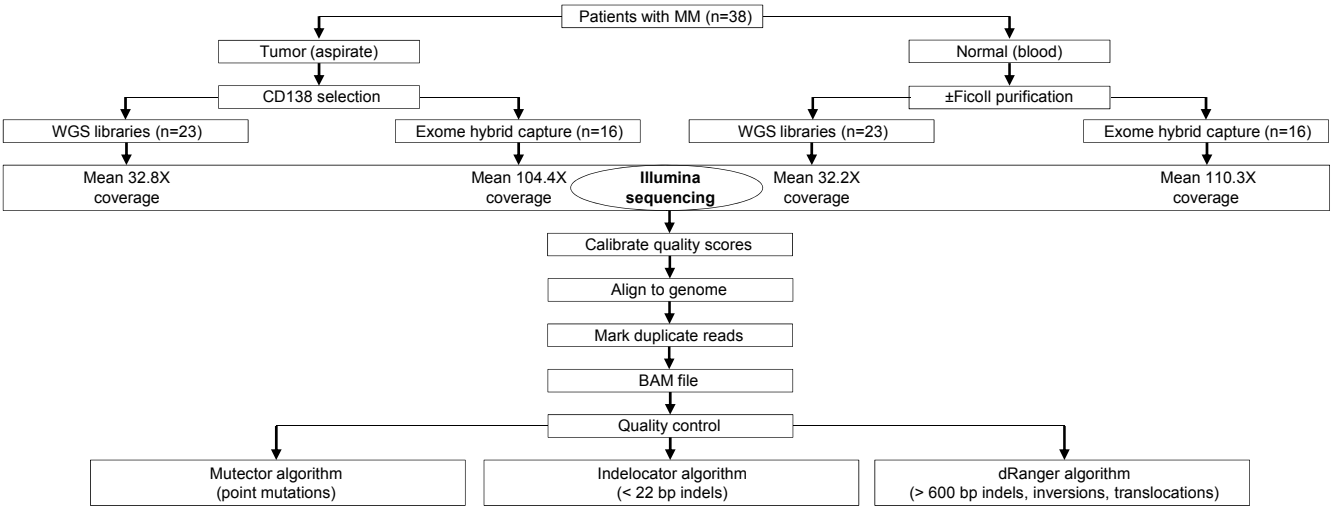
doi:10.1038/nature09837

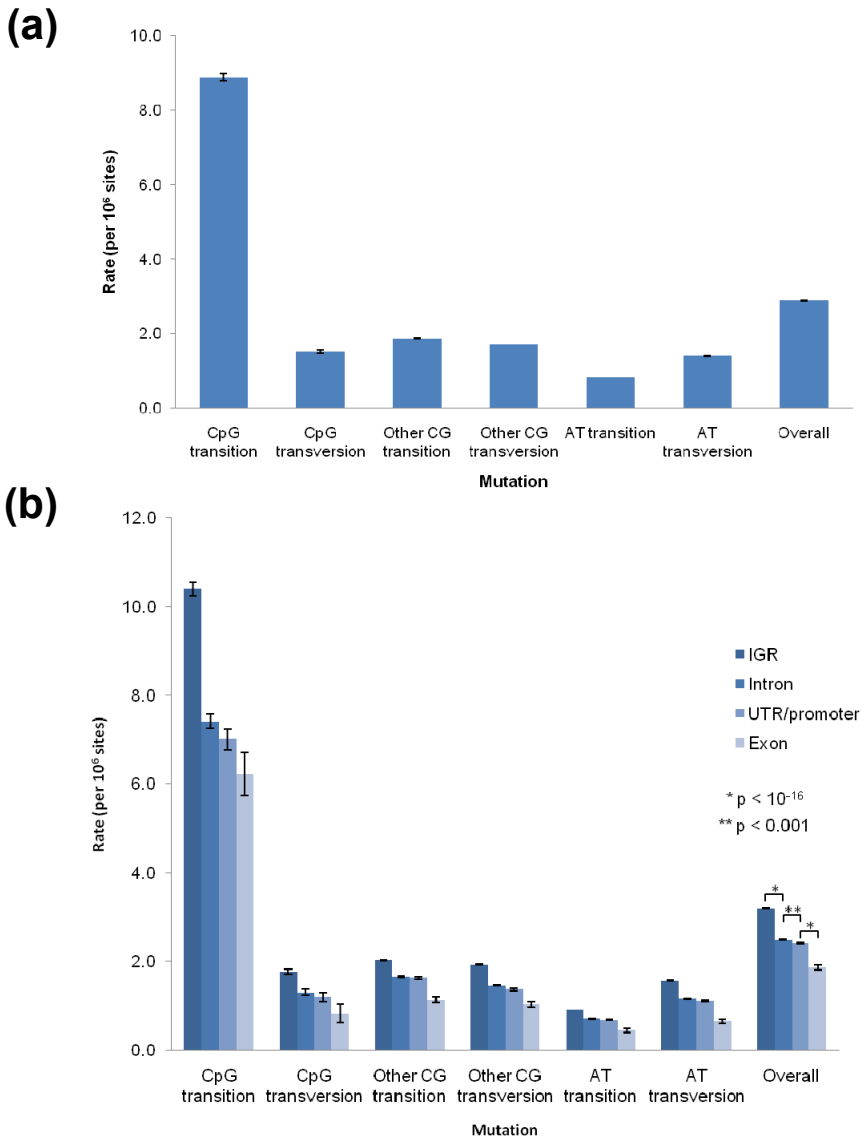


Supplementary Figure 1 – Sequencing and analytical pipeline for determining somatic mutations in MM.

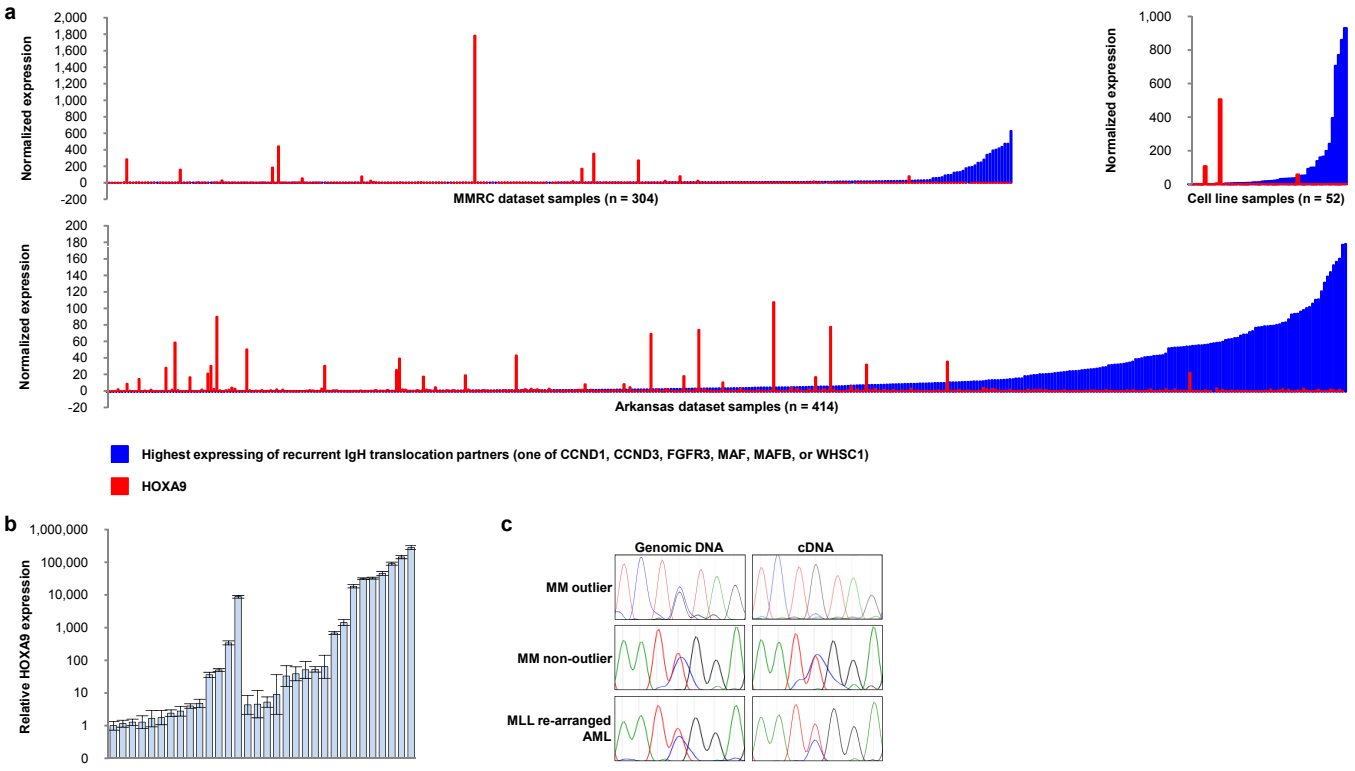
Sensitivity: 67% (all exons) 88%

88% (targeted exons)

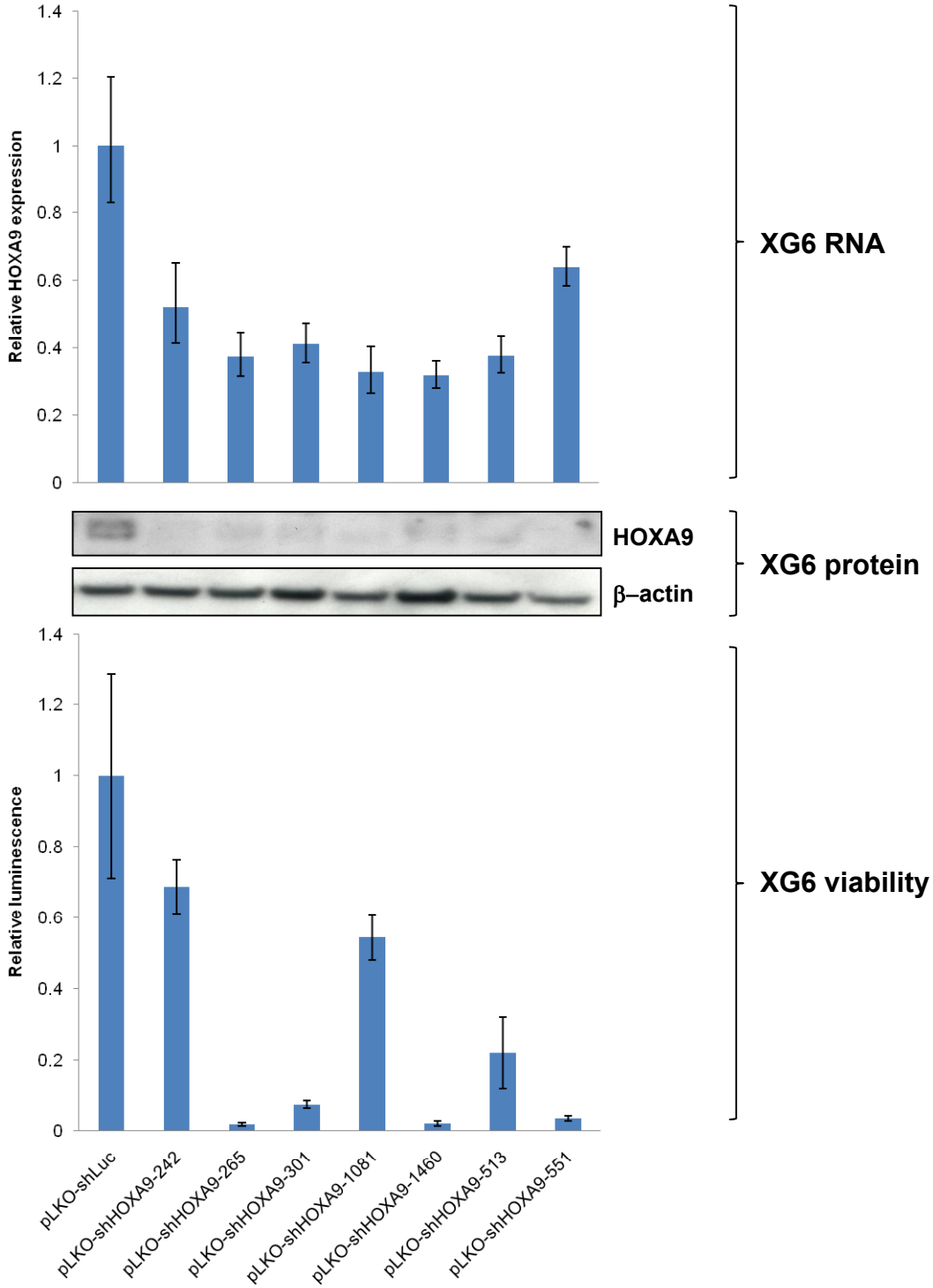
Supplementary Figure 2 – Sensitivity estimations. Sample MMRC0191 was sequenced by both WGS and WES. To estimate sensitivity, supporting reads for each nonsynonymous mutation were assessed manually and likely false positives discarded. Then mutations were placed in three groups: detected in WES only, detected in both datasets, or detected in WGS only. These numbers were used to assess sensitivity of the two sequencing methods (upper set of numbers in Venn diagram). A number of mutations that were detected by WGS only were not targeted by the hybrid capture bait set, so to assess the sensitivity of the muTector caller in WES (as opposed to the library production method), these were excluded from the analysis (lower set of numbers in Venn diagram).



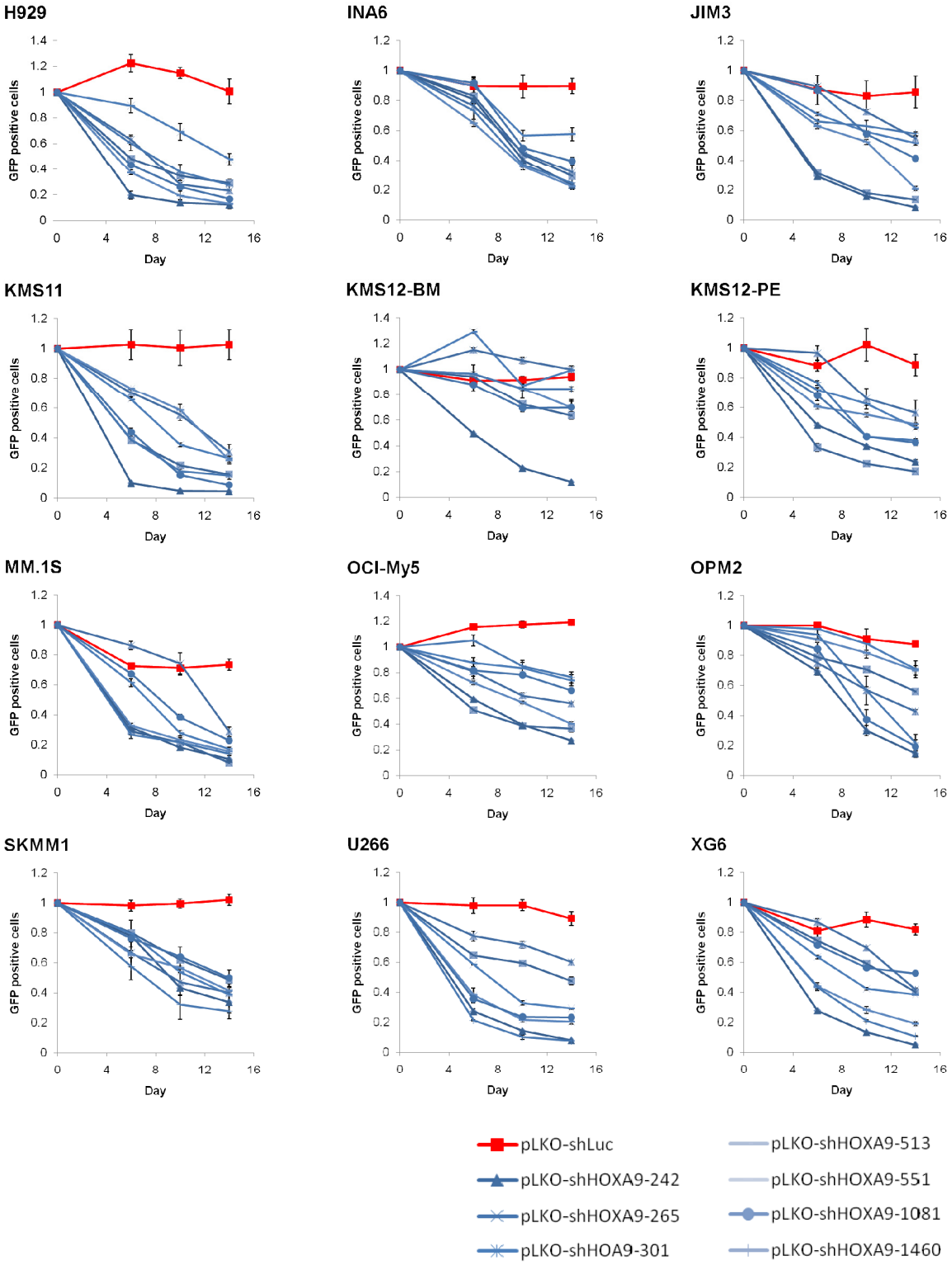
Supplementary Figure 3 – Base- and region-specific somatic mutations rates. (a) Mutation rates by base-specific change. Error bars are ±estimated s.d. (b) Mutation rates by base-specific change in different genomic regions. Error bars are ±estimated s.d.



