7	75910000	76640000	730000	74	0	0.45	35.83
7	101910000	102220000	310000	32	0	0.24	19.42
7	142940000	143190000	250000	26	0	0.24	16.19
7	143510000	143690000	180000	19	0	0.12	13.07
7	149230000	149620000	390000	40	0	0.65	14.46
8	0	140000	140000	15	0	0.09	10.68
8	6930000	8100000	1170000	107	0	0.18	69.46
8	11900000	12430000	530000	43	0	0.45	20.87
9	0	180000	180000	19	0	0.24	11.96
9	38760000	47100000	8340000	733	0	0.07	529.71
9	65230000	66550000	1320000	109	0	0.13	74.25
9	66680000	67880000	1200000	103	0	0.17	68.3
9	67940000	70210000	2270000	186	0	0.14	125.07
10	17830000	18250000	420000	37	0	0.05	27.4
10	45490000	46370000	880000	73	0	0.07	52.3
10	46580000	47910000	1330000	86	0	0.08	59.98
10	48280000	49050000	770000	62	0	0.04	45.88
10	50720000	51660000	940000	83	0	0.36	45.09
10	80920000	81660000	740000	73	0	0.09	52.02
10	88730000	89240000	510000	52	0	0.4	26.98
11	89020000	89460000	440000	45	0	0.27	26.96
13	17930000	18340000	410000	42	0	0.39	20.82
13	51670000	52060000	390000	40	0	0.75	11.03
14	18130000	18490000	360000	37	0	0.27	22.12
14	18550000	19250000	700000	71	0	0.19	46.05

15	18280000	19660000	1380000	139	0	0.58	53.96
15	20660000	21180000	520000	47	0	0.15	31.53
15	26110000	26890000	780000	68	0	0.28	40.07
15	28160000	28890000	730000	74	0	0.27	44.28
15	30230000	30700000	470000	48	0	0.09	33.91
15	80270000	81000000	730000	67	0	0.19	43.6
15	82530000	82900000	370000	31	0	0.56	13.04
16	14690000	15390000	700000	71	0	0.4	36.41
16	16200000	16750000	550000	56	0	0.18	36.45
16	18080000	18690000	610000	62	0	0.16	41.05
16	21260000	21460000	200000	21	0	0.4	10.64
16	21660000	21850000	190000	20	0	0.2	12.75
16	22350000	22520000	170000	18	0	0.15	11.95
16	28250000	28380000	130000	14	0	0.05	10.25
16	28530000	28720000	190000	20	0	0.14	13.42
16	28950000	29720000	770000	78	0	0.58	31.56
16	31850000	32390000	540000	55	0	0.41	27.86
16	32570000	33260000	690000	70	0	0.18	46.09
16	33540000	33760000	220000	23	0	0.33	12.88
17	15370000	15730000	360000	37	0	0.62	14.26
17	16510000	16700000	190000	20	0	0.36	10.71
17	18230000	18680000	450000	46	0	0.3	26.56
17	18870000	19070000	200000	21	0	0.02	15.76
17	20160000	20750000	590000	60	0	0.65	22.01
17	31510000	31880000	370000	27	0	0.02	20.25
17	33290000	33720000	430000	33	0	0.24	20.14
17	36350000	36530000	180000	19	0	0.04	14.03
17	41650000	42130000	480000	49	0	0.13	33.35
18	14110000	15400000	1290000	130	0	0.74	41.89
19	30000	200000	170000	18	0	0.11	12.68
21	13290000	14320000	1030000	104	0	0.52	44.55
22	14450000	15760000	1310000	116	0	0.46	56.77
22	17020000	17330000	310000	32	0	0.42	16.11
22	18670000	19050000	380000	33	0	0.15	22.09
22	19790000	20240000	450000	46	0	0.14	30.96
X	3700000	3950000	250000	26	0	0	19.83
X	52120000	52580000	460000	41	0	0.03	30.55
X	71880000	72110000	230000	24	0	0.08	17.16
X	76150000	76450000	300000	31	0	0.1	21.91
X	76610000	77330000	720000	73	0	0.12	50.39
X	88340000	90160000	1820000	183	0	0.41	92.26

X	90630000	92250000	1620000	163	0	0.43	80.75
X	101330000	101620000	290000	30	0	0.12	20.57
2	165130000	168230000	3100000	311	1	1.42	15.74
2	179540000	190730000	11190000	1120	1	1.41	59.62
2	192520000	199670000	7150000	716	1	1.4	38.71
2	208860000	215860000	7000000	701	1	1.42	35.33
3	82850000	86500000	3650000	366	1	1.56	10.9
3	163570000	168090000	4520000	453	1	1.54	16.22
4	70000	3530000	3460000	341	1	1.12	19.95
4	10000000	36800000	26800000	2666	1	1.23	170.78
4	42670000	48770000	6100000	611	1	1.38	28.82
5	49460000	53100000	3640000	365	1	1.42	21.63
5	61540000	65520000	3980000	399	1	1.49	15.38
5	80740000	94950000	14210000	1417	1	1.47	66.26
5	96510000	110950000	14440000	1441	1	1.42	87.51
5	116310000	123290000	6980000	699	1	1.5	25.99
5	127360000	131310000	3950000	396	1	1.48	16.65
5	160420000	166420000	6000000	601	1	1.48	25.19
8	111150000	115960000	4810000	482	1	1.56	14.68
9	28060000	32220000	4160000	417	1	1.51	22.59
9	70230000	85840000	15610000	1562	1	1.23	124.53
9	103410000	106570000	3160000	317	1	1.42	21.69
10	51680000	59980000	8300000	831	1	1.43	55.25
10	65550000	69560000	4010000	402	1	1.44	24.52
11	48360000	50270000	1910000	192	1	1.22	21.96
11	88160000	89000000	840000	85	1	1.17	11.64
12	7370000	11460000	4090000	410	1	1.37	30.78
12	15060000	25600000	10540000	1055	1	1.55	35.39
12	31090000	34180000	3090000	310	1	1.49	13
12	36160000	43670000	7510000	752	1	1.55	25.53
12	57340000	61280000	3940000	395	1	1.46	25.01
12	68390000	90670000	22280000	2203	1	1.49	113.36
13	52950000	72550000	19600000	1961	1	1.33	152.67
14	39630000	43860000	4230000	424	1	1.57	14.26
15	32460000	35780000	3320000	333	1	1.53	13.08
15	51570000	55340000	3770000	378	1	1.56	11.31
17	47680000	50580000	2900000	291	1	1.56	11.49
17	54130000	58000000	3870000	388	1	1.48	18.73
18	60180000	69460000	9280000	929	1	1.42	52.7
19	47900000	48590000	690000	70	1	1.03	11.83
1	35670000	43240000	7570000	758	3	3.18	109.9

1	93520000	95910000	2390000	240	3	3.54	50.11
1	115940000	117680000	1740000	175	3	3.37	31.72
1	143640000	143820000	180000	19	3	9.78	33.48
1	144100000	144450000	350000	36	3	4.5	14.87
1	144950000	145860000	910000	92	3	4.39	34.59
1	148120000	159770000	11650000	1166	3	4.61	507.82
1	159920000	194970000	35050000	3506	3	4.16	1114.08
1	195100000	197900000	2800000	281	3	3.76	60.86
1	198040000	204180000	6140000	615	3	4.91	313.63
1	204660000	205750000	1090000	110	3	3.97	33.89
1	205820000	220700000	14880000	1489	3	3.58	316.85
1	220770000	221780000	1010000	102	3	3.66	23.85
1	222310000	226800000	4490000	450	3	3.66	106.5
1	226860000	240470000	13610000	1356	3	3.59	297.94
1	241450000	246640000	5190000	520	3	3.45	95.51
2	0	13180000	13180000	1301	3	3.28	224.43
2	14280000	18600000	4320000	427	3	3.17	59.82
2	19230000	34570000	15340000	1532	3	3.17	221.04
2	36200000	40560000	4360000	437	3	3.04	47.83
2	41460000	50940000	9480000	949	3	3.11	121.46
2	52660000	56620000	3960000	397	3	2.9	28.84
2	58490000	65150000	6660000	667	3	2.99	63.45
2	91130000	91180000	50000	6	3	14.35	19.09
2	91640000	91680000	40000	5	3	14.31	18.48
2	132700000	133200000	500000	51	3	3.77	20.17
4	48790000	48860000	70000	8	3	9.45	16.49
4	52380000	58060000	5680000	569	3	2.71	28.61
4	75870000	79840000	3970000	398	3	2.74	22.61
4	82330000	85830000	3500000	351	3	2.64	11.36
4	105630000	116000000	10370000	1038	3	3.03	96.3
4	133140000	135310000	2170000	218	3	3.47	34.04
4	135910000	153560000	17650000	1766	3	5.56	1088.7
4	188420000	190910000	2490000	250	3	3.57	61.12
5	920000	11620000	10700000	1071	3	2.83	73.02
5	13270000	17560000	4290000	430	3	2.79	28.25
5	31080000	34090000	3010000	302	3	2.71	12.09
5	37750000	38960000	1210000	122	3	2.89	10.22
6	110000	9080000	8970000	898	3	3.13	149.33
6	9370000	26770000	17400000	1741	3	2.88	176.68
6	27090000	32040000	4950000	496	3	2.88	52.42
6	32750000	44810000	12060000	1207	3	2.73	109.8

6	45510000	47500000	1990000	200	3	2.67	12.47
6	51900000	53980000	2080000	209	3	2.6	10.71
6	57310000	57780000	470000	48	3	3.9	21.25
6	58840000	58880000	40000	5	3	48.64	86.94
6	105640000	112830000	7190000	720	3	2.51	17.13
6	136380000	140010000	3630000	364	3	2.53	10.7
7	640000	5890000	5250000	526	3	3.59	145.51
7	6000000	6740000	740000	75	3	3.49	19.56
7	6900000	32610000	25710000	2572	3	3.27	444.57
7	33060000	35040000	1980000	199	3	3.08	28.2
7	35260000	43960000	8700000	871	3	3.21	155.08
7	44060000	45720000	1660000	167	3	3.44	41.54
7	45870000	55690000	9820000	973	3	3.11	146.39
7	61260000	62310000	1050000	94	3	2.87	10.97
7	66450000	71620000	5170000	518	3	3.04	88.7
7	72370000	73770000	1400000	141	3	2.72	14.46
7	97700000	99640000	1940000	195	3	2.49	12.22
7	104180000	106440000	2260000	227	3	2.53	10.9
7	126490000	127880000	1390000	140	3	2.67	11.97
7	128100000	135400000	7300000	731	3	2.54	37.83
7	136920000	142920000	6000000	597	3	2.49	24.27
7	147310000	149210000	1900000	191	3	2.51	10.24
7	149640000	151340000	1700000	171	3	2.63	14.07
7	153500000	158610000	5110000	493	3	2.62	38.7
9	200000	8280000	8080000	809	3	2.83	42.04
9	17560000	20390000	2830000	284	3	2.8	12.37
9	139030000	140130000	1100000	111	3	3.1	12.88
10	120000	17810000	17690000	1764	3	3.7	411.9
10	18270000	38550000	20280000	2029	3	3.44	346.56
10	41690000	41850000	160000	17	3	23.6	94.88
13	96230000	100630000	4400000	441	3	2.71	24.3
16	33780000	33930000	150000	16	3	5.86	17.35
16	44960000	45000000	40000	5	3	14.59	19.64
16	69280000	69750000	470000	48	3	6.04	42.57
16	80040000	85960000	5920000	593	3	2.43	11.19
20	20000	1490000	1470000	148	3	2.76	16.1
20	1550000	6850000	5300000	531	3	2.57	34.66
20	8590000	13270000	4680000	469	3	2.51	16.42
20	15320000	25680000	10360000	1037	3	2.65	82.81
20	29280000	52740000	23460000	2344	3	2.65	212.34
20	53920000	62380000	8460000	832	3	2.73	90.57

21	9730000	10200000	470000	48	3	4.88	42.5
21	26250000	27010000	760000	77	3	3.21	18.31
X	5980000	20560000	14580000	1459	3	2.51	52.9
X	37810000	40750000	2940000	295	3	2.74	29.86
X	67770000	68710000	940000	95	3	2.87	12.75
X	148880000	150910000	2030000	204	3	2.61	13.15

Supplementary Table 6. Summary of regions with significant copy number alterations in brain metastasis.

Chromosome	Start position	End position	Size	Number of markers	HMM state	Copy Number	LLR score
1	0	730000	730000	56	0	0.11	23.86
1	12760000	13640000	880000	71	0	0.13	29.3
1	103550000	104090000	540000	43	0	0.48	11.47
1	142210000	142710000	500000	39	0	0.14	16.14
1	142750000	143220000	470000	30	0	0.12	12.77
1	144470000	144870000	400000	35	0	0.2	13.66
1	145880000	146160000	280000	29	0	0.05	13.17
1	146310000	147180000	870000	70	0	0.37	22.56
1	147530000	148100000	570000	52	0	0.6	11.84
2	86920000	88060000	1140000	115	0	0.21	43.96
2	91200000	91620000	420000	43	0	0.49	10.92
2	97050000	97610000	560000	55	0	0.48	14.3
2	109820000	110170000	350000	36	0	0.02	16.7
2	110510000	111100000	590000	44	0	0.04	20.05
2	111730000	112080000	350000	36	0	0.3	12.36
2	130870000	131180000	310000	32	0	0.11	13.62
4	68910000	69620000	710000	61	0	0.22	23.08
5	12840000	13240000	400000	41	0	0.07	18.21
5	68860000	71160000	2300000	231	0	0.13	95.4
5	176980000	177410000	430000	44	0	0.38	13.09
6	115340000	115680000	340000	35	0	0.03	16.14
6	157510000	157980000	470000	42	0	0.01	19.62
6	167750000	168030000	280000	26	0	0.03	11.95
7	62340000	62920000	580000	59	0	0.57	13.56
7	72040000	72340000	300000	31	0	0.15	12.77
7	73790000	74980000	1190000	94	0	0.18	37.11
7	75910000	76630000	720000	73	0	0.55	17.27
7	101910000	102220000	310000	32	0	0.31	10.89
8	6940000	8100000	1160000	106	0	0.2	40.74
8	11910000	12430000	520000	42	0	0.51	10.46
9	38760000	47100000	8340000	733	0	0.06	327.41
9	65230000	66550000	1320000	109	0	0.11	45.86
9	66680000	67880000	1200000	103	0	0.14	42.24
9	67940000	70210000	2270000	186	0	0.12	77.19
10	17830000	18250000	420000	37	0	0.05	16.69
10	45490000	46370000	880000	73	0	0.07	32.21
10	46570000	47910000	1340000	87	0	0.04	38.86
10	48280000	49050000	770000	62	0	0.03	28.42
10	50720000	51660000	940000	83	0	0.32	26.9

10	80920000	81660000	740000	73	0	0.08	31.87
10	88730000	89240000	510000	52	0	0.35	16.14
11	89120000	89460000	340000	35	0	0.1	15
14	18130000	18490000	360000	37	0	0.28	12.96
14	18550000	19270000	720000	73	0	0.24	26.96
15	18280000	19660000	1380000	139	0	0.48	33.64
15	20660000	21060000	400000	41	0	0.16	16.27
15	26210000	26890000	680000	58	0	0.12	24.32
15	28160000	28890000	730000	74	0	0.25	26.57
15	30230000	30710000	480000	49	0	0.1	20.87
15	80370000	81000000	630000	57	0	0.01	26.87
16	14690000	15390000	700000	71	0	0.44	19.71
16	16200000	16760000	560000	57	0	0.22	21.41
16	18080000	18690000	610000	62	0	0.18	24.43
16	31870000	32390000	520000	53	0	0.43	14.88
16	32570000	33260000	690000	70	0	0.2	27.14
17	18230000	18680000	450000	46	0	0.28	15.73
17	31510000	31880000	370000	27	0	0.02	12.5
17	33300000	33720000	420000	32	0	0.2	12.18
17	41650000	42130000	480000	49	0	0.12	20.37
21	13290000	14320000	1030000	104	0	0.57	22.63
22	14450000	15070000	620000	63	0	0.11	26.7
22	18690000	19050000	360000	31	0	0.09	13.37
22	19790000	20230000	440000	45	0	0.12	18.78
X	3700000	3950000	250000	26	0	0	12.28
X	52120000	52580000	460000	41	0	0.04	18.76
X	71890000	72110000	220000	23	0	0.09	10.02
X	76150000	76450000	300000	31	0	0.1	13.33
X	76610000	77330000	720000	73	0	0.14	30.29
X	88340000	90160000	1820000	183	0	0.45	50.32
X	90630000	92250000	1620000	163	0	0.46	44.29
X	101330000	101620000	290000	30	0	0.14	12.38
2	131650000	132700000	1050000	106	1	0.93	13.67
2	165130000	172640000	7510000	752	1	1.37	15.29
2	179470000	204120000	24650000	2466	1	1.31	85.45
2	208790000	215880000	7090000	710	1	1.29	29.55
4	70000	37050000	36980000	3653	1	1.03	306.58
4	42380000	48770000	6390000	640	1	1.27	27.91
5	49460000	53540000	4080000	409	1	1.25	19.3
5	61540000	65520000	3980000	399	1	1.3	14.92
5	74030000	110950000	36920000	3684	1	1.31	127.59

5	113180000	131310000	18130000	1814	1	1.37	39.12
5	138130000	138970000	840000	84	1	0.65	12.98
5	160420000	166880000	6460000	647	1	1.3	24.55
6	57800000	58870000	1070000	102	1	1.08	10.26
9	27870000	32290000	4420000	443	1	1.18	28.97
9	70230000	85930000	15700000	1571	1	0.88	178.63
9	101710000	107620000	5910000	592	1	1.29	23.13
10	51680000	61000000	9320000	933	1	1.25	45.36
10	64350000	70140000	5790000	580	1	1.28	23.47
11	48370000	51410000	3040000	284	1	1.27	14.44
12	7150000	11460000	4310000	432	1	1.17	26.9
12	15060000	34740000	19680000	1969	1	1.37	41.23
12	36160000	45740000	9580000	959	1	1.36	22.83
12	57300000	63190000	5890000	590	1	1.29	23.33
12	68390000	90770000	22380000	2213	1	1.3	86.94
13	34270000	39230000	4960000	497	1	1.37	11.03
13	52960000	72660000	19700000	1971	1	1.19	123.34
15	21140000	22830000	1690000	170	1	1.19	10.26
15	31950000	35910000	3960000	397	1	1.31	13.7
15	40820000	45360000	4540000	455	1	1.34	11.53
15	51570000	55340000	3770000	378	1	1.31	13.27
16	28950000	29720000	770000	78	1	0.66	14.67
17	15360000	16740000	1380000	139	1	1.07	11.99
17	18700000	20780000	2080000	209	1	1.09	17.17
17	47680000	50580000	2900000	291	1	1.29	11.4
17	54110000	58780000	4670000	468	1	1.27	18.96
18	14110000	15400000	1290000	130	1	0.78	20.85
18	60030000	69460000	9430000	944	1	1.25	46.52
19	19650000	24420000	4770000	478	1	1.32	13.15
1	35670000	43240000	7570000	758	3	3.68	184.64
1	93520000	95910000	2390000	240	3	4.23	83.26
1	115940000	118050000	2110000	212	3	3.51	44.27
1	119540000	120330000	790000	80	3	3.1	10.48
1	143640000	143820000	180000	19	3	10.72	32.09
1	144100000	144450000	350000	36	3	5.25	19.65
1	144950000	145860000	910000	92	3	4.98	45
1	147200000	147510000	310000	26	3	4.8	11.89
1	148120000	159780000	11660000	1167	3	5.34	658.26
1	159920000	194970000	35050000	3506	3	4.74	1542.58
1	195100000	197900000	2800000	281	3	4.33	99.55
1	198030000	204180000	6150000	616	3	5.74	396.76

1	204660000	222140000	17480000	1743	3	3.99	520.98
1	222300000	241100000	18800000	1875	3	3.96	549.97
1	241450000	246650000	5200000	521	3	3.71	126.45
2	0	18620000	18620000	1839	3	3.52	384.49
2	19190000	65150000	45960000	4594	3	3.24	699.64
2	91130000	91180000	50000	6	3	16.13	17.25
2	91640000	91680000	40000	5	3	12.96	12.09
2	132720000	133130000	410000	42	3	3.61	11.41
4	52380000	58060000	5680000	569	3	2.67	24.26
4	75870000	79840000	3970000	398	3	2.73	21.02
4	82330000	85830000	3500000	351	3	2.62	11.18
4	104620000	119550000	14930000	1494	3	3.48	285.1
4	119820000	120300000	480000	49	3	3.77	12.25
4	133140000	135310000	2170000	218	3	3.85	55.91
4	135910000	156890000	20980000	2099	3	6.28	1546.73
4	188420000	190910000	2490000	250	3	3.82	67.61
5	910000	12000000	11090000	1110	3	2.94	109.15
5	13260000	17560000	4300000	431	3	2.84	34.93
5	31080000	34090000	3010000	302	3	2.77	19.54
5	34450000	36830000	2380000	239	3	2.77	14.89
5	37750000	43660000	5910000	592	3	2.59	14.07
6	100000	9080000	8980000	899	3	3.55	195.82
6	9370000	26770000	17400000	1741	3	3.25	269.43
6	27090000	32050000	4960000	497	3	3.3	82.74
6	32750000	44880000	12130000	1214	3	3.04	146.5
6	45450000	48010000	2560000	257	3	2.88	21.27
6	50780000	54070000	3290000	330	3	2.75	19.37
6	56280000	57780000	1500000	151	3	3.03	18.14
6	88450000	92060000	3610000	362	3	2.69	16.79
6	105640000	112860000	7220000	723	3	2.72	37.65
6	129850000	140010000	10160000	1017	3	2.63	32.38
7	140000	320000	180000	19	3	5.51	11.36
7	640000	5910000	5270000	528	3	4.65	228.1
7	6000000	6740000	740000	75	3	4.51	30.44
7	6900000	35050000	28150000	2816	3	4.05	861.65
7	35250000	56760000	21510000	2142	3	3.88	593.25
7	62940000	64110000	1170000	118	3	2.95	11.14
7	64840000	66080000	1240000	125	3	2.98	12.92
7	66440000	71610000	5170000	518	3	3.38	97.01
7	72360000	73770000	1410000	142	3	3.39	26.85
7	97690000	101890000	4200000	421	3	2.76	28.01