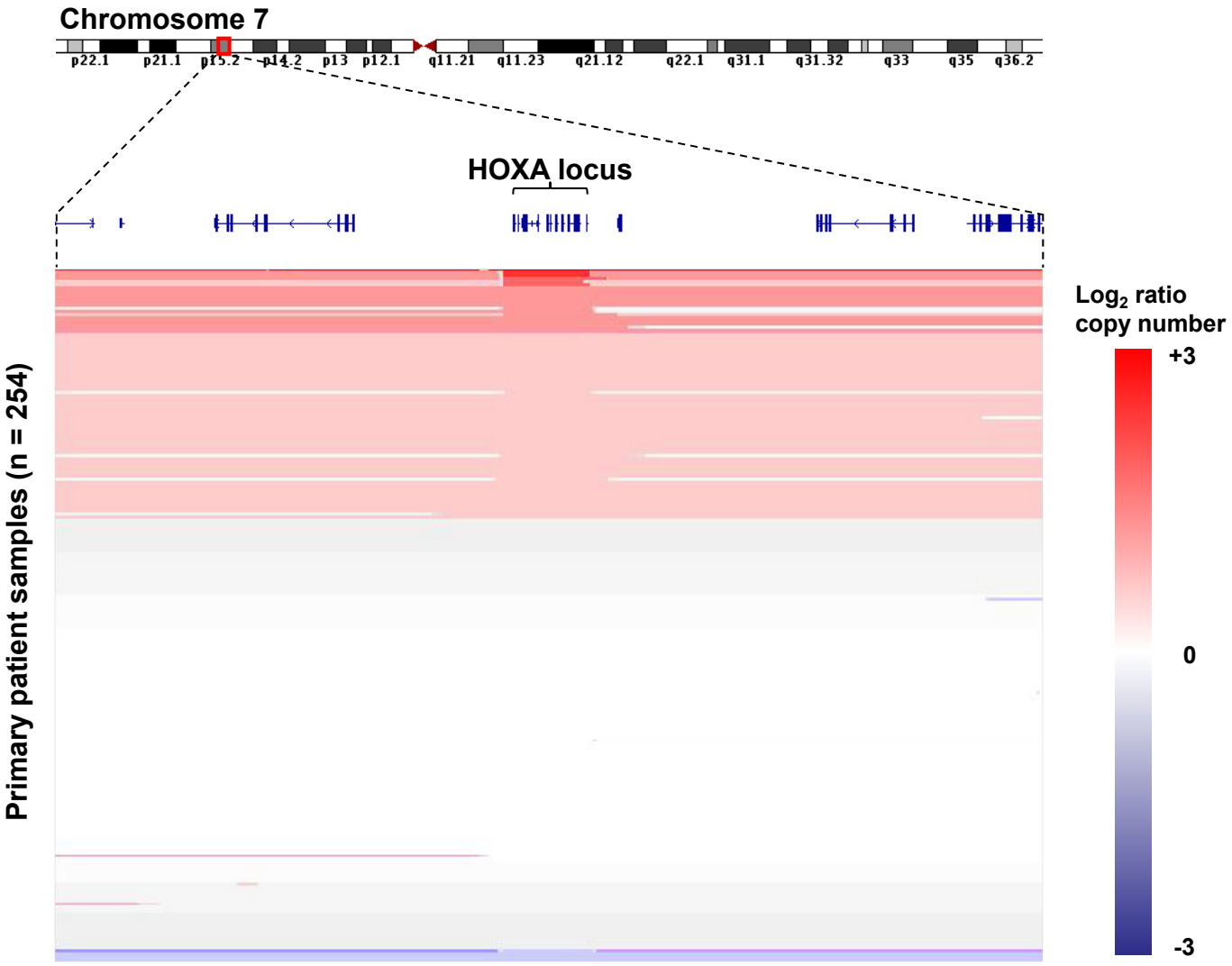
Supplementary Figure 4 – Patterns of *HOXA9* expression in MM. (a) Patterns of *HOXA9* expression (red) compared to those of canonical targets of IgH translocation (blue). (b) Ubiquitous expression of *HOXA9* was demonstrated by qPCR. Expression is relative to that of the lowest expressing cell line, JIM3, and values are normalized to expression of β-actin. Error bars are ± S.E.M. and represent a minimum of 4 technical replicates. (c) Examples of sequencing traces across informative SNPs in MM samples with outlying *HOXA9* expression (top) and non-outlying *HOXA9* expression (middle). Also included is an MLL-rearranged acute leukemia cell line (bottom). The allele-specific patterns of expression were seen in 2/2 informative outliers, 9/9 informative non-outliers, and 1/1 informative MLL-rearranged AML cell line.



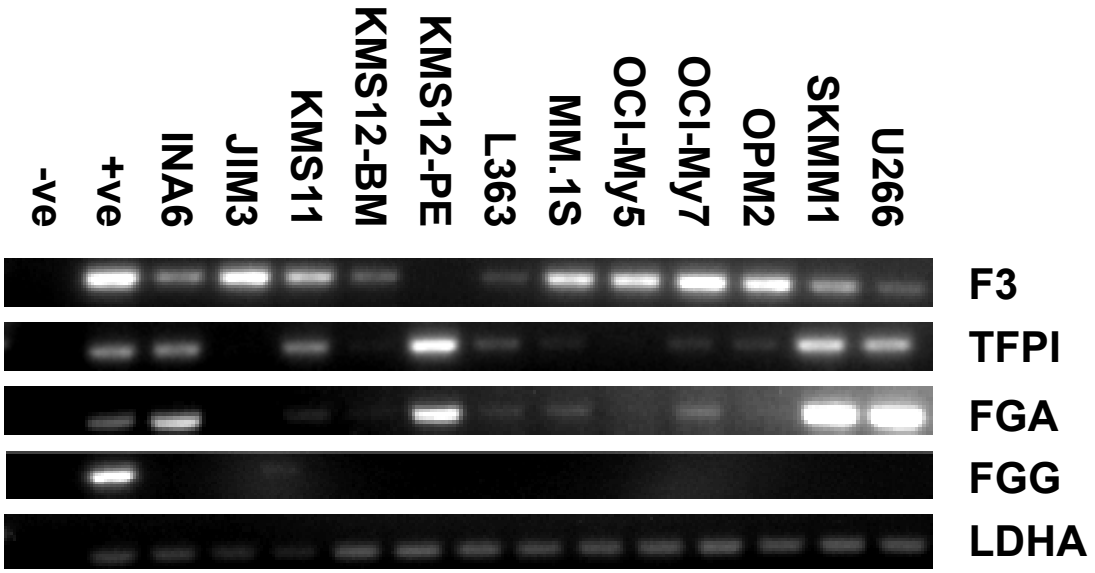
Supplementary Figure 5 – Knockdown of *HOXA9* is associated with reduced viability in the MM cell line XG6. *HOXA9* mRNA expression (top) and protein expression (middle) was assayed three and five days (respectively) post-infection with seven independent lentiviral constructs expressing shRNAs targeting *HOXA9* and a control shRNA targeting luciferase (shLuc). XG6 viability ten days post-infection, as assessed by CellTiterGlo, is shown in the lower panel. Error bars in both graphs are ±S.E.M. and represent a minimum of four technical replicates (mRNA) or three experimental replicates (relative luminescence).



Supplementary Figure 6 – *HOXA9* is essential for MM survival. GFP competition assay in MM cell lines. Following lentiviral infection with seven independent shRNAs that target HOXA9 (blue) or a control shRNA targeting luciferase (shLuc; red), GFP+ cells were monitored by flow cytometry and compared to the proportion of GFP+ cells present in the population 3 days post-infection (designated day 0). Error bars are ±S.E.M. and represent a minimum of three experimental replicates. Differences between GFP+ proportions at day 14 for shLuc and targeting hairpins were significant for all hairpins in all cell lines apart from in KMS12-BM.



Supplementary Figure 7 – Focal amplifications at the *HOXA* locus. A copy number heatmap of the *HOXA* locus and flanking regions in a set of 254 publicly available MM aCGH samples.



Supplementary Figure 8 – Expression of coagulation factors in MM cell lines. F3, TFPI, FGA, and FGG, which were all found to be mutated, were assayed. F5, which is known to be expressed in cells of lymphocytic origin, was not assessed. Positive controls are dermal fibroblasts (F3) or whole liver extract (remainder). An LDHA control was used to ensure approximately even loading.

Overview

• Obtain genome-wide regulatory potential (RP) scores from regulatory potential track in UCSC browser:

http://hgdownload.cse.ucsc.edu/goldenPath/hg18/regPotential7X/

± mask regions of somatic hypermutation.

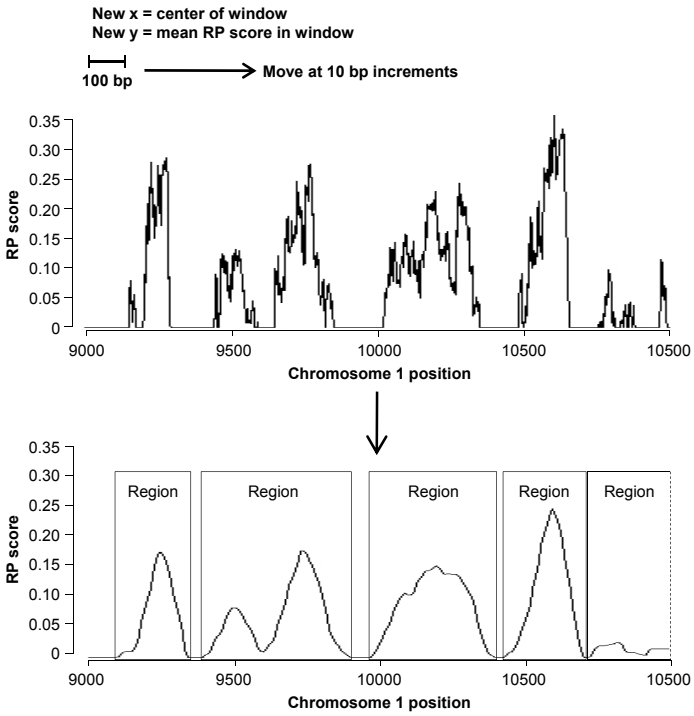
• Smooth RP scores by averaging in a 100 bp window moved at 10 bp increments across genome.

• Generate discrete regions of regulatory potential – regions of contiguous non-zero RP score.

• Determine total good quality coverage and total number of mutations across all 38 samples in each region.

• Use binomial test to calculate probability of seeing at least observed number of mutations in total area covered. Correct for multiple hypotheses testing.

Example: definition of regions in stretch of chromosome 1



2.38 x 10^6 RP regions genome-wide

For a given region:

Total good quality coverage of region across all samples, N

Total mutations in region in all samples, n

Mean mutation rate across all regulatory regions, μ

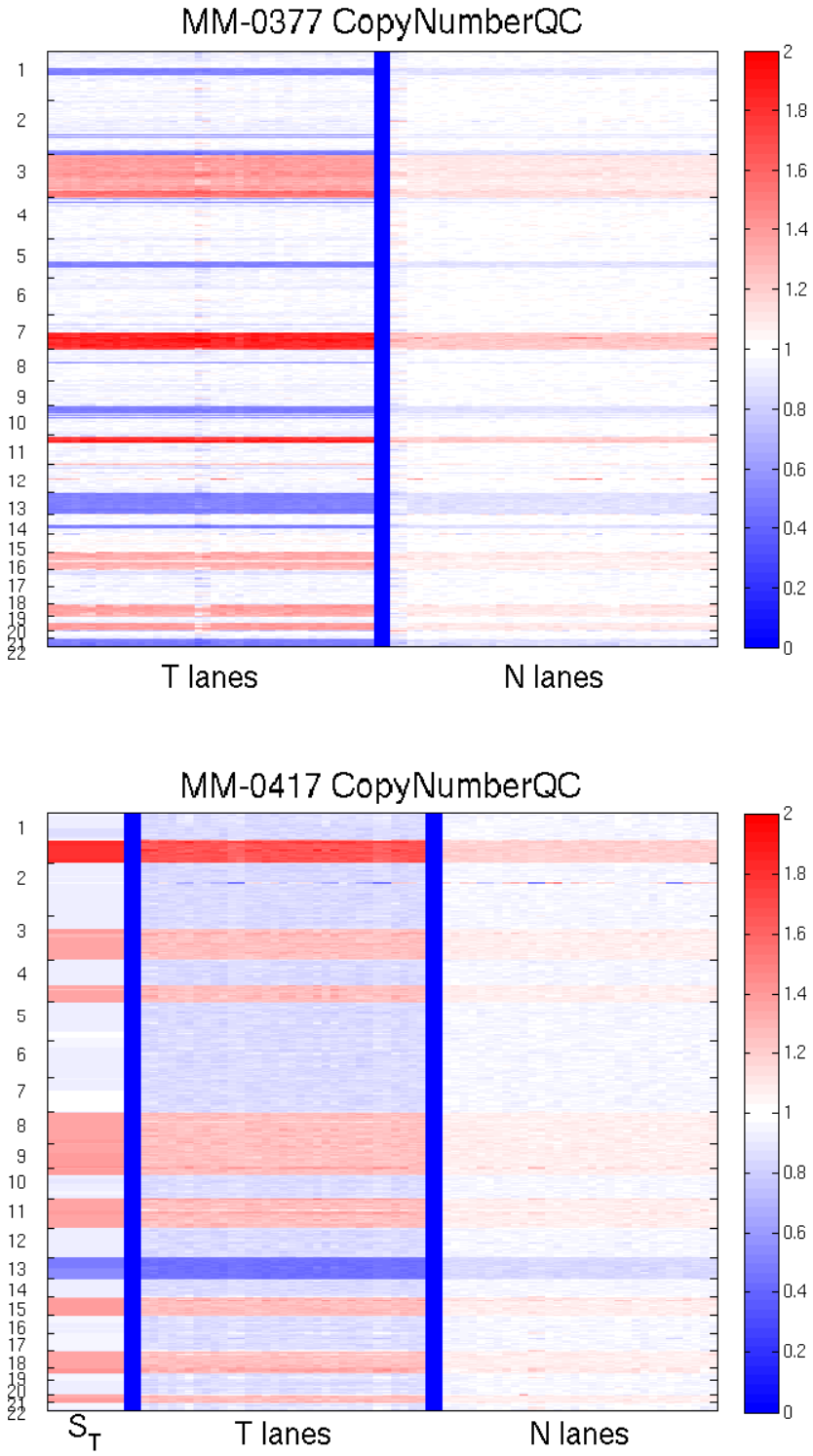
$$p = 1 - \sum_{i=0}^{\lfloor n \rfloor} \binom{N}{i} \mu^i (1-\mu)^{N-i}$$

Benjamini-Hochberg procedure, 2.38x10^6 observations.