7	104050000	108300000	4250000	426	3	2.7	20.88
7	126360000	127880000	1520000	153	3	2.98	16.21
7	128100000	142920000	14820000	1479	3	2.8	103.78
7	147200000	149210000	2010000	202	3	2.85	16.65
7	149640000	153020000	3380000	339	3	2.84	26.52
7	153500000	158610000	5110000	493	3	2.95	50.34
8	139620000	145350000	5730000	563	3	2.58	18.27
9	200000	8880000	8680000	869	3	2.67	36.97
9	13350000	15370000	2020000	203	3	2.73	10.38
9	16000000	20580000	4580000	459	3	2.64	16.29
9	139020000	140130000	1110000	112	3	3.44	21.78
10	70000	17810000	17740000	1769	3	4.04	548.78
10	18270000	38600000	20330000	2034	3	3.71	495.58
10	41690000	41860000	170000	18	3	19.57	66.92
11	68610000	69390000	780000	78	3	4.17	26.72
13	93560000	102880000	9320000	933	3	2.74	53.31
14	93240000	100440000	7200000	721	3	2.51	13.94
16	16780000	16890000	110000	12	3	27.78	58.98
16	52490000	57340000	4850000	486	3	3.06	60.77
16	63290000	68520000	5230000	524	3	2.9	49.13
16	68850000	74300000	5450000	546	3	3.13	75.95
16	75590000	86670000	11080000	1109	3	3.09	146.69
16	86880000	88670000	1790000	177	3	2.93	17.2
19	5850000	6110000	260000	27	3	4.5	10.99
19	16520000	17790000	1270000	128	3	3.26	21.2
20	20000	25680000	25660000	2567	3	2.86	209.94
20	29280000	62380000	33100000	3293	3	3.05	403.24
21	9730000	10200000	470000	48	3	4.13	20.93
21	26250000	27010000	760000	77	3	3.43	16.47
X	5790000	20560000	14770000	1478	3	2.77	91.73
X	21580000	25190000	3610000	362	3	2.63	11.75
X	37340000	47490000	10150000	1016	3	2.68	44.52
X	67770000	69640000	1870000	188	3	2.83	14.31
X	128490000	134060000	5570000	558	3	2.65	20.74
X	134810000	139890000	5080000	509	3	2.58	11.46
X	148870000	150910000	2040000	205	3	2.85	16.53

Supplementary Table 7. Summary of regions with significant copy number alterations in xenograft.

Chromosome	Start position	End position	Size	Number of markers	HMM state	Copy Number	LLR score
1	0	790000	790000	62	0	0.17	19.27
1	12770000	13640000	870000	70	0	0.12	22.97
1	142210000	142700000	490000	38	0	0.11	12.66
1	144470000	144870000	400000	35	0	0.23	10.12
1	145880000	146160000	280000	29	0	0.05	10.29
1	146310000	147180000	870000	70	0	0.41	15.4
2	86920000	88060000	1140000	115	0	0.24	32.76
2	109830000	110170000	340000	35	0	0.02	12.8
2	110520000	111100000	580000	43	0	0.04	15.36
2	130870000	131180000	310000	32	0	0.12	10.56
4	68910000	69620000	710000	61	0	0.21	18.09
5	12840000	13240000	400000	41	0	0.07	14.2
5	68880000	70770000	1890000	190	0	0.04	68.13
5	138140000	138660000	520000	53	0	0.03	19.2
6	115340000	115680000	340000	35	0	0.03	12.73
6	157660000	157980000	320000	33	0	0.01	12.16
7	73790000	74980000	1190000	94	0	0.24	26.79
8	6940000	8100000	1160000	106	0	0.21	31.39
9	38760000	47100000	8340000	733	0	0.06	257.27
9	65230000	66550000	1320000	109	0	0.1	36.51
9	66680000	67880000	1200000	103	0	0.15	32.66
9	67940000	70210000	2270000	186	0	0.13	60.47
10	17830000	18250000	420000	37	0	0.05	13.08
10	45510000	46370000	860000	71	0	0.06	24.85
10	46570000	47910000	1340000	87	0	0.01	32.04
10	48280000	49050000	770000	62	0	0.03	22.52
10	80920000	81660000	740000	73	0	0.08	25.22
14	18090000	19270000	1180000	119	0	0.42	25.87
15	18280000	19660000	1380000	139	0	0.44	29.04
15	26230000	26890000	660000	56	0	0.11	18.7
15	28160000	28850000	690000	70	0	0.21	20.56
15	80380000	81000000	620000	56	0	0.01	20.81
16	16210000	16750000	540000	55	0	0.24	15.7
16	18080000	18690000	610000	62	0	0.22	18.04
16	32570000	33260000	690000	70	0	0.22	20.3
17	18230000	18680000	450000	46	0	0.31	11.81
17	41650000	42130000	480000	49	0	0.15	15.48
22	14450000	15070000	620000	63	0	0.11	20.88
22	18690000	19050000	360000	31	0	0.11	10.35

22	19790000	20230000	440000	45	0	0.16	14.09
X	52120000	52580000	460000	41	0	0.04	14.7
X	76150000	76450000	300000	31	0	0.1	10.45
X	76610000	77330000	720000	73	0	0.16	22.93
X	88350000	90160000	1810000	182	0	0.39	41.25
X	91440000	92250000	810000	82	0	0.32	20.84
1	48350000	51380000	3030000	304	1	1.3	11.13
1	55830000	70880000	15050000	1506	1	1.36	40.03
1	102350000	106680000	4330000	422	1	1.35	11.59
2	89060000	89950000	890000	74	1	0.63	12.01
2	97040000	97620000	580000	57	1	0.52	10.48
2	131660000	132700000	1040000	105	1	0.94	10.89
2	165130000	216400000	51270000	5128	1	1.24	244.72
2	220730000	231130000	10400000	1041	1	1.36	28.07
3	50000	4300000	4250000	426	1	1.36	11.08
4	70000	37200000	37130000	3668	1	0.89	418.91
4	42100000	48770000	6670000	668	1	1.1	49.37
4	177890000	179800000	1910000	192	1	1.21	10.31
5	49460000	68860000	19400000	1941	1	1.28	80.15
5	70790000	131310000	60520000	6044	1	1.2	337.1
5	142610000	148300000	5690000	570	1	1.24	27.35
5	151260000	153420000	2160000	217	1	1.23	10.99
5	154500000	159160000	4660000	465	1	1.38	10.82
5	159930000	167260000	7330000	734	1	1.13	50.9
6	144260000	148520000	4260000	427	1	1.26	19.13
6	151990000	157580000	5590000	560	1	1.34	16.93
7	75910000	76640000	730000	74	1	0.55	13.15
9	27530000	32300000	4770000	478	1	1.1	35.83
9	70230000	87820000	17590000	1760	1	0.75	245.63
9	101220000	108820000	7600000	761	1	1.19	43.9
9	116890000	121730000	4840000	485	1	1.27	21.08
10	51140000	69180000	18040000	1805	1	1.12	128.72
10	82470000	87650000	5180000	519	1	1.23	26.43
10	88730000	96970000	8240000	825	1	1.28	33.39
10	106600000	111580000	4980000	499	1	1.16	31.85
11	48220000	51410000	3190000	299	1	1.22	15.52
11	88140000	90780000	2640000	265	1	1.11	19.42
12	7240000	11520000	4280000	429	1	1.12	30.19
12	13430000	34230000	20800000	2081	1	1.24	100.12
12	36160000	46210000	10050000	1006	1	1.18	59.57
12	56630000	102520000	45890000	4564	1	1.2	253.15

13	17930000	19050000	1120000	113	1	0.87	13.3
13	30710000	43590000	12880000	1289	1	1.31	45.51
13	45420000	72670000	27250000	2726	1	1.14	183.08
15	19790000	26210000	6420000	608	1	1.18	36.16
15	29680000	37500000	7820000	783	1	1.23	38.77
15	43890000	48250000	4360000	437	1	1.25	20.24
15	50410000	55340000	4930000	494	1	1.26	21.93
15	91850000	96340000	4490000	450	1	1.3	17.07
16	14700000	15390000	690000	70	1	0.6	11.82
16	31850000	32410000	560000	57	1	0.53	10.35
17	11490000	15730000	4240000	425	1	1.37	10.07
17	46880000	51930000	5050000	506	1	1.2	28.21
17	63430000	67440000	4010000	392	1	1.26	17.84
18	930000	8320000	7390000	740	1	1.36	18.77
18	13950000	15400000	1450000	146	1	0.9	16.48
18	46780000	52820000	6040000	599	1	1.22	30.81
18	55760000	69640000	13880000	1389	1	1.17	85.62
21	13290000	14320000	1030000	104	1	0.55	18.46
X	90180000	91420000	1240000	125	1	0.78	16.87
1	35670000	43460000	7790000	780	3	4.47	287.12
1	93520000	95910000	2390000	240	3	4.39	84.52
1	109520000	110970000	1450000	146	3	3.1	16.39
1	115940000	118020000	2080000	209	3	3.76	49.36
1	143640000	143820000	180000	19	3	11.76	32.88
1	144100000	144450000	350000	36	3	7.14	31.18
1	144950000	145860000	910000	92	3	5.44	50.56
1	147200000	147510000	310000	26	3	5.13	12.79
1	148090000	159780000	11690000	1170	3	6.92	966.68
1	159920000	197900000	37980000	3799	3	4.99	1768.85
1	198030000	204180000	6150000	616	3	7.79	608.51
1	204660000	222140000	17480000	1743	3	4.27	574.91
1	222300000	241160000	18860000	1881	3	4.64	751.5
1	241450000	246650000	5200000	521	3	4.38	183.1
2	0	13180000	13180000	1301	3	3.98	358.88
2	14570000	18620000	4050000	400	3	3.2	52.34
2	19210000	34570000	15360000	1534	3	3.78	365.71
2	36200000	40540000	4340000	435	3	3.24	59.99
2	41530000	56590000	15060000	1507	3	3.34	236.46
2	57730000	65740000	8010000	802	3	3.22	108.54
2	84890000	86410000	1520000	153	3	3.03	15.04
2	90980000	91180000	200000	21	3	8.71	24.38

2	91640000	91680000	40000	5	3	14.72	11.41
2	96110000	97020000	910000	92	3	3.25	12.97
2	120670000	122710000	2040000	205	3	3.12	23.57
2	127130000	129290000	2160000	217	3	2.84	13.86
2	132720000	132820000	100000	11	3	10.24	15.9
3	12430000	15130000	2700000	271	3	3.22	36.3
3	46480000	50700000	4220000	423	3	3.22	57.1
3	51340000	53890000	2550000	256	3	3.17	31.85
3	72010000	74230000	2220000	223	3	2.75	10.44
3	127200000	130870000	3670000	368	3	3.13	43.21
3	184180000	188220000	4040000	405	3	2.76	19.57
3	194900000	199260000	4360000	430	3	2.82	25.47
4	52380000	58070000	5690000	570	3	2.95	47.86
4	76610000	80100000	3490000	350	3	2.98	31.31
4	82440000	86260000	3820000	383	3	2.83	23.92
4	87940000	90470000	2530000	254	3	2.88	18.2
4	103370000	119550000	16180000	1619	3	3.33	251.41
4	119820000	120370000	550000	56	3	3.59	11.4
4	128860000	130010000	1150000	116	3	3.04	11.6
4	133150000	135310000	2160000	217	3	4.04	62.44
4	135910000	155220000	19310000	1932	3	6.93	1597.92
4	184470000	187320000	2850000	286	3	2.7	10.8
4	188420000	190910000	2490000	250	3	4.54	95.26
5	80000	11630000	11550000	1156	3	3.31	174.21
5	13260000	17560000	4300000	431	3	3.01	40.77
5	31110000	34090000	2980000	299	3	3.04	30.07
5	34460000	38960000	4500000	451	3	2.75	21.45
6	100000	9080000	8980000	899	3	3.96	245.16
6	9370000	26770000	17400000	1741	3	3.41	294.98
6	27090000	32550000	5460000	547	3	4.04	157.45
6	32750000	44890000	12140000	1215	3	3.9	318.87
6	45450000	47920000	2470000	248	3	2.83	15.49
6	51940000	53980000	2040000	205	3	3.04	20.67
6	56280000	57750000	1470000	148	3	3.16	18.24
6	87820000	91260000	3440000	345	3	2.78	17.78
6	105640000	112800000	7160000	717	3	2.92	55.78
6	136540000	140010000	3470000	348	3	2.78	18.23
7	140000	320000	180000	19	3	7.94	19.3
7	640000	6740000	6100000	611	3	6.96	508.95
7	6900000	35050000	28150000	2816	3	4.1	840.42
7	35250000	56760000	21510000	2142	3	4.11	644.07

7	57210000	57560000	350000	36	3	4.29	12.02
7	64840000	71620000	6780000	679	3	3.39	113
7	72360000	73770000	1410000	142	3	4.87	62.92
7	75000000	75890000	890000	90	3	3.59	18.26
7	97480000	101890000	4410000	442	3	4.04	127.53
7	104180000	108090000	3910000	392	3	2.97	34.28
7	126960000	135400000	8440000	845	3	2.93	67.37
7	136920000	142920000	6000000	597	3	3.18	75.71
7	147200000	149210000	2010000	202	3	3.54	39.09
7	149640000	153020000	3380000	339	3	3.53	65.04
7	153500000	158610000	5110000	493	3	3.8	119.71
8	390000	2260000	1870000	188	3	2.98	16.88
8	8120000	11880000	3760000	377	3	2.67	11.81
8	20010000	23480000	3470000	345	3	2.95	28.86
8	27140000	28710000	1570000	158	3	3.05	16.35
8	40800000	43210000	2410000	242	3	2.77	12.25
8	133940000	134930000	990000	100	3	3.1	11.28
8	139650000	145350000	5700000	560	3	3.6	115.51
9	200000	7780000	7580000	759	3	2.84	48.75
9	12990000	19670000	6680000	669	3	2.74	30.2
9	138340000	140130000	1790000	180	3	4.9	80.77
10	70000	17810000	17740000	1769	3	4.76	747.95
10	18270000	38600000	20330000	2034	3	4.21	648.38
10	41690000	43390000	1700000	165	3	8.27	177.95
11	190000	3210000	3020000	301	3	3.64	64.38
11	43850000	48200000	4350000	436	3	2.99	40.12
11	60220000	62550000	2330000	234	3	3.41	39.67
11	63020000	67220000	4200000	421	3	3.55	82.72
11	67530000	69390000	1860000	186	3	3.35	29.49
11	69500000	70970000	1470000	148	3	3.51	27.98
11	71310000	73420000	2110000	212	3	2.9	15.75
11	74520000	76600000	2080000	209	3	2.97	18.48
11	115410000	120360000	4950000	496	3	3.01	47.28
11	124430000	126370000	1940000	195	3	2.88	13.87
13	93750000	102700000	8950000	896	3	2.92	71.11
14	21920000	23200000	1280000	129	3	2.99	11.71
14	68010000	69720000	1710000	172	3	3.01	16.44
14	71950000	77780000	5830000	584	3	2.91	44.3
14	88500000	96290000	7790000	780	3	2.82	46.95
14	98330000	105080000	6750000	676	3	3.39	112.03
16	0	5910000	5910000	592	3	3.67	129.26

16	8450000	14680000	6230000	621	3	2.87	43.08
16	15410000	16190000	780000	79	3	3.29	11.64
16	22540000	25210000	2670000	268	3	2.87	18.37
16	26850000	28240000	1390000	140	3	3.32	21.42
16	30260000	31460000	1200000	121	3	3.45	21.51
16	33780000	33930000	150000	16	3	6.64	12.37
16	47920000	49590000	1670000	168	3	2.99	15.42
16	54790000	57340000	2550000	256	3	3.07	27.34
16	64590000	68530000	3940000	395	3	3.02	38.42
16	68850000	70720000	1870000	188	3	4.05	54.3
16	79480000	80530000	1050000	106	3	3.15	12.95
16	82260000	88670000	6410000	639	3	3.49	118
17	43110000	43410000	300000	31	3	4.52	11.72
18	41320000	44830000	3510000	352	3	2.77	17.93
19	220000	19640000	19420000	1940	3	3.06	201.94
20	20000	6230000	6210000	622	3	3.64	131.92
20	8590000	14010000	5420000	543	3	2.65	15.5
20	15320000	25680000	10360000	1037	3	3.21	136.68
20	29280000	52770000	23490000	2347	3	3.76	552.37
20	53960000	62380000	8420000	828	3	4.32	281.56
21	9730000	10200000	470000	48	3	4.26	15.75
21	26250000	27020000	770000	78	3	3.41	13.21
21	31390000	35160000	3770000	378	3	2.66	11.49
21	36260000	40300000	4040000	405	3	2.63	10.06
X	110000	3680000	3570000	321	3	3.14	38.45
X	6530000	14070000	7540000	755	3	2.82	45.32
X	15120000	20410000	5290000	530	3	2.99	48.65
X	21580000	25210000	3630000	364	3	2.84	23.22
X	37850000	41930000	4080000	409	3	3.25	57.55
X	43180000	48030000	4850000	486	3	2.82	28.94
X	48180000	49050000	870000	88	3	4.02	24.99
X	53030000	54600000	1570000	158	3	3.27	22.72
X	67150000	70810000	3660000	367	3	3.02	35.72
X	70950000	71870000	920000	93	3	3.09	10.24
X	128450000	134060000	5610000	562	3	2.77	28.18
X	134810000	136510000	1700000	171	3	2.86	11.62
X	149000000	150910000	1910000	192	3	3	17.8
X	151710000	153060000	1350000	136	3	3.91	35.88

Supplementary Table 8. Genes found in focal regions (≤ 2 Mbp) with copy number variations in primary tumor.

Chromosome	Start (bp)	End (bp)	Size (bp)	Number of markers	HMM status	Copy number	LLR score	Gene
1	0	790000	790000	62	0	0.21	40.36	
1	1250000	1660000	410000	42	0	0.63	14.96	VWA1,CDC2L1,SSU72,MMP23B,CCNL2,CDC2L2,SLC35E2,MGC10334,DVL1,MRPL20
1	12760000	13650000	890000	72	0	0.16	47.57	PRAMEF9,PRAMEF4,PRAMEF6,HNRPCL1
1	83370000	83720000	350000	36	0	0.47	17.58	
1	103570000	104090000	520000	41	0	0.48	20.4	
1	108560000	108830000	270000	28	0	0.48	13.6	CLCC1
1	115710000	115920000	210000	22	0	0.25	13.62	
1	115940000	117680000	1740000	175	3	3.37	31.72	VANGL1,TTF2,NHLH2,CD2,IGSF3,IGSF2,CASQ2,VTCN1,ATP1A1
1	120340000	120730000	390000	34	0	0.36	19.3	NOTCH2
1	141600000	142710000	1110000	82	0	0.35	44.7	
1	142730000	143220000	490000	32	0	0.16	21.88	
1	143270000	143620000	350000	19	0	0.27	11.71	PDE4DIP
1	143640000	143820000	180000	19	3	9.78	33.48	PDE4DIP,SEC22B
1	144100000	144450000	350000	36	3	4.5	14.87	ANKRD34,ANKRD35,CD160,RBM8A,ITGA10,HFE2
1	144470000	144870000	400000	35	0	0.16	23.88	
1	144950000	145860000	910000	92	3	4.39	34.59	CHD1L,PRKAB2,FMO5,ACP6,GJA5,BCL9,GJA8
1	145880000	146160000	280000	29	0	0.04	21.59	GPR89B
1	146310000	147220000	910000	74	0	0.39	41.89	
1	147520000	148100000	580000	53	0	0.51	26.71	HIST2H2AA4,HIST2H4A,HIST2H4B,HIST2H3C,HIST2H2AA3,HIST2H3A
1	204660000	205750000	1090000	110	3	3.97	33.89	DYRK3,IKBKE,C1orf116,CD55,C4BPB,IL24,LGTN,PFKFB2,C4BPA,CR2,IL10,RASSF5,IL19,MAPKAPK2,IL20,CR1
1	220770000	221780000	1010000	102	3	3.66	23.85	C1orf80,C1orf58,DISP1,TAF1A,TLR5,SUSD4
1	241120000	241430000	310000	32	0	0.85	10	CEP170
2	86920000	88070000	1150000	116	0	0.2	74.87	PLGLB2,CD8B,C2orf59,PLGLB1
2	89060000	89370000	310000	32	0	0.44	15.96	
2	89590000	89950000	360000	37	0	0.57	15.89	
2	91130000	91180000	50000	6	3	14.35	19.09	
2	91200000	91620000	420000	43	0	0.45	20.67	
2	91640000	91680000	40000	5	3	14.31	18.48	
2	95440000	96080000	640000	65	0	0.84	17.19	FAHD2A
2	97040000	97610000	570000	56	0	0.47	26.85	
2	109820000	110170000	350000	36	0	0.02	27.05	RGPD5
2	110520000	111100000	580000	43	0	0.04	31.9	
2	111730000	112080000	350000	36	0	0.27	21.73	
2	113860000	114130000	270000	28	0	0.36	15.41	FOXD4L1,RABL2A
2	130870000	131180000	310000	32	0	0.09	22.63	CFC1