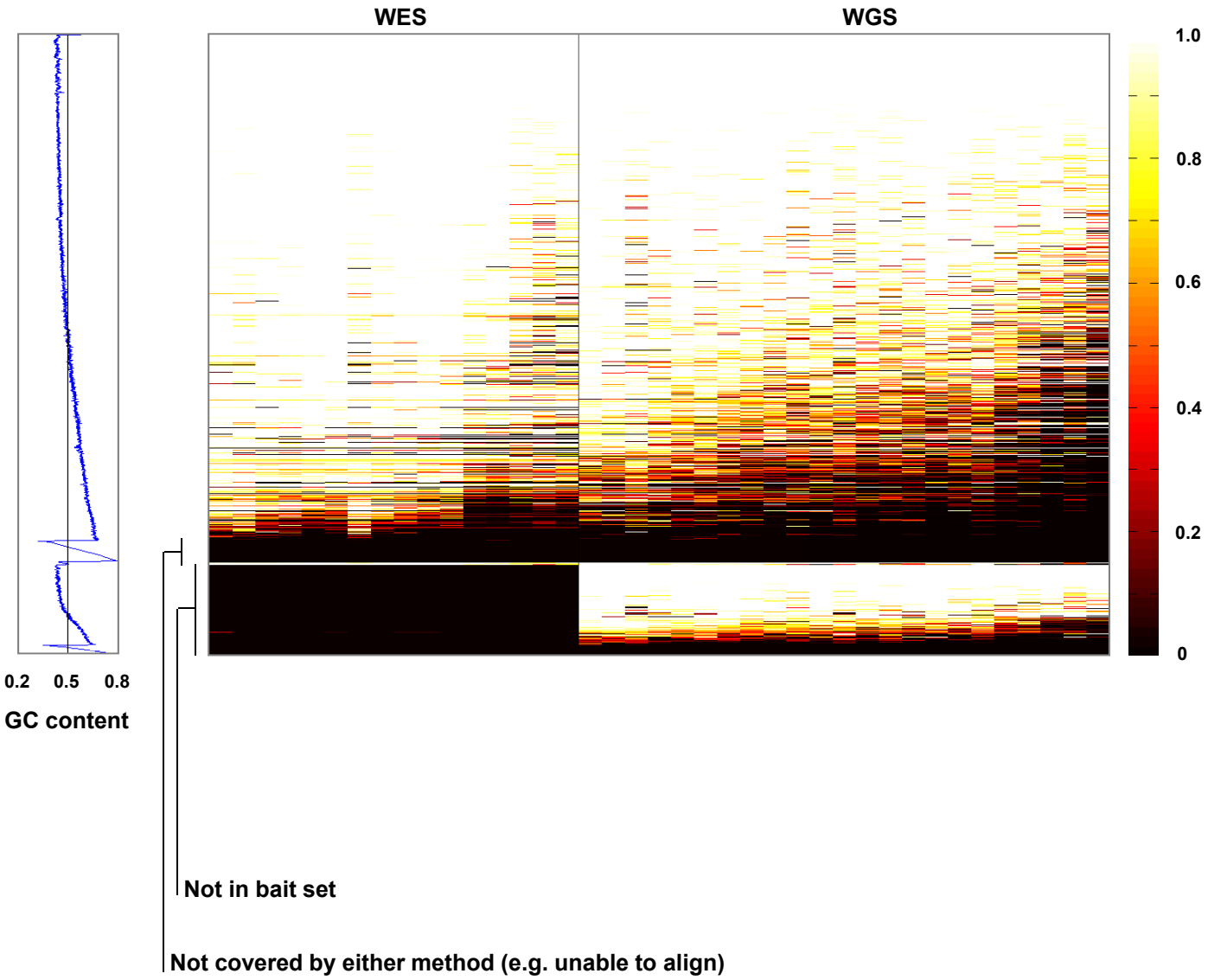
Filtering

Exclude regions with: q > 0.25; mutations confined to a single sample; exclusively coding mutations; identical mutations at an identical base (likely artifact); evidence of misalignment artifact on manual review of reads (majority of included regions subjected to additional PCR and Sanger sequencing).

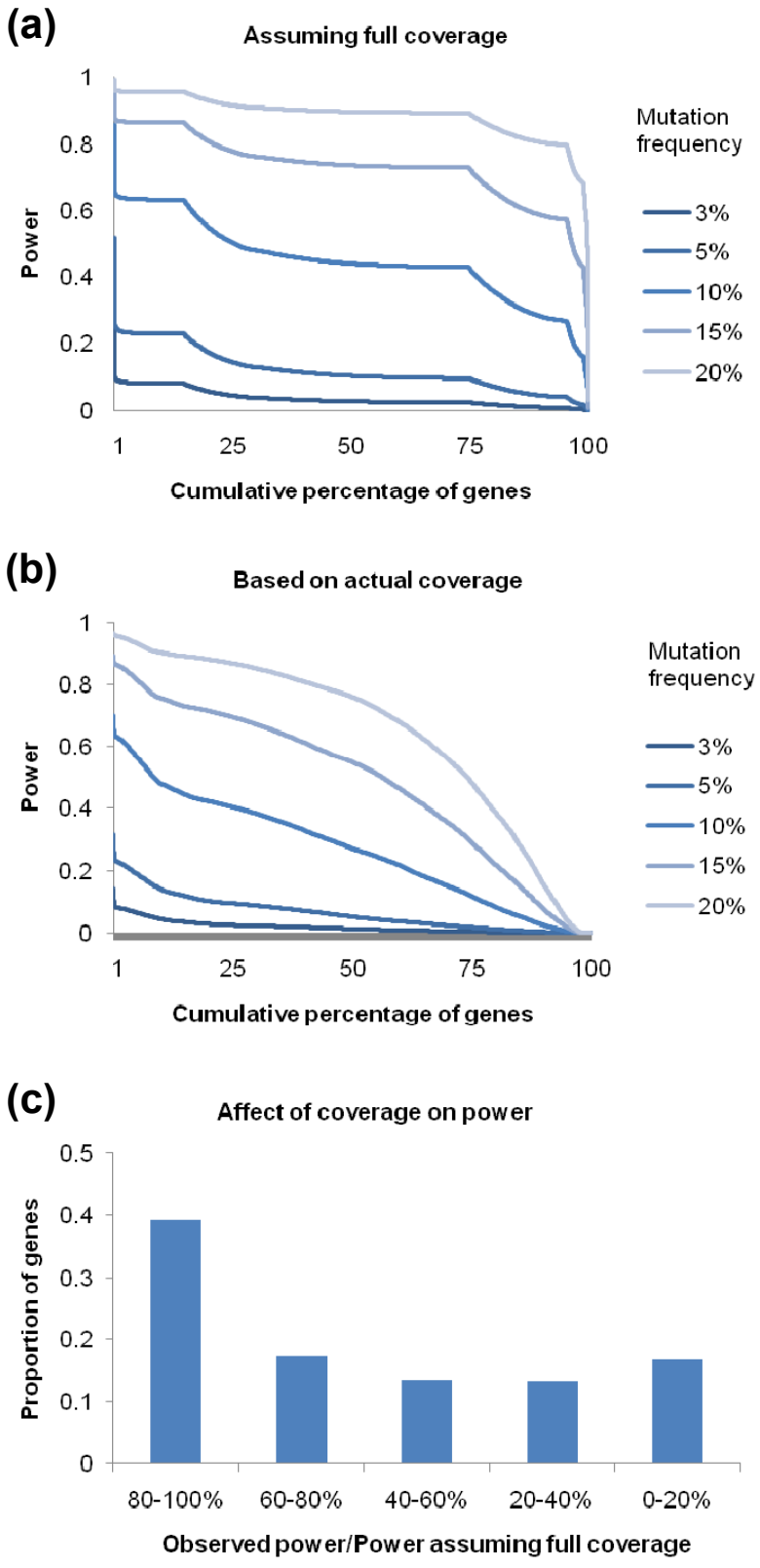
Supplementary Figure 9 – Identification of significantly mutated potential regulatory regions.



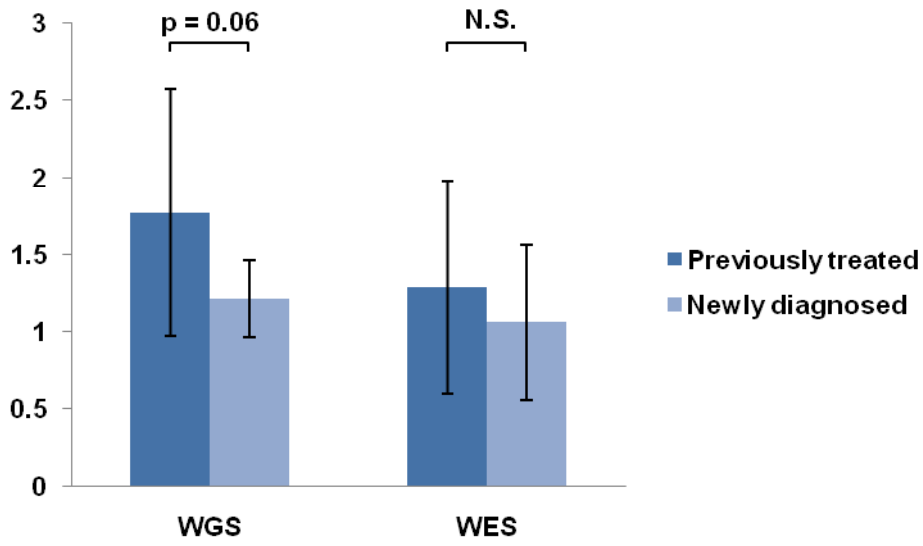
Supplementary Figure 10 – Copy-number profiles showing tumor-in-normal contamination in two samples sequenced by WGS. These samples were excluded from analysis. Tumor (T) lanes are shown on the left and normal (N) lanes on the right. S_T labels an independent aCGH profile for tumor MM-0417.



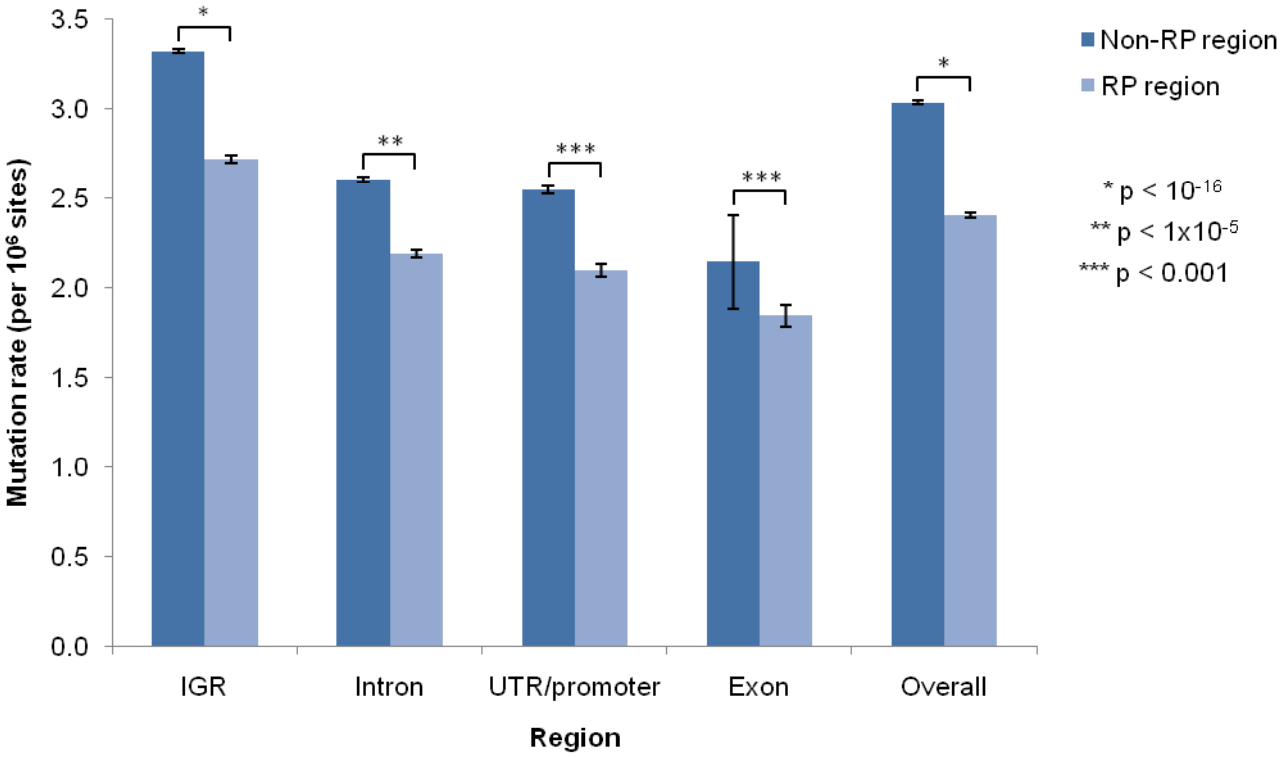
Supplementary Figure 11 – Genomic coverage by sample. In the main plot, samples are arranged in columns and coverage is shown by a heat map (key on the right). Regions not targeted by the hybrid capture bait set are arranged at the bottom of the coverage plot, as indicated. Otherwise, regions are ordered by coverage. GC content is shown in the plot on the left.



Supplementary Figure 12 – Effect of coverage on power. (a) Power to detect genes mutated at frequencies of 20%, 15%, 10%, 5%, and 3% as significant, assuming uniform coverage. (b) As in (a), but recalculated to reflect actual coverage achieved. (c) Distribution of loss of power due to actual coverage. For each gene, the power at observed coverage was divided by the power assuming uniform coverage for each mutational frequency. The mean of these ratios was then taken for each gene and the genes binned as shown.



Supplementary Figure 13 – Nonsynonymous somatic coding mutation rates in previously treated and newly diagnosed patient samples are not significantly different. Error bars are ±estimated s.d. N.S., not significant.



Supplementary Figure 14 – Defined regions of regulatory potential (RP regions) have a lower mutation rate than the remainder of the genome. Region-specific and overall mutation rates are shown for the RP and non-RP regions. Error bars are ±estimated s.d.

Supplementary Methods

Contents

Sequence data generation

Whole Genome Shotgun (WGS) Library Construction

We sheared 1-3 µg of genomic DNA to a range of 100-700 bp using the Covaris E210 instrument. DNA fragments were end-repaired and phosphorylated, followed by adenylation of 3' ends. Standard paired end adaptors were ligated according to the manufacturer's protocol (Illumina). We performed Qiagen min-elute column based cleanups between all enzymatic steps. Adapter ligated fragments were purified with preparatory gel electrophoresis (4% agarose, 85volts, 3 hours) and two bands were excised (500-520bp and 520-540bp) resulting in two libraries per sample with inserts averaging 380bp and 400bp respectively. DNA was extracted from gel bands using Qiagen min-elute columns. The entire volume of final purified fragments was enriched via PCR with Phusion polymerase for 10 cycles.

Each of the resulting WGS libraries was sequenced on an average of 39 lanes of an Illumina GA-II sequencer, using 101 bp paired-end reads, with the aim of reaching 30X average genomic coverage of

distinct molecules per sample. The mean coverage achieved was 33X in the tumors and 32X in the normals.

Whole Exome (WE) Capture Library Construction

We follow the procedure described by Gnirke *et al.*[1] adapted for production-scale exome capture library construction. Exome targets were generated based on CCDS genes, representing 164,687 exons from ~16,500 genes (representing 93% of known, non-repetitive protein-coding genes and spanning ~1% of the genome). DNA oligonucleotides were PCR amplified, then transcribed in vitro in the presence of biotinylated UTP to generate single-stranded RNA "bait." Genomic DNA from primary tumor and patient-matched blood normal was sheared, ligated to Illumina sequencing adapters, and selected for lengths between 200-350 bp. This "pond" of DNA was hybridized with an excess of bait in solution. The "catch" was pulled down by magnetic beads coated with streptavidin, then eluted.