2	132240000	132680000	440000	45	0	0.58	18.25	C2orf27
2	132700000	133200000	500000	51	3	3.77	20.17	LYPD1,GPR39
2	242170000	242350000	180000	19	0	0.04	14.1	ATG4B,ING5
3	46320000	46460000	140000	15	0	0.09	10.61	LTF,CCR5,CCRL2
3	68010000	68140000	130000	14	0	0.05	10.28	FAM19A1
3	76320000	76480000	160000	17	0	0.08	12.25	
3	121760000	121900000	140000	15	0	0.09	10.69	NDUFB4,RABL3
4	8960000	9360000	400000	41	0	0.51	12.64	DEFB131
4	48790000	48860000	70000	8	3	9.45	16.49	
4	68910000	69620000	710000	61	0	0.21	39.44	UGT2B15,TMPRSS11E
4	132800000	133120000	320000	33	0	0.78	10.75	
5	12840000	13250000	410000	42	0	0.11	29.72	
5	20730000	20970000	240000	25	0	0.62	10.61	
5	34110000	34430000	320000	33	0	0.54	15.35	
5	37750000	38960000	1210000	122	3	2.89	10.22	EGFLAM,OSMR,GDNF,LIFR
5	175260000	175480000	220000	23	0	0.29	13.15	THOC3
5	176980000	177410000	430000	44	0	0.41	22.2	
5	180190000	180330000	140000	15	0	0.09	10.64	
6	9100000	9350000	250000	20	0	0.03	14.91	
6	26790000	27070000	280000	29	0	0.6	12.27	
6	45510000	47500000	1990000	200	3	2.67	12.47	RUNX2,CLIC5,CYP39A1,MEP1A,ENPP4,TNFRSF21,GPR110,ENPP5,GPR116
6	57310000	57780000	470000	48	3	3.9	21.25	
6	57800000	58820000	1020000	97	0	0.89	22.68	GUSBL2
6	58840000	58880000	40000	5	3	48.64	86.94	
6	115340000	115680000	340000	35	0	0.03	26.21	
6	157510000	157980000	470000	42	0	0.01	31.71	ARID1B
6	167690000	168030000	340000	32	0	0.21	19.66	MLLT4,TTLL2
7	6000000	6740000	740000	75	3	3.49	19.56	PSCD3,RAC1,MGC12966,ITV1,PMS2,ZNF12,EIF2AK1,KDELR2
7	33060000	35040000	1980000	199	3	3.08	28.2	RP9,NT5C3,NPSR1,BBS9,BMPER
7	44060000	45720000	1660000	167	3	3.44	41.54	DBNL,RAMP3,GCK,PURB,YKT6,MYO1G,MYL7,NPC1L1,AEBP1,OGDH,DDX56,CCM2,ADCY1,ZMIZ2,TBRG4,H2AFV,PGAM2,CAMK2B
7	56780000	57190000	410000	36	0	0.37	19.45	
7	61110000	61240000	130000	14	0	0.07	10.1	
7	61260000	62310000	1050000	94	3	2.87	10.97	
7	62330000	62730000	400000	41	0	0.34	23.09	
7	64600000	64880000	280000	29	0	0.65	10.96	
7	72050000	72350000	300000	31	0	0.12	21.3	NSUN5C,LOC442578,POM121
7	72370000	73770000	1400000	141	3	2.72	14.46	GTF2I,STX1A,RFC2,GTF2IRD1,FZD9,EIF4H,WBSCR27,WBSCR22,WBSCR18,MLXIPL,LIMK1,CLDN3,BCL7B,CL

								DN4,ABHD11,WBSCR28,CLIP2,TBL2,BAZ1B,LAT2
7	73790000	74980000	1190000	94	0	0.14	63.32	GTF2I,DKFZP434A0131,PMS2L5,PMS2L3,NSUN5B,GTF2IRD2,GTF2IRD2B,WBSCR16
7	75910000	76640000	730000	74	0	0.45	35.83	UPK3B,POMZP3,KIAA1505,DTX2
7	97700000	99640000	1940000	195	3	2.49	12.22	GAL3ST4,ZNF789,COPS6,C7orf38,ZKSCAN1,PTCD1,AP4M1,LOC389541,CPSF4,LOC255374,TAF6,AZGP1,STAG3,ATP5J2,ARPC1B,MCM7,ZSCAN21,ARPC1A,BRI3,SMURF1,PDAP1
7	101910000	102220000	310000	32	0	0.24	19.42	RASA4,POLR2J2
7	126490000	127880000	1390000	140	3	2.67	11.97	ARF5,NAG8,IMPDH1,PAX4,GCC1,GRM8,LRRC4,LEP,SND1,ZNF800
7	142940000	143190000	250000	26	0	0.24	16.19	
7	143510000	143690000	180000	19	0	0.12	13.07	ARHGEF5
7	147310000	149210000	1900000	191	3	2.51	10.24	EZH2,CUL1,ZNF212,ZNF398,PDIA4,CNTNAP2
7	149230000	149620000	390000	40	0	0.65	14.46	
7	149640000	151340000	1700000	171	3	2.63	14.07	TMEM176B,CDK5,ABCB8,NUB1,GIMAP7,GIMAP1,GIMAP2,RARRES2,ATG9B,TMEM176A,SMARCD3,GIMAP6,GIMAP4,CRYGN,ABCF2,GIMAP8,FASTK,GIMAP5,KCNH2,RHEB,NOS3,SLC4A2,C7orf29,ACCN3,ASB10,REPIN1,PRKAG2,ABP1
8	0	140000	140000	15	0	0.09	10.68	
8	6930000	8100000	1170000	107	0	0.18	69.46	DEFB103A,DEFB4,SPAG11B
8	11900000	12430000	530000	43	0	0.45	20.87	DUB3
9	0	180000	180000	19	0	0.24	11.96	CBWD1
9	65230000	66550000	1320000	109	0	0.13	74.25	
9	66680000	67880000	1200000	103	0	0.17	68.3	FAM27E3
9	139030000	140130000	1100000	111	3	3.1	12.88	FUT7,MRPL41,C9orf167,ARRDC1,GRIN1,ABCA2,ANAPC2,MGC14327,DPP7,ENTPD2,COBRA1,MAN1B1,LRRC26,PNPLA7,NELF,SLC34A3,TUBB2C,ZMYND19,ENTPD8,EHMT1
10	17830000	18250000	420000	37	0	0.05	27.4	MRC1,MRC1L1
10	41690000	41850000	160000	17	3	23.6	94.88	
10	45490000	46370000	880000	73	0	0.07	52.3	FAM21C
10	46580000	47910000	1330000	86	0	0.08	59.98	ANXA8
10	48280000	49050000	770000	62	0	0.04	45.88	FRMPD2,PTPN20B
10	50720000	51660000	940000	83	0	0.36	45.09	MSMB,LOC387680
10	80920000	81660000	740000	73	0	0.09	52.02	SFTPA1B
10	88730000	89240000	510000	52	0	0.4	26.98	FAM35A
11	48360000	50270000	1910000	192	1	1.22	21.96	OR4A47,FOLH1
11	88160000	89000000	840000	85	1	1.17	11.64	GRM5,TYR
11	89020000	89460000	440000	45	0	0.27	26.96	TRIM49
13	17930000	18340000	410000	42	0	0.39	20.82	

13	51670000	52060000	390000	40	0	0.75	11.03	CKAP2,THSD1,VPS36
14	18130000	18490000	360000	37	0	0.27	22.12	
14	18550000	19250000	700000	71	0	0.19	46.05	ACTBL1
15	18280000	19660000	1380000	139	0	0.58	53.96	LOC283755,POTE15
15	20660000	21180000	520000	47	0	0.15	31.53	GOLGA8E
15	26110000	26890000	780000	68	0	0.28	40.07	GOLGA8G,HERC2
15	28160000	28890000	730000	74	0	0.27	44.28	CHRFAM7A
15	30230000	30700000	470000	48	0	0.09	33.91	ARHGAP11A,CHRNA7
15	80270000	81000000	730000	67	0	0.19	43.6	RPS17
15	82530000	82900000	370000	31	0	0.56	13.04	
16	14690000	15390000	700000	71	0	0.4	36.41	RRN3,NOMO1,NPIP
16	16200000	16750000	550000	56	0	0.18	36.45	NOMO3,ABCC6
16	18080000	18690000	610000	62	0	0.16	41.05	NOMO2
16	21260000	21460000	200000	21	0	0.4	10.64	
16	21660000	21850000	190000	20	0	0.2	12.75	
16	22350000	22520000	170000	18	0	0.15	11.95	
16	28250000	28380000	130000	14	0	0.05	10.25	LOC440350
16	28530000	28720000	190000	20	0	0.14	13.42	EIF3S8,SULT1A1
16	28950000	29720000	770000	78	0	0.58	31.56	SPN,QPRT,C16orf54,KIF22
16	31850000	32390000	540000	55	0	0.41	27.86	
16	32570000	33260000	690000	70	0	0.18	46.09	TP53TG3
16	33540000	33760000	220000	23	0	0.33	12.88	
16	33780000	33930000	150000	16	3	5.86	17.35	
16	44960000	45000000	40000	5	3	14.59	19.64	
16	69280000	69750000	470000	48	3	6.04	42.57	VAC14,HYDIN
17	15370000	15730000	360000	37	0	0.62	14.26	TRIM16,MGC51025
17	16510000	16700000	190000	20	0	0.36	10.71	
17	18230000	18680000	450000	46	0	0.3	26.56	FLJ40244,LOC654346
17	18870000	19070000	200000	21	0	0.02	15.76	GRAP
17	20160000	20750000	590000	60	0	0.65	22.01	
17	31510000	31880000	370000	27	0	0.02	20.25	TBC1D3G
17	33290000	33720000	430000	33	0	0.24	20.14	MRPL45
17	36350000	36530000	180000	19	0	0.04	14.03	KRTAP2-4,KRTAP1-3,KRTAP1-1,KRT39,KRTAP3-1,KRTAP1-5,KRTAP3-2,KRTAP3-3
17	41650000	42130000	480000	49	0	0.13	33.35	NSF,ARL17P1
18	14110000	15400000	1290000	130	0	0.74	41.89	
19	30000	200000	170000	18	0	0.11	12.68	FLJ45445
19	47900000	48590000	690000	70	1	1.03	11.83	PSG9,PSG3,PSG2,PSG4,PSG7
20	20000	1490000	1470000	148	3	2.76	16.1	FKBP1A,RBCK1,TRIB3,SNPH,C20orf54,TCF15,RSPO4,CSNK2A1,SOX12,PSMF1,ANGPT4,NSFL1C,FAM110A,DEFB127,SDCBP2,DEFB129,DEFB126,T

								BC1D20
21	9730000	10200000	470000	48	3	4.88	42.5	TPTE
21	13290000	14320000	1030000	104	0	0.52	44.55	ANKRD21
21	26250000	27010000	760000	77	3	3.21	18.31	APP,CYYR1
22	14450000	15760000	1310000	116	0	0.46	56.77	ACTBL1,CESK1
22	17020000	17330000	310000	32	0	0.42	16.11	DGCR6,PRODH,USP18
22	18670000	19050000	380000	33	0	0.15	22.09	DGCR6L
22	19790000	20240000	450000	46	0	0.14	30.96	LOC375133,HIC2
X	3700000	3950000	250000	26	0	0	19.83	
X	52120000	52580000	460000	41	0	0.03	30.55	XAGE1D,XAGE2
X	67770000	68710000	940000	95	3	2.87	12.75	TMEM28,EFNB1,PJA1
X	71880000	72110000	230000	24	0	0.08	17.16	
X	76150000	76450000	300000	31	0	0.1	21.91	
X	76610000	77330000	720000	73	0	0.12	50.39	TAF9B,PGAM4,ATP7A,COX7B,ATRX
X	88340000	90160000	1820000	183	0	0.41	92.26	TGIF2LX
X	90630000	92250000	1620000	163	0	0.43	80.75	PCDH11X
X	101330000	101620000	290000	30	0	0.12	20.57	NXF2

Supplementary Table 9. Genes found in focal regions (≤ 2 Mbp) with copy number variations in brain metastasis.

Chromosome	Start (bp)	End (bp)	Size (bp)	Number of markers	HMM status	Copy number	LLR score	Gene
1	0	730000	730000	56	0	0.11	23.86	
1	12760000	13640000	880000	71	0	0.13	29.3	PRAMEF9,PRAMEF4,PRAMEF6,HNRPCL1
1	103550000	104090000	540000	43	0	0.48	11.47	
1	119540000	120330000	790000	80	3	3.1	10.48	HSD3B2,HAO2,NOTCH2,REG4,HMGCS2,ADAM30,HSD3B1
1	142210000	142710000	500000	39	0	0.14	16.14	
1	142750000	143220000	470000	30	0	0.12	12.77	
1	143640000	143820000	180000	19	3	10.72	32.09	PDE4DIP,SEC22B
1	144100000	144450000	350000	36	3	5.25	19.65	CD160,ANKRD34,ANKRD35,RBM8A,ITGA10,HFE2
1	144470000	144870000	400000	35	0	0.2	13.66	
1	144950000	145860000	910000	92	3	4.98	45	CHD1L,ACP6,PRKAB2,GJA5,FMO5,BCL9,GJA8
1	145880000	146160000	280000	29	0	0.05	13.17	GPR89B
1	146310000	147180000	870000	70	0	0.37	22.56	
1	147200000	147510000	310000	26	3	4.8	11.89	
1	147530000	148100000	570000	52	0	0.6	11.84	HIST2H2AA4,HIST2H4A,HIST2H4B,HIST2H3C,HIST2H3A,HIST2H2AA3
2	86920000	88060000	1140000	115	0	0.21	43.96	PLGLB1,CD8B,PLGLB2,C2orf59
2	91130000	91180000	50000	6	3	16.13	17.25	
2	91200000	91620000	420000	43	0	0.49	10.92	
2	91640000	91680000	40000	5	3	12.96	12.09	
2	97050000	97610000	560000	55	0	0.48	14.3	
2	109820000	110170000	350000	36	0	0.02	16.7	RGPD5
2	110510000	111100000	590000	44	0	0.04	20.05	
2	111730000	112080000	350000	36	0	0.3	12.36	
2	130870000	131180000	310000	32	0	0.11	13.62	CFC1
2	131650000	132700000	1050000	106	1	0.93	13.67	C2orf27,TUBA3D,POTE2
2	132720000	133130000	410000	42	3	3.61	11.41	GPR39,LYPD1
4	68910000	69620000	710000	61	0	0.22	23.08	TMPRSS11E,UGT2B15
4	119820000	120300000	480000	49	3	3.77	12.25	SEC24D
5	12840000	13240000	400000	41	0	0.07	18.21	
5	138130000	138970000	840000	84	1	0.65	12.98	PAIP2,SLC23A1,CTNNA1,MATR3,UBE2D2,SIL1
5	176980000	177410000	430000	44	0	0.38	13.09	
6	56280000	57780000	1500000	151	3	3.03	18.14	RAB23,ZNF451,BAG2
6	57800000	58870000	1070000	102	1	1.08	10.26	GUSBL2
6	115340000	115680000	340000	35	0	0.03	16.14	
6	157510000	157980000	470000	42	0	0.01	19.62	ARID1B
6	167750000	168030000	280000	26	0	0.03	11.95	MLLT4
7	140000	320000	180000	19	3	5.51	11.36	
7	6000000	6740000	740000	75	3	4.51	30.44	ZNF12,PSCD3,RAC1,MGC12966,EIF2AK1,KDELR2,JTV1,PMS2

7	62340000	62920000	580000	59	0	0.57	13.56	
7	62940000	64110000	1170000	118	3	2.95	11.14	ZNF588
7	64840000	66080000	1240000	125	3	2.98	12.92	ASL,RCP9,C7orf42,LOC285908,RABGEF1,GUSB,VKORC1L1
7	72040000	72340000	300000	31	0	0.15	12.77	LOC442578,NSUN5C,POM121
7	72360000	73770000	1410000	142	3	3.39	26.85	GTF2I,STX1A,RFC2,GTF2IRD1,FZD9,EIF4H,WBSCR27,WBSCR22,MLXIPL,WBSCR18,LIMK1,CLDN3,BCL7B,ABHD11,CLDN4,WBSCR28,NSUN5,CLIP2,TBL2,BAZ1B,LAT2
7	73790000	74980000	1190000	94	0	0.18	37.11	GTF2I,DKFZP434A0131,PMS2L5,PMS2L3,NSUN5B,GTF2IRD2,GTF2IRD2B,WBSCR16
7	75910000	76630000	720000	73	0	0.55	17.27	UPK3B,POMZP3,KIAA1505,DTX2
7	101910000	102220000	310000	32	0	0.31	10.89	RASA4,POLR2J2
7	126360000	127880000	1520000	153	3	2.98	16.21	ARF5,NAG8,IMPDH1,PAX4,GCC1,GRM8,LRRC4,LEP,SND1,ZNF800
8	6940000	8100000	1160000	106	0	0.2	40.74	DEFB103A,DEFB4,SPAG11B
8	11910000	12430000	520000	42	0	0.51	10.46	DUB3
9	65230000	66550000	1320000	109	0	0.11	45.86	
9	66680000	67880000	1200000	103	0	0.14	42.24	FAM27E3
9	139020000	140130000	1110000	112	3	3.44	21.78	FUT7,MRPL41,C9orf167,ARRDC1,GRIN1,ABCA2,ANAPC2,MGC14327,DPP7,ENTPD2,COBRA1,MAN1B1,LRRC26,PNPLA7,NELF,SLC34A3,TUBB2C,ZMYND19,ENTPD8,EHMT1
10	17830000	18250000	420000	37	0	0.05	16.69	MRC1,MRC1L1
10	41690000	41860000	170000	18	3	19.57	66.92	
10	45490000	46370000	880000	73	0	0.07	32.21	FAM21C
10	46570000	47910000	1340000	87	0	0.04	38.86	ANXA8
10	48280000	49050000	770000	62	0	0.03	28.42	FRMPD2,PTPN20B
10	50720000	51660000	940000	83	0	0.32	26.9	MSMB,LOC387680
10	80920000	81660000	740000	73	0	0.08	31.87	SFTPA1B
10	88730000	89240000	510000	52	0	0.35	16.14	FAM35A
11	68610000	69390000	780000	78	3	4.17	26.72	TPCN2,FGF4,CCND1,FGF19,MYEOV,FGF3,ORAOV1
11	89120000	89460000	340000	35	0	0.1	15	TRIM49
14	18130000	18490000	360000	37	0	0.28	12.96	
14	18550000	19270000	720000	73	0	0.24	26.96	ACTBL1
15	18280000	19660000	1380000	139	0	0.48	33.64	LOC283755,POTE15
15	20660000	21060000	400000	41	0	0.16	16.27	GOLGA8E
15	21140000	22830000	1690000	170	1	1.19	10.26	NDN,MKRN3,C15orf2
15	26210000	26890000	680000	58	0	0.12	24.32	GOLGA8G,HERC2
15	28160000	28890000	730000	74	0	0.25	26.57	CHRFAM7A
15	30230000	30710000	480000	49	0	0.1	20.87	ARHGAP11A,CHRNA7
15	80370000	81000000	630000	57	0	0.01	26.87	RPS17
16	14690000	15390000	700000	71	0	0.44	19.71	RRN3,NOMO1,NPIP

16	16200000	16760000	560000	57	0	0.22	21.41	NOMO3,ABCC6
16	16780000	16890000	110000	12	3	27.78	58.98	
16	18080000	18690000	610000	62	0	0.18	24.43	NOMO2
16	28950000	29720000	770000	78	1	0.66	14.67	SPN,QPRT,C16orf54,KIF22
16	31870000	32390000	520000	53	0	0.43	14.88	
16	32570000	33260000	690000	70	0	0.2	27.14	TP53TG3
16	86880000	88670000	1790000	177	3	2.93	17.2	DBNDD1,FANCA,CYBA,MGC16385,TUBB3,SPG7,GALNS,FLJ20186,SPIRE2,CPNE7,PRDM7,MC1R,RPL13,AFG3L1,APRT,CDK10,CBFA2T3,ANKRD11,ZFPM1,MVD,LOC348180,SNAI3,GAS8,CDH15,IL17C,ZNF276
17	15360000	16740000	1380000	139	1	1.07	11.99	PIGL,ZNF287,TRIM16,UBB,TRPV2,NCOR1,ADORA2B,PRR6,TTC19,MGC51025
17	18230000	18680000	450000	46	0	0.28	15.73	FLJ40244,LOC654346
17	31510000	31880000	370000	27	0	0.02	12.5	TBC1D3G
17	33300000	33720000	420000	32	0	0.2	12.18	MRPL45
17	41650000	42130000	480000	49	0	0.12	20.37	NSF,ARL17P1
18	14110000	15400000	1290000	130	1	0.78	20.85	
19	5850000	6110000	260000	27	3	4.5	10.99	CAPS,RFX2,NDUFA11,RANBP3,ACSBG2
19	16520000	17790000	1270000	128	3	3.26	21.2	B3GNT3,ABHD8,FAM129C,INSL3,MDS032,CRSP7,USHBP1,NR2F6,PGLS,NY-SAR-48,MAP1S,MYO9B,C19orf62,MRPL34,F2RL3,BST2
21	9730000	10200000	470000	48	3	4.13	20.93	TPTE
21	13290000	14320000	1030000	104	0	0.57	22.63	ANKRD21
21	26250000	27010000	760000	77	3	3.43	16.47	APP,CYYR1
22	14450000	15070000	620000	63	0	0.11	26.7	ACTBL1
22	18690000	19050000	360000	31	0	0.09	13.37	
22	19790000	20230000	440000	45	0	0.12	18.78	LOC375133,HIC2
X	3700000	3950000	250000	26	0	0	12.28	
X	52120000	52580000	460000	41	0	0.04	18.76	XAGE1D,XAGE2
X	67770000	69640000	1870000	188	3	2.83	14.31	DLG3,P2RY4,DGAT2L4,PDZD11,TMEM28,ARR3,EDA,IGBP1,KIF4A,EFNB1,PJA1
X	71890000	72110000	220000	23	0	0.09	10.02	
X	76150000	76450000	300000	31	0	0.1	13.33	
X	76610000	77330000	720000	73	0	0.14	30.29	TAF9B,PGAM4,ATP7A,COX7B,ATRX
X	88340000	90160000	1820000	183	0	0.45	50.32	TGIF2LX
X	90630000	92250000	1620000	163	0	0.46	44.29	PCDH11X
X	101330000	101620000	290000	30	0	0.14	12.38	NXF2

Supplementary Table 10. Genes found in focal regions (≤ 2 Mbp) with copy number variations in xenograft.