Resulting exome sequencing libraries from the process described above were sequenced on three lanes of an Illumina GA-II sequencer, using 76 bp paired-end reads[1]. The mean coverage achieved was 104X in the tumors and 110X in the normals.

Illumina sequencing

Libraries were quantified using a SYBR Green qPCR protocol with specific probes for the ends of the adapters. The qPCR assay measures the quantity of fragments properly adapter-ligated that are appropriate for sequencing. Based on the qPCR quantification, libraries were normalized to 2nM and then denatured using 0.1 N NaOH. Cluster amplification of denatured templates occurred according to manufacturer's protocol (Illumina) using V2 Chemistry and V2 Flowcells (1.4mm channel width). SYBR Green dye was added to all flowcell lanes to provide a quality control checkpoint after cluster amplification to ensure optimal cluster densities on the flowcells. Flowcells were paired-end sequenced (2x101bp for WGS and 2x76bp for WE) on Genome Analyzer II's, using V3 Sequencing-by-Synthesis kits and analyzed with the Illumina v1.3.4 pipeline. Standard quality control metrics including error rates, % passing filter reads, and total Gb produced were used to characterize process performance prior to downstream analysis. The Illumina pipeline generates data files that contain the reads and qualities.

Sequence data processing

Data were processed using two consecutive pipelines:

(1) The sequencing data-processing pipeline, called "Picard", developed by the Sequencing Platform at the Broad Institute, starts with the reads and qualities produced by the Illumina software for all lanes and libraries generated for a single sample (either tumor or normal) and produces, at the end of the pipeline, a single BAM file (http://samtools.sourceforge.net/SAM1.pdf) representing the sample. The final BAM file stores all reads with well-calibrated qualities together with their alignments to the genome (only for reads that were successfully aligned).

(2) The Cancer Genome Analysis pipeline, also known as "Firehose", developed in the Cancer Program at the Broad Institute, starts with the BAM files for the tumor and patient-matched

normal samples and performs various analyses, including quality control, local-realignment, mutation calling, small insertion and deletion identification, rearrangement detection, coverage calculations and others (see details below).

Several of the tools used in these pipelines were developed jointly by the Broad's Sequencing Platform, Medical and Population Genetics Program and the Cancer Program (additional details regarding parts of the pipeline focused on germ-line events, also used for medical and population genetics, will be described elsewhere; DePristo *et al*., in preparation).

The sequencing data-processing pipeline

We generated a BAM file for each sample using the sequencing data processing pipeline, known as "Picard" (http://picard.sourceforge.net/; Fennel T. *et al*., unpublished). Picard consists of four steps (briefly described below): (1) recalibration of base qualities, (2) alignment to the genome, (3) aggregation of lane and library data, and (4) marking of duplicate reads.

(1) Base-quality recalibration

Each base is associated with a Phred-like quality Q score[2] representing the probability that the base call is erroneous. The Q score represents $-10*\log_{10}$(Probability of error), rounded to an integer value. In order to make sure that Q30 bases indeed have a 1 in a 1000 chance of being wrong we used a GATK tool (http://www.broadinstitute.org/gatk) that empirically recalibrates the qualities based on the original Q score (generated by the Illumina software), the read-cycle, the lane, the tile, the base in question and the preceding base. The original quality scores are also kept in the BAM file in the read-level OQ tag.

(2) Alignment to the genome

Alignment is performed using MAQ[3] [http://maq.sourceforge.net/] to the NCBI Human Reference Genome Build 36.3. The reads in the BAM file are sorted according to their chromosomal position. Unaligned reads are also stored in the BAM file such that all reads that passed the Illumina quality filter (PF reads) are kept in the BAM.

(3) Aggregation of lane- and library-level data

Multiple lanes and libraries are aggregated into a single BAM per sample. Lane-level BAM files are combined to library-level BAM files and these are then combined to sample-level BAM files. The BAM files contain read-groups that represent the library and lane information. Information regarding the read groups appears in the BAM header (see the BAM file specifications in http://samtools.sourceforge.net/SAM1.pdf).

(4) Marking of duplicated reads

Molecular duplicates are flagged using the MarkDuplicates algorithm from Picard (http://picard.sourceforge.net/). The method identifies pairs of reads in which both ends map to the

exact same genomic position as being multiple reads of the same DNA molecule and hence marks all but the first as duplicates.

The BAM files that are produced by the Picard pipeline are then delivered to dbGaP. In this study we delivered 52 files representing 26 WGS tumor/normal pairs and an additional 26 files representing 13 WE tumor/normal pairs.

The Cancer Genome Analysis pipeline ("Firehose")

The Cancer Genome Analysis pipeline consists of a set of tools for analyzing next-generation data representing tumor DNA samples and their patient-matched normal DNA samples. In order to build a robust pipeline we developed a pipeline infrastructure for managing analysis workflows, called *Firehose* – representing the need to handle the flood of next-generation and high-throughput data (Voet D. *et al*., unpublished). Firehose manages the input files, the analysis tools and the output files, and keeps track of where the data reside, what needs to be executed on each file and in what order, and what is currently running. It also keeps track of versions of the data and methods to enable reproducing the analysis and results. Firehose uses GenePattern[4] as its execution engine, which is responsible for actually running the pipelines and modules based on parameters and inputs files specified by Firehose.

The analysis contains the following steps (which are detailed below):

(1) Quality control – ensuring that all data match their corresponding patient and that there are no swaps between tumor and normal data for the same individual.
(2) Local-realignment of reads – reads in regions that potentially harbor small insertions or deletions are jointly realigned to improve detection of indels and to decrease the number of false positive single nucleotide variations caused by misaligned tips of reads.
(3) Identification of somatic single nucleotide variations (SSNVs) – candidate SSNVs are detected using a statistical analysis of the bases and qualities in the tumor and normal BAMs that map to the studied genomic site. Post-filtering of candidate mutations removes systematic artifacts. For WGS data, we interrogate every position along the genome, and for WE data, we search for mutations in the neighborhood of the targeted exons (where the majority of reads are located). We also indicate for every analyzed base whether it is sufficiently covered for confident identification of point mutations.
(4) Identification of somatic small insertions and deletions (SINDELs)– SINDELs are detected by first identifying putative events looking at the tumor BAM (with high sensitivity but also a high false-positive rate), and then filtering out noisy events and potential germline events (using the normal data).
(5) Identification of inter-chromosomal and large intra-chromosomal structural rearrangements (SRs) – candidate rearrangements are identified as groups of paired-end reads which connect genomic regions with an unexpected orientation and/or distance on the same chromosome or from different chromosomes. Next, the method applies filters to remove germline and false-positive calls.

(6) Calculation of coverage– calculates coverage statistics across the genome broken up according to different genomic zones. The zones include intergenic regions, exons, introns, untranslated regions (UTRs), and promoters. Each zone was further divided into regulatory potential (RP) regions and non-RP regions (see below).
(7) Mutation rate calculation – calculates mutation rates based on the detected mutations (SSNVs and SINDELs) and the coverage statistics. Mutations (and bases) are further partitioned into mutation categories such as mutations in (i) Cs or Gs in CpG dinucleotides, (ii) As or Ts, (iii) other Cs or Gs, (iv) mutations the disrupt the genes such as frameshift SINDELs and non-sense mutations and (v) in-frame SINDELs.
(8) Identification of significantly mutated genes, COSMIC sites, or gene sets – significantly mutated genes/ gene sets are detected by comparing the observed number of mutations (from each category) across the samples to the expected number based on the background mutation rates and the covered bases in all samples.
(9) Identification of significantly mutated regions with regulatory potential (RP regions) – RP regions are identified from a UCSC track. Significantly mutated regions are detected by comparing the observed number of mutations across the samples to the expected number based on the background mutation rates and the covered bases in all samples.
(10) Mutation impact analysis – functional impact (FI) scores for all non-synonymous point mutations were calculated using the xvar.org website (http://xvar.org/). This step is not yet automated and was performed manually.

(1) Quality-control

Matching Individual

Genotypes were determined from SNP6.0 arrays (whenever available for the sample) using the Birdseed algorithm[5]. Homozygous non-reference sites were compared to observed bases for each lane separately. Lanes which had <95% concordance to SNP arrays were excluded from the analysis.

Tumor and Normal Matching

We detected tumor/normal swaps using two methods.

(1) For WGS data, we sequenced two libraries for each sample (tumor and normal). The insert size distribution is a characteristic of the library. Lanes with an insert-size distribution that does not match the distribution of the other lanes generated from the same library are excluded from the analysis.
(2) For WGS and WE data, we compared the copy-number profile of each lane (assessed using the depth of coverage in windows of 100kb along the genome) to the profile determined by SNP or aCGH arrays. Tumor lanes that do not match the expected profile or normal lanes that deviate from the expected flat profile were excluded from the analysis.

Exclusion of tumor-in-normal samples

By studying the copy-number profile of the normal lanes, we were able to detect various levels of contamination of tumor cells in the normal samples (Supplementary Fig. 10). Although patients with frank plasma cell leukemia had been excluded from the study, it was noted that contaminated samples had all been Ficoll purified (potentially selecting for clonotypic cells) and had been donated by patients who had received multiple courses of treatment for MM (and who were therefore at increased risk for extra-medullary disease). As a result of this contamination, we excluded 4 samples that had a high level of tumor-in-normal contamination and kept 3 samples with low level contamination that did not seem to affect our ability to detect somatic events.

(2) Local Realignment

The purpose of this step is to take into account, and ensure the consistency of, all the evidence for an indel available from multiple reads mapped to the same region. When placing reads one-at-a-time (as most short read aligners do, including MAQ that was used for this study) several problems may occur due to indels:

(a) An aligner may not be considering placements with indels at all. For example, MAQ does not consider indels with unpaired sequencing data. Even with paired data, as in this study, when both ends are mapped (potentially sub-optimally) without an indel, MAQ will not further look for a better alignment with an indel.
(b) Even when indels are considered, whenever an indel occurs close to the end of the read, the aligner often prefers a gapless alignment with a few mismatches at the end of the read.
(c) Sequencing errors and/or variations in base qualities in individual reads may result in indels placed inconsistently at different nearby locations, especially in highly repetitive, low-complexity regions.

Often, there is a mixed situation in which some reads place the indel correctly (when it is in the middle of the read) while a few more reads that would have the same indel near the end are placed with mismatches and no gap. Not correcting these placements reduces the ability to detect indels and increases false positive indel and single-nucleotide variation calls.

We applied the IndelRealigner module in GATK (DePristo M. *et al.*, submitted) [http://www.broadinstitute.org/gatk] that performs multiple sequence alignment of reads next to putative indel sites identified by either the presence of an indel in at least one read or a run of consistent consecutive mismatches.

(3) Somatic single nucleotide variation detection

Mutation detection for both whole genome and capture data was performed using a highly sensitive and specific method we have developed in-house called *muTector* (Cibulskis K. *et al.*, in preparation). In brief, muTector consists of three steps.

(1) Preprocessing the aligned reads in the tumor and normal sequencing data. In this step we ignore reads with too many mismatches or very low quality scores since these represent noisy reads that introduce more noise than signal.

(2) A statistical analysis that identifies sites that are likely to carry somatic mutations with high confidence. The statistical analysis predicts a somatic mutation by using two Bayesian classifiers – the first aims to detect whether the tumor is non-reference at a given site and, for those sites that are found as non-reference, the second classifier makes sure the normal does not carry the variant allele. In practice the classification is performed by calculating a LOD score (log odds) and comparing it to a cutoff determined by the log ratio of prior probabilities of the considered events. For the tumors we calculate

$$\mathrm{LOD}_T = \log_{10}\left(\frac{P(\text{observed data in tumor}\,|\,\text{site is mutated})}{P(\text{observed data in tumor}\,|\,\text{site is reference})}\right)$$, and for the normal

$$\mathrm{LOD}_N = \log_{10}\left(\frac{P(\text{observed data in normal}\,|\,\text{site is reference})}{P(\text{observed data in normal}\,|\,\text{site is mutated})}\right).$$

Since we expect somatic mutations to occur at a rate of ~1 in a Mb, we require $\mathrm{LOD}_T > \log_{10}\left(0.5\times10^{-6}\right) \approx 6.3$ which guarantees that our false positive rate, due to noise in the tumor, is less than half of the somatic mutation rate. In the normal, not in dbSNP sites, we require $\mathrm{LOD}_N > \log_{10}\left(0.5\times10^{-2}\right) \approx 2.3$ since non-dbSNP germline variants occur roughly at a rate of 100 in a Mb. This cutoff guarantees that the false positive somatic call rate, due to missing the variant in the normal, is also less than half the somatic mutation rate.

(3) Post-processing of candidate somatic mutations to eliminate artifacts of next-generation sequencing, short read alignment and hybrid capture. For example, sequence context can cause hallucinated alternate alleles but often only in a single direction. Therefore, we test that the alternate alleles supporting the mutations are observed in both directions.

As muTector attempts to call mutations it also generates a coverage file (in a wiggle file format[6], which indicates for every base whether it is sufficiently covered in the tumor and normal to be sensitive enough to call mutations – see section on coverage below). We currently use cutoffs of at least 14 reads in the tumor and at least 8 in the normal (these cutoffs are applied after removing noisy reads in the preprocessing step).

Accuracy of muTector

In order to estimate the specificity of the method, we selected a semi-random set of 100 somatic single nucleotide variations in coding exons. Initial selection was random, but for each gene with more than one mutation, other observed variants were selected for genotyping. We attempted to design Sequenom genotyping assays for these 100 mutations and assay design was successful for 92. 87 of these 92 mutations were validated as somatic mutations (Supplementary Table 4), yielding an estimated true positive rate of 95% (95% CI, 88%-98%). All 5 mutations that failed to be confirmed were not present in the tumor. Larger validation efforts in other datasets have consistently estimated the true positive rate at ~90%.

Effect of coverage on mutation detection and sensitivity

Sensitivity is more challenging to assess than FP rate, owing to the lack of a set of "ground truth" mutations. The mutation rates of *NRAS* and *KRAS* were towards the upper end of the range of their published prevalence in MM, implying good sensitivity in this single case. Sensitivity is not uniform for all genes, however, and is influenced to a large extent by exonic coverage. This, in turn, is influenced by GC content (with lower coverage in more GC-rich areas, often due to difficulty in performing alignment of reads) and, in the case of WES, by whether exons were targeted by the bait and whether the bait was successful in capturing the prey (Supplementary Fig. 11). Non-uniform coverage results in reduced sensitivity for some genes (Supplementary Fig. 12). Thus, for example, our power to detect a mutation with a 20% frequency as significant would be greater than 0.8 for the majority of genes, assuming uniform coverage (Supplementary Fig. 12a). However, the non-uniform coverage results in a greater than 0.8 power for only about half the genes (Supplementary Fig. 12b). In about 17% of genes, the power to detect significant mutations is reduced by more than 80% owing to poor coverage (Supplementary Fig. 12c).

To attempt to better define our sensitivity, we examined the sample for which we had performed both WES and WGS (Supplementary Fig. 2). We first excluded false positive mutations (by manual review of supporting reads). We then assessed the numbers of mutations identified by muTector in WES alone, in both WES and WGS, and in WGS alone. This suggested sensitivities of 67% for WES and 88% for WGS. Reduced sensitivity in WES was entirely due to an absence of targeting by the bait set. When analysis is restricted to targeted regions, the sensitivity of muTector in WES is the same as that in WGS (88%).

Annotation of mutations

(4) Each mutation was annotated with additional information regarding the following parameters.
   (1) The genomic zone – exon, intron, promoter, UTR, intergenic region (IGR).
   (2) Position in protein.
   (3) Mutation type – non-synonymous, silent, splice site.
   (4) Amino acid change.
   (5) Protein domain.

Somatic mutations are listed in Supplementary Table 3.

(4) Detection of short insertions and deletions

Indel calling operates on locally realigned data (see above) and consists of two steps: (i) calling putative indel events (with high sensitivity); (ii) filtering the initial putative calls.