Chromosome	Start (bp)	End (bp)	Size (bp)	Number of markers	HMM status	Copy number	LLR score	Gene
1	0	790000	790000	62	0	0.17	19.27	
1	12770000	13640000	870000	70	0	0.12	22.97	PRAMEF9,PRAMEF4,PRAMEF6,HNRPCL1
1	109520000	110970000	1450000	146	3	3.1	16.39	EPS8L3,KCNA2,PROK1,KCNC4,GSTM3,PSMA5,AMIGO1,RBM15,GSTM4,AMPD2,CELSR2,GSTM5,KIAA1324,HBXIP,FAM40A,AHCYL1,CSF1,GSTM1,GPR61,GNAT2,SORT1,UBL4B,SARS,SLC6A17,ALX3,PSRC1,KCNA10,GSTM2
1	142210000	142700000	490000	38	0	0.11	12.66	
1	143640000	143820000	180000	19	3	11.76	32.88	PDE4DIP,SEC22B
1	144100000	144450000	350000	36	3	7.14	31.18	ANKRD34,ANKRD35,CD160,HFE2,RBM8A,ITGA10
1	144470000	144870000	400000	35	0	0.23	10.12	
1	144950000	145860000	910000	92	3	5.44	50.56	CHD1L,PRKAB2,FMO5,ACP6,GJA5,BCL9,GJA8
1	145880000	146160000	280000	29	0	0.05	10.29	GPR89B
1	146310000	147180000	870000	70	0	0.41	15.4	
1	147200000	147510000	310000	26	3	5.13	12.79	
2	84890000	86410000	1520000	153	3	3.03	15.04	VAMP5,TGOLN2,TMSB10,MRPL35,KCMF1,RNF181,IMMT,PTCD3,POLR1A,MAT2A,GNLY,SFTPB,VAMP8,USP39,CAPG
2	86920000	88060000	1140000	115	0	0.24	32.76	PLGLB2,CD8B,C2orf59,PLGLB1
2	89060000	89950000	890000	74	1	0.63	12.01	
2	90980000	91180000	200000	21	3	8.71	24.38	
2	91640000	91680000	40000	5	3	14.72	11.41	
2	96110000	97020000	910000	92	3	3.25	12.97	ANKRD39,CNNM3,CIAO1,ASTL,CNNM4,ARID5A,NCAPH,ANKRD23,ASCC3L1,SEMA4C,DUSP2,KIAA1754L,STARD7
2	97040000	97620000	580000	57	1	0.52	10.48	
2	109830000	110170000	340000	35	0	0.02	12.8	RGPD5
2	110520000	111100000	580000	43	0	0.04	15.36	
2	130870000	131180000	310000	32	0	0.12	10.56	CFC1
2	131660000	132700000	1040000	105	1	0.94	10.89	POTE2,C2orf27,TUBA3D
2	132720000	132820000	100000	11	3	10.24	15.9	
4	68910000	69620000	710000	61	0	0.21	18.09	UGT2B15,TMPRSS11E
4	119820000	120370000	550000	56	3	3.59	11.4	SEC24D
4	128860000	130010000	1150000	116	3	3.04	11.6	PHF17,PLK4,LARP2
4	177890000	179800000	1910000	192	1	1.21	10.31	AGA,VEGFC,NEIL3
5	12840000	13240000	400000	41	0	0.07	14.2	
5	68880000	70770000	1890000	190	0	0.04	68.13	SMN1,SMN2,NAIP,OCLN,SERF1A,GTF2H2
5	138140000	138660000	520000	53	0	0.03	19.2	CTNNA1,SIL1,MATR3
6	56280000	57750000	1470000	148	3	3.16	18.24	RAB23,BAG2,ZNF451

6	115340000	115680000	340000	35	0	0.03	12.73	
6	157660000	157980000	320000	33	0	0.01	12.16	
7	140000	320000	180000	19	3	7.94	19.3	
7	57210000	57560000	350000	36	3	4.29	12.02	
7	72360000	73770000	1410000	142	3	4.87	62.92	GTF2I,STX1A,RFC2,GTF2IRD1,FZD9,EIF4H,WBSCR27,WBSCR22,WBSCR18,MLXIPL,LIMK1,CLDN3,BCL7B,CLDN4,ABHD11,WBSCR28,NSUN5,CLIP2,TBL2,BAZ1B,LAT2
7	73790000	74980000	1190000	94	0	0.24	26.79	GTF2I,DKFZP434A0131,PMS2L5,PMS2L3,NSUN5B,GTF2IRD2,GTF2IRD2B,WBSCR16
7	75000000	75890000	890000	90	3	3.59	18.26	STYXL1,HIP1,ZP3,CCL24,YWHAG,CCL26,MDH2
7	75910000	76640000	730000	74	1	0.55	13.15	UPK3B,POMZP3,KIAA1505,DTX2
8	390000	2260000	1870000	188	3	2.98	16.88	ARHGEF10,DLGAP2,FBXO25,MYOM2
8	6940000	8100000	1160000	106	0	0.21	31.39	DEFB103A,DEFB4,SPAG11B
8	27140000	28710000	1570000	158	3	3.05	16.35	EPHX2,CHRNA2,ESCO2,PBK,TRIM35,SCARA3,FZD3,PNOC,CLU,ZNF395,FBXO16,PTK2B
8	133940000	134930000	990000	100	3	3.1	11.28	TG,ST3GAL1,SLA,NDRG1,WISP1
9	65230000	66550000	1320000	109	0	0.1	36.51	
9	66680000	67880000	1200000	103	0	0.15	32.66	FAM27E3
9	138340000	140130000	1790000	180	3	4.9	80.77	MAMDC4,LCN12,LCN6,TRAF2,C9orf167,GRIN1,ABCA2,MGC14327,DPP7,ENTPD2,AGPAT2,MAN1B1,NELF,KIAA1984,INPP5E,ZMYND19,ENTPD8,C8G,EHMT1,FUT7,MRPL41,C9orf86,FBXW5,ARRDC1,CLIC3,SDCCAG3,ANAPC2,SNAPC4,EGFL7,COBRA1,LRRC26,PNPLA7,C9orf163,CARD9,TMEM141,SLC34A3,TUBB2C,EDF1,PTGDS
10	17830000	18250000	420000	37	0	0.05	13.08	MRC1,MRC1L1
10	41690000	43390000	1700000	165	3	8.27	177.95	FXYD4,HNRPF,ZNF239,RET
10	45510000	46370000	860000	71	0	0.06	24.85	FAM21C
10	46570000	47910000	1340000	87	0	0.01	32.04	ANXA8
10	48280000	49050000	770000	62	0	0.03	22.52	FRMPD2,PTPN20B
10	80920000	81660000	740000	73	0	0.08	25.22	SFTPA1B
11	67530000	69390000	1860000	186	3	3.35	29.49	LRP5,CHKA,MTL5,FGF4,GAL,MRGPRD,MYEOV,CPT1A,FGF3,ORAOV1,IGHMBP2,TCIRG1,TPCN2,SAPS3,MRGPRF,CCND1,FGF19,SUV420H1,MRPL21
11	69500000	70970000	1470000	148	3	3.51	27.98	KRTAP5-10,KRTAP5-7,NADSYN1,CTTN,PPFIA1,FADD,TMEM16A,SHANK2,DHCR7
11	124430000	126370000	1940000	195	3	2.88	13.87	CDON,FEZ1,FAM118B,DCPS,CHEK1,PATE,ACRV1,TIRAP
13	17930000	19050000	1120000	113	1	0.87	13.3	TUBA3C,TPTE2
14	18090000	19270000	1180000	119	0	0.42	25.87	ACTBL1