The indel calling step is performed by counting indel events in reads at every locus (in the tumor BAM) and applying basic cutoffs on statistics such as e.g. the indel allele-fraction (fraction of indel-containing reads). These high sensitivity calls are further filtered in the next step by examining additional characteristics of the alignments in the neighborhood such as the average number of mismatches in the reads, distribution of base qualities and others. The events are further annotated as germline or somatic

based on whether any evidence for the event at the same locus is observed in the normal data. Further details will be provided elsewhere (Sivachenko *et al*., in preparation).

Indel validation

We attempted to design Sequenom assays for all called indels. It was possible to design assays for 10/23. Of these, 80% (95% CI 44-97%) were positively validated. Other small indels were subject to manual review of supporting reads using the Integrative Genomic Viewer (IGV; Robinson J. *et al*., in preparation) and false positive calls excluded.

Validated indels are listed in Supplementary Table 4.

(5) Identification of chromosomal rearrangements

Rearrangement detection

For detection of chromosomal rearrangements, we have developed the *dRanger* algorithm (Lawrence M.S. *et al*., in preparation). The first step of the algorithm is identification of groups of read-pairs in the tumor that are discordant, i.e. mapped to locations that are distant from each other in the genome, either on different chromosomes or farther apart on the same chromosome than would be expected from the insert-size distribution of the fragment library (which is typically 400 +/- 50bp). For intra-chromosomal pairs, we use a cutoff of 600bp for pairs of standard orientation (i.e. one read on the forward strand and the other read on the reverse strand and mapped to a later position on the chromosome), and 200bp for pairs of anomalous orientation (any other configuration, including both pairs on the same strand). Each such set of discordant pairs corresponds to a potential rearrangement event. For each set, the matched normal is examined to count how many (if any) read-pairs in the normal also support the event (and thus identify it as a germline, as opposed to a somatic, event). Additionally, a panel of normals is examined, to identify germline events that may have a low detection rate due to poor mapability or other factors. Next, a series of filtering metrics are computed for each potential rearrangement.

(1) The fraction of reads in the vicinity of each endpoint that have mapping quality of zero.
(2) The number of distinct kinds of discordant pairs in the vicinity of each endpoint.
(3) The standard deviation of the starting positions of the supporting reads.

These filtering metrics are combined into an overall quality measure, where 0 indicates a likely artifact and 1 indicates a likely true event. Finally, a score is assigned to each rearrangement by multiplying the number of supporting reads times the quality.

Rearrangements were annotated according to the RefSeq database. For each rearrangement, each endpoint was annotated as to whether it occurred in an intergenic region or a gene, and, if the latter, whether the endpoint was in an intron, a UTR, or an exon. For rearrangements with both endpoints located in genes, the rearrangement was further annotated as to whether it could potentially cause a gene fusion (either in frame or out of frame).

All reported rearrangements were further filtered for their ability to disrupt protein coding of genes (Supplementary Table 3). This is in contrast to their ability to affect normal transcript level, which is harder to predict with confidence. Thus, reported rearrangements include the following: deletions and tandem duplications affecting at least part of one coding exon, but not all coding exons in a gene; inversions with a breakpoint between the ATG and stop codon, but not limited to a single intron; and translocations with a breakpoint between the ATG and stop codon. It should be noted that this filtering will exclude many of the recurrent IgH translocations, in which the breakpoint of the target gene often lies up to 1 Mb away from the transcriptional start site (by contrast, WHSC1 mutations were frequently found, as their breakpoint often lies within the WHSC1 gene).

Assembly of breakpoint sequences

For each predicted rearrangement, the nucleotide-level structure of the chimeric junction was determined using our *BreakPointer* algorithm (Drier Y. *et al*., in preparation). Briefly, the algorithm looks for reads that mapped to either side of the rearrangement and had a pairmate that the aligner was unable to align. These unmapped pairmates are then subjected to a modified Smith-Waterman alignment procedure with the ability to jump between the two reference sequences at the best fitting point.

Rearrangement validation

Large-scale PCR validation in other projects yielded a TP rate of 90% for rearrangements with at least 8 supporting reads, 85% for rearrangements with at least 4 supporting reads, and 80% for rearrangements with at least 2 supporting reads. To increase our specificity, we performed manual review of supporting reads for all reported rearrangements (i.e. those predicted to disrupt protein coding – see above). It should be noted that, compared to PCR validation, the dRanger false positive rate as assessed by manual read review was very similar for rearrangements with high numbers of supporting reads, but much higher for rearrangements with 2 supporting reads (the majority of called rearrangements). It is thus likely that filtering by manual review of supporting reads results in higher specificity but lower sensitivity calls than validation by PCR.

(6) Calculation of coverage

For purposes of determining the significance of observed mutation patterns, a base was defined as being “covered” if there were at least 14 reads that overlapped the position in the tumor and 8 reads in the normal. The number of covered bases was tabulated across the genomes of the WGS samples and the exomes of the WE samples.

Genomic territory was broken down according to a series of criteria. First, the genome was divided into genes and intergenic regions (IGR), according to the RefSeq database. Then, within each gene, the transcribed sequence was divided into exons, introns, and 5’- and 3’-untranslated regions. Furthermore, a “promoter” region was imputed to exist in the 3-kb region directly upstream from the 5’-UTR.

To capture the fact that the genome contains many regions that are highly repetitive or otherwise problematic, genomic territory was further split into "good" and "bad". This was done empirically using the observed characteristics of sequence data from a normal sample (MM-0319). A region was called "bad" if it contained one or more of the following.

(1) A high proportion of reads with mapping quality equal to zero, which is the convention that the aligner program Maq uses to indicate that the read could have been placed at any of a number of equivalent locations in the genome, and that specific position was chosen randomly. This indicates a highly repetitive sequence where variant calls are necessarily unreliable.
(2) A large number of different kinds of discordant pairs.
(3) An extremely high concentration of non-reference bases.

(7) Background mutation rate calculation

To account for the fact that certain base contexts are known to have increased mutation rates, e.g. C residues in CpG dinucleotides , we calculated separate context-specific mutation rates for transitions and transversions affecting CpGs, other C or G, or AT basepairs. We also calculated these rates separately for the various zones (e.g. exon vs. intron, good vs. bad). Although the mutation rate in samples from relapsed patients was higher than in samples from newly diagnosed patients, the difference was not significantly different (Supplementary Fig. 13).

We compared mutation rates in the introns of commonly expressed genes to those in rarely expressed genes in MM. We used the MMRC expression dataset (see below) to divide the genes of the genome into seven categories: (1) expressed in >75% of multiple myeloma samples; (2) expressed in 50-75%; (3) expressed in 25-50%; (4) expressed in 5-25%; (5) expressed in at least one sample and less than 5%; (6) no expression detected in any sample; and (7) no expression data. We then computed intronic somatic mutation rates in these 7 categories. We chose to exclude intronic rates in category (6) because this will include poorly performing probe sets and ubiquitously expressed genes whose basal expression levels are very low and undetectable by Affymetrix profiling (e.g. transcription factors). We also excluded intronic rates in category (7), for obvious reasons. These data are shown in Fig. 1a.

(8) Identification of significantly mutated genes

For analysis of mutation data and identification of significantly mutated genes and extragenic elements, we have developed an algorithm called MutSig (Lawrence *et al.*, in preparation), based in part on methods we have published elsewhere[7, 8]. In brief, we tabulate the number of mutations and the number of successfully sequenced (i.e. "covered") bases for each gene. The counts are broken down by mutation context category (CpG, other C:G, A:T). For each gene, we calculate the probability of seeing the observed constellation of mutations or a more extreme one, given the background mutation rates calculated across the dataset. This is done by convoluting a set of binomial distributions, as described previously[9]. This p-value is then adjusted for multiple hypotheses according to the Benjamini-Hochberg procedure for controlling False Discovery Rate (FDR), obtaining a q-value.

We extended our significance analysis beyond single genes by looking at gene sets. We downloaded the list of canonical pathways used in Gene Set Enrichment Analysis (GSEA). This list contains 639 gene sets corresponding to known pathways or gene families. We considered all pathways that contained at least one gene in the set of genes targeted in WE sequencing, a list of 616 gene sets. For each gene set, we tabulated the number of mutations in the geneset (i.e. mutations occurring in any component gene), as well as the total number of covered bases in all genes in the geneset. Counts were broken down by base-context category as in the single-gene analysis. A p-value was calculated for each gene set as above, and then a q-value was computed to account for the list of 616 hypotheses.

(9) Identification of significantly mutated regions with regulatory potential

In addition to cataloguing all point mutations, small indels, and larger re-arrangements that would disrupt protein coding regions, we wanted to assess whether it was possible to detect non-coding mutations in regulatory regions (promoters, enhancers, silencers, etc.). The genome-wide annotation of these regions is very limited compared to coding regions, so we adopted the following strategy (see also Supplementary Fig. 9).

(1) Define genome-wide regions of "regulatory potential" (RP regions).
(2) Assess the numbers of mutations seen in each RP region for significance and correct for multiple hypothesis testing.
(3) Perform filtering and validation.

Each of these steps is outlined below.

Definition of RP regions

We downloaded the regulatory potential track from the UCSC browser[10, 11] (http://hgdownload.cse.ucsc.edu/goldenPath/hg18/regPotential7X/). See Kolbe *et al.*[11] for full details of how this RP score was defined, but briefly, the method involved training Markov models on three-way (human/mouse/rat) alignments of experimentally defined regulatory regions and three-way alignments of ancestral repeat regions, representing neutral DNA. The model was then applied to a genome-wide three-way alignment and the RP score calculated from the log-ratios of the transition probabilities of the two Markov models at any given position.

The RP scores as downloaded represent base-to-base scores. To define our RP regions, we processed the scores by passing a sliding window of 100 bp over each chromosome, moved at increments of 10 bp, and taking transitions between zero and any nonzero score to be the boundaries. This procedure yielded a list of a total 2.38 million RP regions for the entire hg18 genome.

We compared the background mutation rates in the RP and non-RP regions from WGS. We found lower observed somatic mutation rates in RP regions compared to non-RP regions (Supplementary Fig. 14). This effect persisted even when controlling for base context, with the difference being seen for each individual base-context category.

Assessing RP regions for significance

For each RP region, we calculated the number of mutations observed across the panel of 23 patients sequenced by WGS, and the number of covered bases. We performed a p-value calculation and an FDR correction for the 2.38 million hypotheses. This yielded a list of RP regions ranked by significance level.

Filtering and validation

We noted that many of the top regions were situated in the various immunoglobulin loci (IgH, Igκ, and Igλ), known to be targeted by somatic hypermutation. We also observed a region spanning the promoter, first non-coding exon, and part of the first intron of *BCL6*, another region known to undergo somatic hypermutation[12]. This identification of known regions of somatic hypermutation, shown in Supplementary Table 9, was encouraging, but we were keen to identify mutations in regulatory regions that may be drivers of MM pathogenesis. We therefore repeated the analysis following masking of known regions of somatic hypermutation. This yielded 116 regions with $q < 0.25$. We excluded 37 regions because all of the mutations were confined to a single sample. We further excluded one region that included the first coding exon of NRAS and in which all 5 mutations were non-synonymous coding mutations within this exon.

We then performed manual review of the supporting reads for the remaining regions. This excluded 60 regions, leaving 18 potential significantly mutated regulatory regions (Table 2). 11/18 of these regions were subjected to validation by PCR and Sanger sequencing (PCR primers and conditions are shown in Supplementary Table 11). All 11 tested sets of mutations were validated as true positives, confirming high specificity of filtering by manual review.

(10) Assessment of the functional impact of mutations

For each mutation, we obtained an estimate of the likelihood that the mutation impacts the protein functionally, using the xvar.org website (http://xvar.org; B. Reva, personal communication) to calculate a Functional Impact (FI) score[13]. We compared the distribution of these FI scores across the mutations found in significantly mutated genes vs. all other genes by the Kolmogorov-Smirnov test (Fig. 1b). To exclude the possibility that the difference was due to mutations in any single highly conserved gene, we repeated the calculation, sequentially leaving out each gene (and both genes for NRAS and KRAS). For each leave-one-out test, the difference remained significant. To test whether the significant difference was due to the set of genes or set of mutations within those genes, we generated FI scores for all possible mutations in the 10 significantly mutated genes and compared this distribution to the FI scores for the observed set of mutations within those genes. The observed FI scores were significantly higher than the null distribution of null FI scores , suggesting that the mutations themselves were targeting functional regions within the genes (data not shown).

Other methods

Publicly available expression and copy number datasets

Two expression datasets were used. One, from the University of Arkansas (n=414), was derived from newly diagnosed patients with MM[14]. The second, from the Multiple Myeloma Research Consortium (MMRC; n=304), was derived from a mix of newly diagnosed and previously treated patients with MM. Both were obtained using the Affymetrix U133 Plus 2.0 arrays and both are available for download from the Multiple Myeloma Genomics Portal (MMGP; http://www.broadinstitute.org/mmgp). The copy number dataset (n=254) is also from the MMRC and is derived from a subset of the same patients contributing to the expression dataset. It was obtained using the Agilent 244K aCGH platform. It is available for download from the MMGP.

Gene set enrichment analysis (GSEA) for FAM46C co-expressed genes

GSEA was performed using version 2.06 (http://www.broadinstitute.org/gsea/downloads.jsp). The gene list was constructed by ranking of Pearson correlation of expression with FAM46C (probe set 226811_at). The tested datasets were derived from the 639 C2 Canonical Pathways (http://www.broadinstitute.org/msigdb/index.jsp). They were filtered for size according to the default settings (range 15-500), yielding 395 genesets. P-values were obtained by permutation (n=100) and adjusted for multiple hypotheses according to the Benjamini-Hochberg procedure for controlling FDR, yielding a q-value.

Outlier sum statistic (OSS) calculation

A variant of the OSS[15] was used. For calculation of the OSS, samples are divided into two groups and the OSS calculated on a metric in one of the groups. In this case, it was reasoned that it would be informative to look for outlier events occurring in MM samples lacking an obvious driver. Samples were therefore segregated based on presence or absence of a recurrent IgH translocation (targeting one of CCND1, CCND3, FGFR3/WHSC1, MAF, or MAFB), for which expression data can provide an accurate surrogate[16]. Thus segregated, the OSS was applied as described for each probe set in the expression dataset. As the OSS may be driven by both the levels of gene expression in outliers and by the number of outliers, the ranked list of genes was prioritized by a second measure. For this, a permutation test (n=1000) was applied and the observed OSS compared to a null distribution of OSS. Note that this procedure does not yield a p-value, owing to the sparse distribution of outliers in the dataset. Nonetheless, it afforded a useful prioritization of potential driver genes and genes were filtered for a permutation score of less than 0.05. The top 20 hits are shown in Supplementary Table 12. *HOXA9* was ranked number 3 behind a pseudogene (TSPY6P) and a hypothetical protein gene (LOC283352), so was prioritized for further investigation.

The pattern of outlier *HOXA9* expression in MM is shown in Supplementary Figure 4a. Some further explanatory comments are worth making about this figure. Different normalization methods were applied to the raw microarray images in the Arkansas and MMRC/cell line datasets (MAS5 for Arkansas,

robust multi-array analysis – RMA – for MMRC and cell lines). It is likely that this accounts for apparent differences in *HOXA9* outlier expression values between Arkansas and MMRC/cell line datasets. However, the frequency of outliers was the same (10%) in both the Arkansas dataset and the MMRC dataset. The normalized outlier expression values span a very wide range in both datasets and some are expressed only a little higher than the level of noise. Hence these may not be obvious when plotted. However, qPCR of *HOXA9* (Supplementary Fig. 4b; see below) shows ubiquitous expression and the outliers are reliably differentiated from non-outliers by this method. Ubiquitous expression of transcription factors at a level undetectable by microarrays appears to be a common event (unpublished observations based on RNA sequencing).

It will be important to assess correlation between HMT mutation status and *HOXA9* expression. However, there is insufficient power to investigate this relationship. Nevertheless, we would hypothesize that histone modifying gene mutation would drive bi-allelic expression, which is associated with non-outlier status (Supplementary Fig. 4c). In these cases, we do see abnormal H3K27Me3 enrichment (Fig. 3a), which is negatively correlated with expression levels (Fig. 3b). As noted in the main text, outlier status is associated with mono-allelic expression (Supplementary Fig. 4c), which suggests a *cis*-activating mechanism in these cases.