14	21920000	23200000	1280000	129	3	2.99	11.71	CMTM5,MMP14,CEBPE,DAD1,MRPL52,BCL2L2,PSMB5,IL25,PRMT5,MYH6,JUB,MYH7,ZFHX2,AP1G2,SLC7A8,EFS,ABHD4,PABPN1,DHRS2,RBM23,LRP10
14	68010000	69720000	1710000	172	3	3.01	16.44	SMOC1,SLC8A3,RAD51L1,SFRS5,ZFP36L1,ACTN1,FLJ39779,C14orf162
15	18280000	19660000	1380000	139	0	0.44	29.04	LOC283755,POTE15
15	26230000	26890000	660000	56	0	0.11	18.7	GOLGA8G,HERC2
15	28160000	28850000	690000	70	0	0.21	20.56	CHRFAM7A
15	80380000	81000000	620000	56	0	0.01	20.81	RPS17
16	14700000	15390000	690000	70	1	0.6	11.82	RRN3,NOMO1,NPIP
16	15410000	16190000	780000	79	3	3.29	11.64	ABCC1,KIAA0430,ABCC6,MYH11
16	16210000	16750000	540000	55	0	0.24	15.7	NOMO3,ABCC6
16	18080000	18690000	610000	62	0	0.22	18.04	NOMO2
16	26850000	28240000	1390000	140	3	3.32	21.42	GSG1L,NSMCE1,IL21R,GTF3C1,IL4R
16	30260000	31460000	1200000	121	3	3.45	21.51	ERAF,COX6A2,FUS,STX1B,ZNF688,SLC5A2,ITGAM,LOC283932,PRSS36,ITGAX,BCL7C,ARMC5,VKORC1,POL3S,SEPT1,FBXL19,SEPHS2,CTF1,RNF40,PYCARD,ITGAD,PRSS8,ITGAL
16	31850000	32410000	560000	57	1	0.53	10.35	
16	32570000	33260000	690000	70	0	0.22	20.3	TP53TG3
16	33780000	33930000	150000	16	3	6.64	12.37	
16	47920000	49590000	1670000	168	3	2.99	15.42	CYLD,NOD2,PAPD5,BRD7,ADCY7,ZNF423
16	68850000	70720000	1870000	188	3	4.05	54.3	DDX19B,AP1G1,CALB2,DHX38,TAT,MARVELD3,FUK,PHLPPL,DHODH,VAC14,FLJ11171,SF3B3,ZNF19,HPR,ST3GAL2,AARS,HYDIN,HP
16	79480000	80530000	1050000	106	3	3.15	12.95	GCSH,PKD1L2,ASCIZ,PLCG2,GAN,CENPN,BCMO1,C16orf46
17	18230000	18680000	450000	46	0	0.31	11.81	FLJ40244,LOC654346
17	41650000	42130000	480000	49	0	0.15	15.48	ARL17P1,NSF
17	43110000	43410000	300000	31	3	4.52	11.72	OSBPL7,TBX21,PNPO,SP6,CDK5RAP3,KPNB1,MRPL10
18	13950000	15400000	1450000	146	1	0.9	16.48	
21	9730000	10200000	470000	48	3	4.26	15.75	TPTE
21	13290000	14320000	1030000	104	1	0.55	18.46	ANKRD21
21	26250000	27020000	770000	78	3	3.41	13.21	APP,CYYR1
22	14450000	15070000	620000	63	0	0.11	20.88	ACTBL1
22	18690000	19050000	360000	31	0	0.11	10.35	
22	19790000	20230000	440000	45	0	0.16	14.09	LOC375133,HIC2
X	48180000	49050000	870000	88	3	4.02	24.99	WDR45,CACNA1F,GRIPAP1,PPP1R3F,FTSJ1,PQBP1,RBM3,GATA1,EBP,HDAC6,CCDC22,LMO6,PCSK1N,PORCN,SYP,KCND1,WAS,TBC1D25,WDR13,SUV39H1
X	52120000	52580000	460000	41	0	0.04	14.7	XAGE1D,XAGE2

X	53030000	54600000	1570000	158	3	3.27	22.72	FGD1,GNL3L,HSD 17B10,SMC1A,FA M120C,WNK3,IQS EC2,JARID1C,HU WE1
X	70950000	71870000	920000	93	3	3.09	10.24	HDAC8,RPS4X,PI N4,ERCC6L
X	76150000	76450000	300000	31	0	0.1	10.45	
X	76610000	77330000	720000	73	0	0.16	22.93	TAF9B,PGAM4,AT P7A,COX7B,ATRX
X	88350000	90160000	1810000	182	0	0.39	41.25	TGIF2LX
X	90180000	91420000	1240000	125	1	0.78	16.87	PCDH11X
X	91440000	92250000	810000	82	0	0.32	20.84	PCDH11X
X	134810000	136510000	1700000	171	3	2.86	11.62	ARHGEF6,GPR112, ZIC3,CD40LG,BRS 3,SLC9A6,SAGE1, RBMX
X	149000000	150910000	1910000	192	3	3	17.8	MTM1,CD99L2,H MGB3,GPR50,GAB RE,MAGEA4,CNG A2,MTMR1,FATE1, PASD1
X	151710000	153060000	1350000	136	3	3.91	35.88	TMEM187,CETN2, BGN,L1CAM,MEC P2,SSR4,DUSP9,L CAP,BCAP31,UCH L5IP,IRAK1,AVPR2 ,IDH3G,MAGEA1,P NMA5,RENBP,AB CD1,ARHGAP4,TR EX2,ATP2B3

Supplementary Table 11. Cross comparison of copy numbers in primary tumor, metastasis, and xenograft derived from Illumina SNP array, aCGH, and whole genome sequencing. For primary tumor, we obtained data from Illumina SNP array and whole genome sequencing platforms; For metastasis, we obtained data from aCGH and whole genome sequencing platforms; For xenograft, we obtained data from all three platforms.

		Illumina SNP array		aCGH		whole genome sequencing		
		Primary Tumor	Metastasis	Metastasis	Xenograft	Primary Tumor	Metastasis	Xenograft
Illumina SNP array	Primary Tumor	1	0.542757145	0.288327893	0.365774914	0.498693966	0.528172936	0.580700291
	Metastasis	0.542757145	1	0.570716906	0.560213347	0.639529316	0.702807281	0.644766932
aCGH	Metastasis	0.288327893	0.570716906	1	0.524596597	0.554298819	0.607901012	0.507122842
	Xenograft	0.365774914	0.560213347	0.524596597	1	0.599758389	0.637676329	0.609845802
Whole genome sequencing	Primary Tumor	0.498693966	0.639529316	0.554298819	0.599758389	1	0.969916045	0.892043426
	Metastasis	0.528172936	0.702807281	0.607901012	0.637676329	0.969916045	1	0.923103136
	Xenograft	0.580700291	0.644766932	0.507122842	0.609845802	0.892043426	0.923103136	1

Supplementary Table 12. Summary of libraries used for structural variation analysis.

Samples	Library name	Mean insert size (bp)	SD (bp)	Read length
Brain metastasis	Library 1	173.38	28.45	64.14
Brain metastasis	Library 2	262.4	48.43	75.00
Brain metastasis	Library 3	176.71	23.82	75.00
Brain metastasis	Library 4	292.61	49.77	75.00
Brain metastasis	Library 5	117.03	19.01	75.00
Brain metastasis	Library 6	335.13	98.97	75.00
Peripheral blood	Library 1	182.93	27.46	79.45
Peripheral blood	Library 2	311.74	54.63	78.38
Peripheral blood	Library 3	197.23	24.56	100.00
Peripheral blood	Library 4	316.91	45.15	100.00
Peripheral blood	Library 5	170.28	21.44	75.00
Peripheral blood	Library 6	170.87	24.27	75.00
Peripheral blood	Library 7	386.5	65.75	75.00
Peripheral blood	Library 8	290.77	40.99	75.00
Peripheral blood	Library 12	120.47	17.17	75.00
Peripheral blood	Library 13	176.49	60.42	39.00
Peripheral blood	Library 14	178.36	61.77	39.00
Peripheral blood	Library 15	177.48	62.99	39.00
Peripheral blood	Library 16	174.59	61.18	39.00
Primary tumor	Library 1	204.05	29.9	63.33
Primary tumor	Library 2	200.53	116.05	72.57
Primary tumor	Library 3	212.84	29.35	62.26
Primary tumor	Library 4	227.34	124.68	73.43
Xenograft	Library 1	189.01	26.2	71.68
Xenograft	Library 2	141.17	109.78	35.78
Xenograft	Library 3	188.59	26.84	74.55
Xenograft	Library 4	140.45	104.82	36.00

Supplementary Table 13. Assembled translocations.

Type	Tumor source	Chromosome A	Breakpoint A	Orientation A	Chromosome B	Breakpoint B	Orientation B	Gene
Translocation	Primary Tumor, Metastasis, Xenograft	1	245548334	minus	2	64855174	plus	ZNF496
Translocation	Primary Tumor, Metastasis, Xenograft	2	64855565	plus	6	144243118	minus	C6orf94
Translocation	Primary Tumor, Metastasis, Xenograft	4	188855443	plus	9	139022260	plus	ABCA2
Translocation	Primary Tumor, Metastasis, Xenograft	1	204459091	plus	4	147603427	minus	SLC10A7
Translocation	Primary Tumor, Xenograft	1	232964339	plus	5	142123065	plus	
Translocation	Primary Tumor, Metastasis, Xenograft	1	35723320	plus	19	6102013	minus	KIAA0319L, ACSBG2
Translocation	Metastasis, Xenograft	2	65010855	plus	6	144244490	minus	C6orf94
Translocation	Primary Tumor, Metastasis, Xenograft	2	165126335	plus	16	4537865	plus	GRB14
Translocation	Primary Tumor, Metastasis, Xenograft	3	188010736	minus	19	17188979	plus	USE1
Translocation	Primary Tumor, Metastasis, Xenograft	4	89034073	plus	6	44329592	plus	HSP90AB3P, HSP90AB1
Translocation	Xenograft	4	133969991	minus	18	9304740	plus	
Translocation	Metastasis, Xenograft	6	31958079	plus	10	42184694	minus	EHMT2
Translocation	Primary Tumor, Xenograft	7	97691541	minus	19	16528270	plus	TECPR1, SLC35E1
Translocation	Primary Tumor	7	107452378	plus	20	59581275	minus	LAMB4, CDH4
Translocation	Metastasis, Xenograft	12	10874018	plus	14	99382253	minus	EML1
Translocation	Primary Tumor, Metastasis, Xenograft	16	362509	minus	17	3842170	minus	TMEM8A
Translocation	Metastasis, Xenograft	16	442130	plus	17	3720863	plus	RAB11FIP3, CAMKK1
Translocation	Primary Tumor, Metastasis, Xenograft	16	69630532	plus	17	43100610	plus	HYDIN, KPNB1
Translocation	Metastasis	7	142047745	minus	9	33642293	minus	TCRVB

Supplementary Table 14. GO annotation for genes enriched in metastasis and/or xenograft.

GO	Description	Genes
GO:0005524	ATP binding	TXNDC6 NRK ADCY3 MAP3K8 TP53 DYNC2H1
GO:0008270	zinc ion binding	TADA2A ZNF786 DPEP3 TP53
GO:0005737	cytoplasm	TXNDC6 PID1 DLG5 ADCY3 WWTR1
GO:0006350	cellular transcription	FOXI1 ZNF786 MYCBP2 WWTR1
GO:0003700	transcription factor activity	FOXI1 TADA2A NRK TP53
GO:0005634	nucleus	FOXI1 RBM47 PTPRJ ZNF786
GO:0005886	plasma membrane	PAQR7 SLC44A1 DYNC2H1
GO:0045449	regulation of cellular transcription	TADA2A NRK
GO:0005515	protein binding	PTPRJ MAP3K8 DHDDS
GO:0016021	integral to membrane	PAQR7 SLC44A1 NALCN
GO:0000287	magnesium ion binding	ADCY3 MAP3K8
GO:0005887	integral to plasma membrane	PTPRJ ADCY3
GO:0006468	protein amino acid phosphorylation	NRK MAP3K8
GO:0004872	receptor activity	PAQR7 CHRNA9
GO:0005509	calcium ion binding	CHRNA9
GO:0005856	cytoskeleton	TXNDC6
GO:0030054	cell junction	PTPRJ CHRNA9
GO:0005829	cytosol	MAP3K8
GO:0003723	RNA binding	RBM47 RBMX2
GO:0007275	multicellular organismal development	PAQR7 DYNC2H1

Supplementary Table 15. 454 read counts for RT-PCR products of 11 mutations in excel spreadsheet.

E. Supplementary References

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