Focal amplifications of the HOXA locus are seen in about 5% of patients. Some of these are associated with outlier expression status of *HOXA9*. There are, however, samples with outlier expression and no amplification and *vice versa*. We would speculate that small increases of *HOXA9* achieved by a 1 or 2 copy number gain may be beneficial to MM cells (we do not have sufficient RNA from outlier samples to test this relationship), but that this would be insufficient to drive very high levels of expression. This phenomenon would account for samples with amplification but not outlier expression. On the other hand, a *cis*-activating event might be sufficient to drive high expression and would not require an amplification, accounting for those samples with very high expression but lacking an amplification. For those in which both phenomena are seen, one might expect that a proportion of the samples with a *cis*-activating event would subsequently amplify the affected region as this would provide a further selective advantage.

It will also be important to assess the relationship between histone modifying gene mutations and the histone methyl marks. This is beyond the scope of this study as we do not possess the relevant samples to assess the latter in the patients whose DNA was sequenced. Conversely, establishing mutation status in MM cell lines, in which we do have data on histone methylation status, is not possible with current mutation detection algorithms as these are unable to differentiate private SNPs from somatic mutations in the absence of matched normal DNA.

Cell lines

The following MM cell lines were used in the study: H929, INA6, JIM3, KMS11, KMS12-BM, KMS12-PE, L363, MM.1S, OPM2, OCI-My5, OCI-My7, SKMM1, U266, and XG6. For allele-specific expression in AML, the cell line MOLM14 was used. All cells were grown in RPMI 1640 media (Fisher Scientific)

supplemented with 10% fetal bovine serum (Sigma Aldrich). Media for INA6 and XG6 were supplemented with 2 ng/ml IL-6 (R and D Systems). Cells were grown at 37°C in 5% CO_2.

RT-PCR

As outlined in the main text, a statistically significant collection of mutations was discovered amongst members of the extrinsic clotting pathway. RT-PCR was used to assess whether these coagulation factors were expressed in MM cell lines. F5 expression was not assessed, as F5 is known to be expressed in cells of the lymphocytic lineage. RNA was extracted using a mini-prep kit (Qiagen). DNase digestion was performed if genomic DNA bands subsequently proved problematic. cDNA was produced using a first strand synthesis kit (Promega) and PCR was performed. Forward and reverse primers were designed to different exons so that cDNA and genomic DNA bands could be distinguished. Primer sequences and conditions of the reactions are shown in Supplementary Table 13. Positive control cDNA was obtained from dermal fibroblasts (F3) or whole liver extract (the remainder). An LDHA control was included to ensure approximately equal loading of cDNA. Results are shown in Supplementary Fig. 8.

Assessment of HOXA9 protein expression

Immunoblotting was performed using an anti-HOXA9 antibody (Millipore). The correct band size was ascertained by reference to published data with the same antibody[17] and by retroviral overexpression of HOXA9. An antibody against β-actin (Cell Signaling Technology) was used as a loading control.

Assessment of HOXA9 mRNA expression

RNA was extracted from cells using a miniprep kit (Qiagen) according to manufacturer's instructions. First strand synthesis and real-time PCR (RT-qPCR) were performed using a one-step kit on a 7900 thermal cycler and an inventoried probe-primer set, Hs00365956_m1 (all Applied Biosystems) using the ΔΔCT protocol, according to the manufacturer's instructions. β-actin (Applied Biosystems) was used as an endogenous loading control. For assessment of basal expression levels, expression was reported relative to that in the lowest expressing cell line (JIM3). For assessment of knock-down, expression was reported relative to that in cells infected with the control hairpin, shLuc. As aberrant patterns of H3K27Me3 enrichment were also seen in the promoters of the *HOXA9* flanking genes (*HOXA7* and *HOXA10*), gene expression of these was assessed by the same method. However, *HOXA7* and *HOXA10* expression was found to be completely absent (data not shown).

Chromatin immunoprecipitation (ChIP) assay for histone 3 lysine 27 trimethyl (H3K27Me3) promoter enrichment

ChIP was performed as described[18] (also, Adli *et al*., in preparation). ~0.5-1.0x10^7 cells were crosslinked with 1% formaldehyde for 10 minutes at 37°C. Cells were quenched with glycine for 5 minutes and washed twice with ice cold PBS. Cell pellets were re-suspended in 500 μl of lysis buffer (1% SDS, 10mM EDTA, 50mM Tris-HCl, ph 8.1) and incubated on ice for 10 minutes. The lysate was diluted by adding 500 μl ChIP dilution buffer (0.01% SDS, 1.1% Triton X-100, 1.2mM EDTA, 16.7mM Tris-HCl, ph 8.1). The

chromatin was sonicated for 5 minutes using a Branson 250 sonicator at 40% power amplitude (pulses: 0.7 seconds on, 1.3 seconds off). Chromatin was then immunoprecipitated overnight in a total volume of 10ml ChIP dilution buffer containing protease inhibitor cocktails (Roche) with 10 μg H3K27Me3 (Millipore). Enrichment was detected at the *HOXA9* promoter by SYBR Green qPCR (primers: CGCTCTCATTCTCAGCATTG sense; CCACGCTTGACACTCACACT antisense).

HOXA9 knock-down

shRNA constructs

shRNAs cloned into vector pLKO.1 were obtained from The RNAi Consortium (TRC), via Open Biosystems (http://www.openbiosystems.com/RNAi/shrnaLibraries/). shRNAs have been named according to the first base targeted in the human cDNA. A shRNA targeting luciferase (shLuc) was used as a negative control. For GFP competition experiments, the puromycin cassette of pLKO.1 was replaced by eGFP by cloning into the BamHI/KpnI sites.

Generation of virus for knock-down

Virus was produced according to TRC protocols (http://www.broadinstitute.org/rnai/public/resources/protocols). Briefly, HEK 293T cells were co-transfected with shRNA plasmid and packaging plasmids containing gag, tat, rev, and VSV-G genes. Virus was harvested at 40 hours post-infection, passed through 0.45 μm filters, and used fresh for shRNA infection.

Assessing degree of HOXA9 knock-down

Cells at $4x10^6$/ml were infected in 6-well dishes. $2x10^6$ cells per well were plated with 2 ml fresh virus and Polybrene (hexadimethrine bromide; Sigma Aldrich) to a final concentration of 8 μg/ml (1 μg/ml for XG6, which was sensitive to higher concentrations). Spinoculation at 750 g for 30 minutes was performed. Media was replaced at 24 hours ± puromycin dihydrochloride (Sigma Aldrich) at 2.5 μg/ml. Infection efficiencies in excess of 80% were confirmed by comparing viable cell counts in puromycin-selected *versus* non-selected cultures (mock-infected cells ensured efficacy of puromycin). RNA was obtained 72 hours post-infection and cell lysates were obtained at 120 hours post-infection, prior to any hairpin effects on viability being observed. Residual cell cultures were continued for up to 2 weeks to ensure correlation of hairpin effects with effects observed in phenotypic assays. *HOXA9* mRNA and protein was assessed as described above. Degree of knock-down was determined by comparing *HOXA9* expression in response to infection with a particular shRNA *versus HOXA9* expression in cells that had been infected with shLuc.

Assessing effects of HOXA9 knockdown

Cells were plated in replicates in 96-well plate format with fresh virus at multiple titers and Polybrene to a final concentration of 8 μg/ml (1 μg/ml for XG6). Spinoculation at 900 g for 90 minutes was performed. Media was then immediately refreshed. Cells were assessed at 72 hours on a BD-LSR II flow cytometer

(Becton Dickinson). Dead cells were excluded using a forward-scatter/side-scatter gating strategy that had been determined in a previous optimization experiment using 7-AAD (Becton-Dickinson). Proportion of infected cells was assessed by measuring GFP on a single channel. For each cell line/shRNA combination, replicates from a single titer were selected for further assessment. The titer selected was that which achieved closest to 50% GFP+ cells at 72 hours. GFP+ proportion was then measured every 96 hours for two weeks and expressed relative to the proportion at 72 hours (designated day 0; Fig. 3c and Supplementary Fig. 6). In a separate confirmatory experiment, cells were plated in 96-well format as described above using the minimal viral titer that had been shown to achieve 80% infection efficiency at 72 hours. Cell viability was then assessed at 72 hours (baseline) using CellTiter-Glo (Promega) and at two subsequent time-points (Supplementary Fig. 5 and data not shown).

We note that the levels of mRNA and protein knock-down do not correlate well. This is a frequently observed phenomenon and the levels of protein knock-down are the more important to consider[19]. Nevertheless, there remains some disconnect between the levels of protein knock-down and the severity of the phenotype. Even though many of these hairpins have been previously validated for specific effects in MLL leukemia, including a rescue experiment[17], it is possible that some exhibit an element of off-target toxicity. Nevertheless, it is highly unlikely that all of the effects of all of the hairpins are non-specific. Importantly, no hairpin was found that knocked down HOXA9 and which had no effect on MM cell line viability.

Determination of DIS3 and FAM46C mutation status in cell lines

To identify suitable models for future functional characterization of DIS3 and FAM46C mutations, we determined the mutation status in several MM cell lines. For DIS3, we only examined the catalytic RNB domain, in which we had observed all the mutations in the primary patient samples. We performed PCR on cDNA (DIS3) or genomic DNA (FAM46C) with tiled primer pairs (primer sequences and reaction conditions in Supplementary Table 14). We then performed Sanger sequencing using the same primers. 2/15 tested cell lines had point mutations in the DIS3 RNB domain (Supplementary Table 15). Both mutations were associated with loss of the other allele *via* chromosome 13 deletion. 4/16 tested cell lines had mutations in FAM46C (Supplementary Table 16). Two were point mutations and two were indels resulting in a frame-shift. 3/4 mutations were associated with loss of the other allele *via* 1p deletion. A fifth FAM46C mutation in an additional cell line (LP1) was identified by examining 244K aCGH profiles of MM cell lines (Supplementary Table 16). This comprised focal bi-allelic loss of the 5' end of the gene and was associated with absent FAM46C expression (FAM46C is otherwise ubiquitously expressed in MM). These data suggest that the FAM46C mutations result in loss of function.

References

1. Gnirke, A., et al. Solution hybrid selection with ultra-long oligonucleotides for massively parallel targeted sequencing. *Nat Biotechnol*. **27**, 182-9 (2009).
2. Ewing, B., et al. Base-calling of automated sequencer traces using phred. I. Accuracy assessment. *Genome Res*. **8**, 175-85 (1998).

3. Li, H., Ruan, J., and Durbin, R. Mapping short DNA sequencing reads and calling variants using mapping quality scores. *Genome Res*. **18**, 1851-8 (2008).
4. Reich, M., et al. GenePattern 2.0. *Nat Genet*. **38**, 500-1 (2006).
5. Korn, J.M., et al. Integrated genotype calling and association analysis of SNPs, common copy number polymorphisms and rare CNVs. *Nat Genet*. **40**, 1253-60 (2008).
6. Rhead, B., et al. The UCSC Genome Browser database: update 2010. *Nucleic Acids Res*. **38**, D613-9
7. Ding, L., et al. Somatic mutations affect key pathways in lung adenocarcinoma. *Nature*. **455**, 1069-75 (2008).
8. Comprehensive genomic characterization defines human glioblastoma genes and core pathways. *Nature*. **455**, 1061-8 (2008).
9. Getz, G., et al. Comment on "The consensus coding sequences of human breast and colorectal cancers". *Science*. **317**, 1500 (2007).
10. King, D.C., et al. Evaluation of regulatory potential and conservation scores for detecting cis-regulatory modules in aligned mammalian genome sequences. *Genome Res*. **15**, 1051-60 (2005).
11. Kolbe, D., et al. Regulatory potential scores from genome-wide three-way alignments of human, mouse, and rat. *Genome Res*. **14**, 700-7 (2004).
12. Migliazza, A., et al. Frequent somatic hypermutation of the 5' noncoding region of the BCL6 gene in B-cell lymphoma. *Proc Natl Acad Sci U S A*. **92**, 12520-4 (1995).
13. Reva, B., Antipin, Y., and Sander, C. Determinants of protein function revealed by combinatorial entropy optimization. *Genome Biol*. **8**, R232 (2007).
14. Zhan, F., et al. The molecular classification of multiple myeloma. *Blood*. **108**, 2020-8 (2006).
15. Tibshirani, R. and Hastie, T. Outlier sums for differential gene expression analysis. *Biostatistics*. **8**, 2-8 (2007).
16. Bergsagel, P.L. and Kuehl, W.M. Molecular pathogenesis and a consequent classification of multiple myeloma. *J Clin Oncol*. **23**, 6333-8 (2005).
17. Faber, J., et al. HOXA9 is required for survival in human MLL-rearranged acute leukemias. *Blood*. **113**, 2375-85 (2009).
18. Ku, M., et al. Genomewide analysis of PRC1 and PRC2 occupancy identifies two classes of bivalent domains. *PLoS Genet*. **4**, e1000242 (2008).
19. Sahin, O., et al. Combinatorial RNAi for quantitative protein network analysis. *Proc Natl Acad Sci U S A*. **104**, 6579-84 (2007).

Sample ID	Age at Diagnosis	Gender	Race	Heavy chain class	Light chain class	Hyperdiploidy (HD) and/or IgH translocation	Other cytogenetics	Treatment status	Sequencing method
MMRC0004	36	Male	Caucasian	IgG	Kappa			Untreated	WE
MMRC0028	44	Male	Caucasian	IgG	Not available	t(4;14)	del 13q14	Untreated	WE
MMRC0173	41	Female	Asian	Not available	Not available	HD	del 13q14	Treated	WGS
MMRC0191	56	Female	African American	IgG	Lambda	HD		Treated	Both
MMRC0216	59	Female	Caucasian	Cannot assign	Kappa	HD		Untreated	WE
MMRC0242	71	Male	Hispanic	IgG	Lambda	Not available	del 13q14	Treated	WGS
MMRC0244	56	Female	Caucasian	IgG	Kappa	HD		Untreated	WE
MMRC0282	60	Male	Caucasian	Not detected	Kappa	HD	del 13q14	Treated	WE
MMRC0284	41	Male	Caucasian	Cannot assign	Kappa	t(11;14)		Untreated	WE
MMRC0286	50	Female	Caucasian	IgA	Kappa	t(14;16)	del 13q14	Untreated	WE
MMRC0308	55	Female	Caucasian	IgG	Lambda	t(4;14)	del 13q14	Treated	WE
MMRC0309	61	Male	Caucasian	IgA	Lambda	t(14;16)	del 13q14	Untreated	WGS
MMRC0319	55	Male	Caucasian	IgM	Kappa	HD; t(4;14)		Untreated	WGS
MMRC0322	69	Male	Caucasian	IgG	Kappa	Not available	del 13q14	Untreated	WE
MMRC0329	37	Female	Caucasian	IgG	Kappa	HD	del 13q14**	Treated	WE
MMRC0332	66	Male	Caucasian	IgG	Lambda	HD; t(4;14)		Treated	WGS
MMRC0335	56	Male	Caucasian	IgA	Kappa	t(11;14)		Treated	WGS
MMRC0338	63	Male	Caucasian	IgG	Kappa	Not available		Untreated	WGS
MMRC0343	62	Male	Caucasian	Not detected	Kappa	t(11;14)	del 13q14; del 17p13	Treated	WGS
MMRC0344	69	Female	Caucasian	IgG	Lambda	Not available		Treated	WGS
MMRC0347	58	Male	Caucasian	IgG	Lambda	t(11;14)	del 17p13	Untreated	WE
MMRC0356	52	Male	Hispanic	IgG	Kappa	HD; t(11;14)*	del 13q14	Untreated	WGS
MMRC0359	63	Male	Caucasian	IgG	Kappa	t(11;14)	del 13q14; del 1p32	Untreated	WE
MMRC0375	72	Male	Caucasian	IgA	Kappa	t(11;14)	del 13q14	Treated	WGS
MMRC0376	56	Male	Caucasian	IgA	Kappa	t(4;14)	del 13q14	Untreated	WGS
MMRC0381	72	Male	Caucasian	IgG	Kappa	HD	del 13q14	Untreated	WE
MMRC0383	69	Male	Caucasian	IgG	Kappa	t(11;14)	del 13q14	Treated	WGS
MMRC0387	60	Female	Caucasian	IgG	Kappa	HD		Untreated	WGS
MMRC0389	37	Male	Caucasian	IgE	Kappa	HD; t(14;20)	del 13q14	Treated	WGS
MMRC0390	71	Female	Caucasian	IgG	Lambda	t(11;14)		Treated	WGS
MMRC0392	59	Male	Caucasian	IgG	Lambda	HD; t(6;14)	del 13q14	Treated	WGS
MMRC0406	59	Female	Caucasian	IgA	Kappa	HD		Untreated	WGS
MMRC0408	58	Male	Caucasian	IgA	Lambda	HD	del 1p32**	Untreated	WGS
MMRC0412	49	Male	Caucasian	IgG	Kappa	HD	del 1p32	Treated	WGS
MMRC0421	45	Male	Caucasian	IgA	Not available	t(4;14)		Treated	WGS
MMRC0423	51	Male	African American	IgA	Kappa			Treated	WE
MMRC0425	65	Female	Caucasian	IgG	Kappa	Not available		Untreated	WGS
MMRC0427	62	Male	Other	IgG	Lambda	t(11;14)	del 13q14	Treated	WE

*Spiked CCND1 expression absent, despite t(11;14)
** Focal bi-allelic deletion at *CDKN2C* or *RB1*

Supplementary Table 1 – Clinical characteristics of patients providing samples for sequencing. Hyperdiploidy and IgH translocations were determined by FISH and/or aCGH and/or gene expression profiles. Treatment status refers to whether the patient had received treatment at the time of sample donation.

	Whole Genome (n = 23)		Whole Exome (n = 16)		Total (n = 39)	
	Total	**Mean**	**Total**	**Mean**	**Total**	**Mean**
Nonsynonymous point mutations						
Missense	721	31.3	416	26.1	1141	29.3
Nonsense	49	2.1	25	1.6	74	1.9
Splice site	22	1.0	7	0.4	29	0.7
Read-through	1	0.04	0	0	1	0.03
	793	**34.6**	**448**	**28.1**	**1245**	**31.9**
Small indels						
Frame-shift deletion	5	0.2	4	0.3	9	0.2
In-frame deletion	5	0.2	2	0.1	7	0.2
Frame-shift insertion	2	0.09	2	0.1	4	0.1
In-frame insertion	1	0.04	0	0	1	0.03
	13	**0.6**	**8**	**0.5**	**21**	**0.5**
Larger rearrangements						
Translocations	204	8.7	N/A		N/A	
Deletions	105	4.6	N/A		N/A	
Insertions	23	1.0	N/A		N/A	
Tandem duplications	32	1.4	N/A		N/A	
Long-range	78	3.4	N/A		N/A	
Complex	33	1.4	N/A		N/A	
	475	**20.7**				

Supplementary Table 2 – Somatic events disrupting protein-coding regions. Only rearrangements with a breakpoint resulting in the disruption of protein coding are included. Long-range events are those with breakpoints separated by more than 1 Mb. Complex rearrangements are those involving two or more separate events.

Gene	Chr	Position (strand)	2nd gene	Chr	Position (strand)	Type	AA change	Sample	Previously treated
A2M	12	9139481				Missense	R645H	MMRC0332	Treated
AADAT	4	171219720				Splice site	V379_splice	MMRC0427	Treated
AASS	7	121528670				Missense	R466Q	MMRC0392	Treated
ABCA12	2	215583394				Missense	A793D	MMRC0322	Untreated
ABCA12	2	215532039				Missense	M1965L	MMRC0356	Untreated
ABCA13	7	48362407				Missense	R3435W	MMRC0191	Treated
ABCC1	16	16020092(+)	PRKCB	16	23931585(-)	Long range		MMRC0344	Treated
ABCE1	4	146260624				Missense	N338S	MMRC0381	Untreated
ACAD11	3	133858909(+)	NPHP3	3	133885257(-)	Deletion		MMRC0191	Treated
ACAD9	3	130096876				Missense	R127K	MMRC0389	Treated
ACBD3	1	224439435(-)		1	224458761(+)	Tandem duplication		MMRC0421	Treated
ACBD5	10	27537271				Missense	E403D	MMRC0389	Treated
ACOXL	2	111315566(-)		23	105246739(-)	Translocation		MMRC0191	Treated
ACTL6A	3	180770623				Missense	D17E	MMRC0425	Untreated
ACTN3	11	66086153				Missense	A754T	MMRC0412	Treated
ACTRT1	X	127013232				Missense	V212A	MMRC0191	Treated
ADAD1	4	123561875				Missense	F488L	MMRC0376	Untreated
ADAM17	2	9562800				Frame shift deletion	G486fs	MMRC0427	Treated
ADAM17	2	9585504				Missense	D161N	MMRC0191	Treated
ADAM18	8	39610001(+)		8	40122511(-)	Deletion		MMRC0332	Treated
ADAM18	8	39644716				Missense	E457K	MMRC0338	Untreated
ADAM22	7	87405341(+)		7	93095395(+)	Long range		MMRC0425	Untreated
ADAM29	4	176134318				Missense	M356T	MMRC0425	Untreated
ADAM9	8	38984621				Missense	R53G	MMRC0347	Untreated
ADAMTS1	21	27134136				Missense	G594A	MMRC0387	Untreated
ADAMTS18	16	75947338				Missense	S487I	MMRC0191	Treated
ADAMTS19	5	128960221				Missense	N475K	MMRC0332	Treated
ADAMTS2	5	178602608(+)		5	178711536(-)	Deletion		MMRC0408	Untreated
ADAMTS20	12	42063959				Missense	D1514G	MMRC0335	Treated
ADAMTS8	11	129781224				Nonsense	Y703*	MMRC0191	Treated
ADAMTS9	3	64555038				Missense	R1431H	MMRC0425	Untreated
ADAMTS9	3	64594464				Missense	N663T	MMRC0425	Untreated
ADAMTSL1	9	18896858				Missense	W1710C	MMRC0332	Treated
ADAMTSL3	15	82357635				Missense	G497R	MMRC0329	Treated
ADCY2	5	7810576				Missense	K657N	MMRC0375	Treated
ADCY2	5	7837525				Missense	S811F	MMRC0412	Treated
ADNP	20	48942218				Missense	D814N	MMRC0282	Treated
ADNP2	18	75995981				Missense	L565S	MMRC0319	Untreated
AFAP1	4	7827366				Missense	G604S	MMRC0387	Untreated
AFAP1L1	3	143784143(+)		5	148692173(-)	Translocation		MMRC0191	Treated
AFF1	4	88085017(+)		4	88133105(-)	Deletion		MMRC0332	Treated
AFG3L2	18	12341180				Missense	I486V	MMRC0309	Untreated
AGAP2	12	56414108				Missense	G506E	MMRC0389	Treated
AGBL4	1	49116754(+)		1	76244110(-)	Long range		MMRC0412	Treated
AHNAK2	5	128274788(+)		14	104511997(-)	Translocation		MMRC0191	Treated
AIM1L	1	26536734				Missense	P131T	MMRC0376	Untreated
AKAP6	14	32085771				Missense	L721I	MMRC0347	Untreated
AKAP6	14	32084721				Nonsense	R371*	MMRC0406	Untreated
AKR1B15	7	133903503				Nonsense	Y40*	MMRC0408	Untreated
ALCAM	3	106653896(+)		3	155190940(-)	Long range		MMRC0191	Treated
ALCAM	3	106606779(-)		5	96552937(-)	Translocation		MMRC0375	Treated
ALDH1A2	15	56122206(-)		17	50044110(+)	Translocation		MMRC0191	Treated
ALDH1L1	3	127356171				Missense	N212K	MMRC0319	Untreated
ALDH1L2	12	103983243				Missense	E240K	MMRC0344	Treated
ALMS1	2	73533019				Missense	Q1952K	MMRC0412	Treated
ALOX12B	17	7919747				Missense	E515D	MMRC0392	Treated
ALOX12B	17	7920252				Missense	D500N	MMRC0392	Treated
ALOX12B	17	7924355				Missense	L226P	MMRC0173	Treated
ALOX12B	17	7916890(+)	SLC37A1	21	42832836(+)	Translocation		MMRC0392	Treated
ALOX15B	17	7884260(-)	MYH10	17	8412781(-)	Inversion		MMRC0392	Treated
ALOX15B	17	7884094(+)	PIGL	17	16114874(+)	Long range		MMRC0392	Treated
ALOXE3	17	7950718(-)	NTN1	17	8927833(-)	Inversion		MMRC0392	Treated
ALOXE3	17	7951129(+)	SLC37A1	21	42833530(-)	Translocation		MMRC0392	Treated
ALPK2	18	54387075(+)		18	54415713(-)	Deletion		MMRC0319	Untreated
AMT	3	49431460				Missense	N275K	MMRC0392	Treated
ANGPTL5	11	101276446				Nonsense	Q196*	MMRC0344	Treated
ANK2	4	114190342				Missense	N3K	MMRC0329	Treated
ANK2	4	114488891				Missense	S1461L	MMRC0389	Treated
ANK2	4	114494274				Missense	P1684Q	MMRC0389	Treated

Supplementary Table 3 – All somatic mutations qualitatively affecting protein coding. Included are point mutations, small indels, and larger rearrangements with breakpoints within genes. Complex rearrangements (as detailed in figure 1b) have been expanded into individual events.

Gene	Chr	Position (strand)	2nd gene	Chr	Position (strand)	Type	AA change	Sample	Previously treated
ANKRD30A	10	37548386				Missense	E1191A	MMRC0242	Treated
ANKRD30A	10	37476319				Missense	S435P	MMRC0389	Treated
ANKRD50	4	125811674				Missense	D736E	MMRC0390	Treated
ANKRD57	2	109730452				Missense	A366V	MMRC0359	Untreated
ANO3	11	26503799				Missense	G245V	MMRC0421	Treated
ANO6	12	43982136				Missense	P48L	MMRC0338	Untreated
ANTXR2	4	81016850(+)		4	81067994(-)	Deletion		MMRC0191	Treated
ANXA13	8	124766077				Missense	G262E	MMRC0421	Treated
ANXA2	15	58433523(+)		15	58451240(-)	Deletion		MMRC0376	Untreated
ANXA2	15	58431220				Missense	N258S	MMRC0421	Treated
AP1M1	19	16199994				Missense	H288P	MMRC0191	Treated
APOH	17	61641168				Missense	Q283E	MMRC0389	Treated
AQP7	9	33375852				Missense	G180R	MMRC0375	Treated
ARHGAP15	2	142931546(+)		2	143720455(-)	Deletion		MMRC0389	Treated
ARHGAP26	5	142220883(-)		16	66403657(+)	Translocation		MMRC0425	Untreated
ARHGEF10	8	1830101				Missense	E466K	MMRC0387	Untreated
ARHGEF15	17	8163084				Missense	R690C	MMRC0392	Treated
ARHGEF3	3	56764144				Frame shift insertion	P99fs	MMRC0381	Untreated
ARID1A	1	26967029				Missense	D1050E	MMRC0356	Untreated
ARID2	12	44540952				Missense	M1625I	MMRC0286	Untreated
ARID3C	9	34613427				Missense	K287M	MMRC0319	Untreated
ARID4A	14	57842916(+)	KIAA0586	14	58046228(-)	Deletion		MMRC0319	Untreated
ARL15	5	53635635(+)		14	55603989(-)	Translocation		MMRC0191	Treated
ARMC9	2	231835342				Missense	Y369F	MMRC0282	Treated
ARNTL2	12	27412578				Nonsense	R50*	MMRC0028	Untreated
ARPP-21	3	35700306				Missense	D86Y	MMRC0338	Untreated
ARRDC1	9	139629369				Missense	Q420H	MMRC0286	Untreated
ASB15	7	123057383				Missense	E523G	MMRC0242	Treated
ASH1L	1	153715219				Missense	KM1355>NL	MMRC0412	Treated
ASH1L	1	153580068				Nonsense	R2691*	MMRC0381	Untreated
ASH2L	8	38091659				Missense	F254S	MMRC0329	Treated
ASNS	7	97320361				Missense	T475A	MMRC0335	Treated
ASPM	1	195328870				Missense	I3077F	MMRC0383	Treated
ATAD3A	1	1445795				Missense	A277P	MMRC0375	Treated
ATG2A	11	64431333				Missense	K934N	MMRC0173	Treated
ATG7	3	11447811(-)	AATK	17	76734959(+)	Translocation		MMRC0387	Untreated
ATM	11	107629789				Nonsense	S646*	MMRC0191	Treated
ATOH1	4	94970059				Missense	L320S	MMRC0309	Untreated
ATOH8	2	85835519				Missense	R232S	MMRC0427	Treated
ATP10B	5	159982131				Missense	V554I	MMRC0335	Treated
ATP1A4	1	158411149				Missense	G767R	MMRC0244	Untreated
ATP2C1	3	131545181(-)		3	132163563(+)	Tandem duplication		MMRC0425	Untreated
ATP4B	13	113351788				Missense	A260T	MMRC0406	Untreated
ATP6V0A1	1	224308027(-)		17	37879120(-)	Translocation		MMRC0425	Untreated
ATP6V1C2	2	10835279				Missense	E315Q	MMRC0392	Treated
ATP7B	8	68849483(-)		13	51448093(+)	Translocation		MMRC0319	Untreated
ATP8B4	15	47999826				Missense	W611S	MMRC0242	Treated
ATP9A	20	49815595(-)	SALL4	20	49839479(-)	Inversion		MMRC0332	Treated
AUTS2	7	69233117(+)		7	69445909(-)	Deletion		MMRC0332	Treated
AXIN2	17	60899765(+)		17	60975400(-)	Deletion		MMRC0421	Treated
AXL	19	46454269				Nonsense	Y694*	MMRC0335	Treated
AXL	19	46454269				Nonsense	Y694*	MMRC0343	Treated
B3GALTL	13	30725160(+)		13	30767593(-)	Deletion		MMRC0412	Treated
B4GALNT4	11	369940				Missense	R855C	MMRC0381	Untreated
BACE2	17	12270501(+)		21	41533322(-)	Translocation		MMRC0392	Treated
BAG4	8	34928411(-)		8	38161702(-)	Long range		MMRC0412	Treated
BAIAP2L1	7	97766488(+)		15	60584713(-)	Translocation		MMRC0191	Treated
BAZ2B	2	159890491				Missense	S2043Y	MMRC0332	Treated
BCAN	1	154886150(+)		1	154902665(+)	Inversion		MMRC0242	Treated
BCAP29	7	107046037				Missense	R240T	MMRC0191	Treated
BCAS4	20	48891729				Missense	G125E	MMRC0329	Treated
BCKDHB	6	80937777				Missense	D231E	MMRC0344	Treated
BICC1	10	60228971				Nonsense	Q560*	MMRC0335	Treated
BLMH	17	25586084(+)		17	25605465(-)	Deletion		MMRC0191	Treated
BMP6	6	7615208(-)		6	7699953(+)	Tandem duplication		MMRC0406	Untreated
BMS1	10	42632094				Missense	V791M	MMRC0387	Untreated
BRAF	7	140127871				Missense	G469A	MMRC0344	Treated
BRCA1	17	38510440				Missense	C44F	MMRC0344	Treated
BRE	2	28408035(-)	C11orf65	11	107817836(+)	Translocation		MMRC0191	Treated

Supplementary Table 3 (continued)

Gene	Chr	Position (strand)	2nd gene	Chr	Position (strand)	Type	AA change	Sample	Previously treated
BSN	3	49664376				Nonsense	E795*	MMRC0332	Treated
BTBD11	12	106533023				Missense	T652M	MMRC0282	Treated
BTBD7	14	92830943				Missense	R59K	MMRC0322	Untreated
BTLA	3	113667901				Missense	S157T	MMRC0191	Treated
BTRC	10	103288069				Missense	A536G	MMRC0286	Untreated
C10orf111	10	15178691				Missense	S47R	MMRC0282	Treated
C10orf118	10	115881059				Missense	E646D	MMRC0004	Untreated
C10orf72	10	49971922(+)	C10orf128	10	50039012(-)	Deletion		MMRC0335	Treated
C10orf84	10	120054455(+)		10	120064906(-)	Deletion		MMRC0191	Treated
C10orf96	10	118101377(+)	PNLIPRP3	10	118197108(-)	Deletion		MMRC0344	Treated
C11orf24	11	67786495				Missense	A182T	MMRC0216	Untreated
C11orf61	11	124142701				Missense	G369R	MMRC0412	Treated
C11orf90	11	90014673(-)		11	93215404(-)	Long range		MMRC0338	Untreated
C12orf11	12	12928113(-)		12	26956842(-)	Long range		MMRC0421	Treated
C12orf11	12	26957771				Missense	P564L	MMRC0421	Treated
C12orf30	12	110994115				Nonsense	R335*	MMRC0282	Treated
C12orf35	12	32026928				Missense	A591V	MMRC0335	Treated
C13orf30	13	42256206				Missense	M1I	MMRC0347	Untreated
C14orf43	1	46481870(-)		14	73270266(+)	Translocation		MMRC0191	Treated
C15orf55	8	57009317(+)		15	32431688(-)	Translocation		MMRC0335	Treated
C16orf91	16	1416310				Missense	P105Q	MMRC0392	Treated
C17orf46	17	40693261(-)	PRPSAP1	17	71851808(+)	Long range		MMRC0425	Untreated
C17orf68	17	8082189(-)	MYH10	17	8406630(-)	Inversion		MMRC0392	Treated
C17orf68	17	8072916				Missense	T1081A	MMRC0322	Untreated
C17orf71	17	54642550				Missense	S119T	MMRC0244	Untreated
C18orf19	18	13671976				Missense	G34A	MMRC0389	Treated
C19orf33	19	43487387				In frame deletion	V88_K89>V	MMRC0412	Treated
C1orf101	1	242790743				Missense	V394F	MMRC0242	Treated
C1orf14	1	181175260				Missense	E274D	MMRC0343	Treated
C1orf14	1	181135742				Read-through	*654L	MMRC0383	Treated
C1orf163	1	52926231				Frame shift insertion	S148fs	MMRC0286	Untreated
C1orf26	1	183410506				Missense	V202F	MMRC0375	Treated
C1orf64	1	16201730(-)		1	16203618(-)	Inversion		MMRC0406	Untreated
C1orf95	1	224830735(+)		22	21558309(+)	Translocation		MMRC0425	Untreated
C20orf107	20	54541893				Missense	S30N	MMRC0408	Untreated
C20orf117	20	34887558(+)	SAMHD1	20	34974001(-)	Deletion		MMRC0387	Untreated
C20orf117	20	34899889(-)	SAMHD1	20	34961798(+)	Tandem duplication		MMRC0356	Untreated
C20orf132	20	35182854				Splice site	C659_splice	MMRC0412	Treated
C20orf152	20	34031821				Missense	Q90H	MMRC0359	Untreated
C20orf194	20	3199122				Missense	A913P	MMRC0383	Treated
C20orf20	20	60901255				Missense	F144L	MMRC0412	Treated
C20orf26	10	36256547(-)		20	19989182(+)	Translocation		MMRC0191	Treated
C22orf43	22	22294283				In frame deletion	D126_A127>A	MMRC0412	Treated
C2CD3	11	73426367				Missense	Q1895H	MMRC0286	Untreated
C2orf61	2	23491513(-)		2	47208515(-)	Long range		MMRC0191	Treated
C2orf71	2	29148851				Missense	S594F	MMRC0028	Untreated
C2orf71	2	29148816				Missense	D606N	MMRC0322	Untreated
C2orf86	2	63430182(+)		23	118279592(+)	Translocation		MMRC0335	Treated
C2orf86	2	63430398(-)		23	118279776(-)	Translocation		MMRC0335	Treated
C3orf38	3	88288258				Missense	R258L	MMRC0389	Treated
C3orf64	3	69136988				Missense	H170N	MMRC0406	Untreated
C4orf43	4	164647655				Missense	K8N	MMRC0335	Treated
C5	9	122784867				Missense	V1093I	MMRC0376	Untreated
C5orf34	5	43541813				Nonsense	W242*	MMRC0392	Treated
C6orf125	6	33786327(+)	IP6K3	6	33801238(+)	Inversion		MMRC0191	Treated
C6orf138	6	48143998				Missense	S118F	MMRC0309	Untreated
C6orf146	6	4014219				Missense	E413K	MMRC0389	Treated
C6orf15	6	31187264				In frame deletion	G262_G284>G	MMRC0028	Untreated
C6orf170	6	121468888				Missense	S1149P	MMRC0376	Untreated
C7orf50	7	809715(+)		7	1015815(-)	Deletion		MMRC0392	Treated
C9orf30	9	102252848				Nonsense	Q203*	MMRC0389	Treated
C9orf78	1	19228814(-)		9	131632155(+)	Translocation		MMRC0191	Treated
C9orf85	9	73777444				Frame shift insertion	E114fs	MMRC0356	Untreated
C9orf93	9	15581381				Nonsense	Q124*	MMRC0319	Untreated
CA3	8	86541652				Missense	G111R	MMRC0412	Treated
CACNA1A	12	10717042(-)		19	13356240(+)	Translocation		MMRC0344	Treated
CACNA1B	9	139893325				Splice site	P95_splice	MMRC0376	Untreated
CACNA1C	3	67360306(-)		12	2353255(-)	Translocation		MMRC0191	Treated
CADPS	3	62398862				Missense	R1245H	MMRC0332	Treated

Supplementary Table 3 (continued)

Gene	Chr	Position (strand)	2nd gene	Chr	Position (strand)	Type	AA change	Sample	Previously treated
CALCR	7	92928104				Missense	V239I	MMRC0390	Treated
CALR3	19	16454284				Missense	A299P	MMRC0308	Treated
CAMK1D	10	12843023				Missense	L124V	MMRC0389	Treated
CAMK1D	10	12437494(-)		X	145395207(-)	Translocation		MMRC0343	Treated
CAMK4	5	110842426(+)		5	111028801(-)	Deletion		MMRC0332	Treated
CAMK4	5	110826946(+)		10	78141709(-)	Translocation		MMRC0309	Untreated
CAMLG	5	134106601(-)	DDX46	5	134141589(+)	Tandem duplication		MMRC0425	Untreated
CAMTA1	1	7727615				Missense	W1439S	MMRC0242	Treated
CAMTA1	1	7721013				Missense	R1356W	MMRC0338	Untreated
CANT1	17	74504779				Missense	N174I	MMRC0335	Treated
CAPG	2	85482538				Missense	V26G	MMRC0347	Untreated
CAPN12	19	43924381				Missense	F146L	MMRC0191	Treated
CAPZA1	1	112998752				Missense	R121T	MMRC0286	Untreated
CARD11	7	2930442				Missense	Y631H	MMRC0375	Treated
CARD11	7	2925677				Missense	D789N	MMRC0425	Untreated
CASC1	12	25228630(+)		12	27084669(+)	Long range		MMRC0421	Treated
CASC1	12	25229286(-)		12	27064168(+)	Long range		MMRC0421	Treated
CASC1	12	25237517(+)		12	27084863(-)	Long range		MMRC0421	Treated
CASK	X	41299822				Missense	S606L	MMRC0173	Treated
CASP8AP2	6	90615866(+)	PTPRN2	7	157695832(-)	Translocation		MMRC0191	Treated
CBLB	3	106953138				Nonsense	W194*	MMRC0425	Untreated
CBLN1	16	47870979				Missense	S140L	MMRC0244	Untreated
CCDC111	1	224073101(+)		4	185850137(+)	Translocation		MMRC0344	Treated
CCDC123	19	38100631(+)	RHPN2	19	38213530(-)	Deletion		MMRC0389	Treated
CCDC123	19	38136359				Splice site	Q164_splice	MMRC0427	Treated
CCDC144NL	17	20710609				Splice site	A139_splice	MMRC0242	Treated
CCDC147	10	106114629				Missense	I197V	MMRC0244	Untreated
CCDC153	11	118569089				Missense	G111S	MMRC0343	Treated
CCDC157	22	29096840				Missense	Q316E	MMRC0347	Untreated
CCDC158	4	77507878				Missense	E475K	MMRC0286	Untreated
CCDC46	17	61388149				Missense	T589D	MMRC0286	Untreated
CCDC72	2	234756563(-)		3	48457441(-)	Translocation		MMRC0191	Treated
CCL2	17	29607891				Missense	P78T	MMRC0421	Treated
CCND1	11	69165273				Missense	Q4R	MMRC0322	Untreated
CCND1	11	69165400				Missense	K46N	MMRC0335	Treated
CD109	6	74576508				Missense	A1146T	MMRC0191	Treated
CD14	5	139991746				Missense	T336S	MMRC0421	Treated
CD163	12	7545124				Missense	R112H	MMRC0387	Untreated
CD1B	1	156566379				Missense	L165R	MMRC0282	Treated
CD200	3	113542439				Missense	V5M	MMRC0173	Treated
CD244	1	158691054(-)		1	159071543(+)	Tandem duplication		MMRC0356	Untreated
CD247	1	165693972(-)	SLC30A6	2	32270590(+)	Translocation		MMRC0356	Untreated
CD300LG	17	39281478				Nonsense	E24*	MMRC0335	Treated
CD3G	11	117728342				Missense	R166Q	MMRC0383	Treated
CDC2	10	62217876				Missense	V124G	MMRC0173	Treated
CDC20B	5	54488620(-)		10	38545191(-)	Translocation		MMRC0191	Treated
CDC25C	5	137689142(-)	KDM3B	5	137772951(-)	Inversion		MMRC0344	Treated
CDC25C	5	137654248				Missense	H208Q	MMRC0332	Treated
CDC25C	3	135595261(+)		5	137658217(-)	Translocation		MMRC0191	Treated
CDC42BPB	14	102522651				Missense	V206L	MMRC0390	Treated
CDH11	16	63596246				Missense	A10T	MMRC0282	Treated
CDH19	18	62369362				Missense	V242I	MMRC0427	Treated
CDH2	18	23836997				Missense	G328S	MMRC0383	Treated
CDH2	18	23847649				Missense	V132A	MMRC0392	Treated
CDH20	18	57317640				Missense	P163R	MMRC0427	Treated
CDH8	16	60412508				Missense	H282Q	MMRC0387	Untreated
CDK4	12	56431115				Missense	G127D	MMRC0383	Treated
CDK4	12	56431697				Missense	R24L	MMRC0383	Treated
CDK5RAP1	12	10328091(-)		20	31432819(-)	Translocation		MMRC0344	Treated
CDON	11	125396467				Missense	Q79E	MMRC0389	Treated
CDYL	6	4880867				Missense	D271N	MMRC0319	Untreated
CECR2	22	16351270(-)		22	16925642(+)	Tandem duplication		MMRC0425	Untreated
CELA1	12	50026682				Missense	V3G	MMRC0329	Treated
CELSR2	1	109597054				Missense	T944P	MMRC0381	Untreated
CENPF	1	212882949				Missense	V1549F	MMRC0322	Untreated
CENPJ	13	24378627				Missense	W517G	MMRC0408	Untreated
CEP110	9	122964045				Missense	E1727V	MMRC0191	Treated
CEP170	1	241395510				Nonsense	S694*	MMRC0332	Treated
CEP290	12	87048252				Missense	R198K	MMRC0338	Untreated

Supplementary Table 3 (continued)

Gene	Chr	Position (strand)	2nd gene	Chr	Position (strand)	Type	AA change	Sample	Previously treated
CETN2	X	151748801				Splice site	K54_splice	MMRC0344	Treated
CFTR	7	117069732				Missense	G1241V	MMRC0191	Treated
CGN	1	149774199				Missense	L988V	MMRC0329	Treated
CGN	1	149757906				Missense	S96L	MMRC0389	Treated
CHD3	17	7751997				Missense	G1755V	MMRC0329	Treated
CHD3	17	7755593				Missense	P2049S	MMRC0338	Untreated
CHD3	17	7749732				Missense	V1462I	MMRC0412	Treated
CHD9	11	74132346(+)		16	51839852(-)	Translocation		MMRC0343	Treated
CHIA	1	111664495				Missense	P331T	MMRC0335	Treated
CHIA	1	111656482				Missense	T68I	MMRC0392	Treated
CHL1	3	379902				Missense	Q474L	MMRC0376	Untreated
CHRM2	7	136351244				Missense	K364N	MMRC0412	Treated
CHRM3	1	238137889				Missense	R172K	MMRC0387	Untreated
CHRNA5	3	112366549(+)		15	76663044(+)	Translocation		MMRC0344	Treated
CHRNA6	8	42731315				Missense	R96H	MMRC0408	Untreated
CHRNB2	1	152808899				Missense	R73Q	MMRC0387	Untreated
CHRNB3	8	42605616(+)		8	42672519(-)	Deletion		MMRC0392	Treated
CHRND	2	233106997				Missense	A387V	MMRC0421	Treated
CHST5	16	74120718				Missense	R356C	MMRC0347	Untreated
CIR1	2	174923653				Missense	Q220K	MMRC0381	Untreated
CIR1	2	174921781				Missense	S348N	MMRC0383	Treated
CKAP5	11	46779415				Missense	T332A	MMRC0421	Treated
CKM	19	50507001				Missense	G167C	MMRC0319	Untreated
CKM	19	50507001				Missense	G167C	MMRC0173	Treated
CLCN1	7	142759173				Missense	I987T	MMRC0308	Treated
CLIC4	1	25039121				Splice site	K199_splice	MMRC0282	Treated
CLIP1	12	121397950				Missense	I466M	MMRC0329	Treated
CLIP4	2	29220129				Missense	M233I	MMRC0343	Treated
CLMN	14	94739168(-)		14	94949481(+)	Tandem duplication		MMRC0425	Untreated
CLRN3	10	129572036				Missense	S108Y	MMRC0332	Treated
CLTC	17	55115537				Missense	R1350T	MMRC0375	Treated
CLVS2	1	94566893(+)		6	123377440(+)	Translocation		MMRC0332	Treated
CMBL	5	10339506				Missense	M142I	MMRC0387	Untreated
CMKLR1	12	107209782				Missense	T363I	MMRC0343	Treated
CMTM2	16	65171151				Missense	E47V	MMRC0282	Treated
CMTM7	3	32411457(+)	DCTD	4	184063778(-)	Translocation		MMRC0309	Untreated
CMYA5	5	79066681				Missense	I2113V	MMRC0375	Treated
CMYA5	5	79065734				Missense	P1797Q	MMRC0389	Treated
CNBD1	8	83533762(-)		8	88093821(-)	Long range		MMRC0421	Treated
CNBD1	8	83666013(+)		8	88105353(+)	Long range		MMRC0421	Treated
CNGB3	8	87710281				Missense	D488N	MMRC0335	Treated
CNOT6	5	179928794				Missense	S369Y	MMRC0338	Untreated
CNOT6L	4	78860752				Missense	P509T	MMRC0421	Treated
CNTN3	3	74497474				Missense	C339F	MMRC0332	Treated
CNTN4	3	3053994				Missense	R364W	MMRC0173	Treated
CNTN5	11	99441414(+)		11	99458113(-)	Deletion		MMRC0319	Untreated
CNTNAP2	7	146814054				Missense	T589P	MMRC0004	Untreated
CNTNAP5	2	124857362(-)		14	46063526(-)	Translocation		MMRC0191	Treated
COG5	7	106658328				Missense	L743F	MMRC0389	Treated
COL12A1	6	75856549				Nonsense	R2980*	MMRC0423	Treated
COL16A1	1	31918125(-)		1	31950230(+)	Tandem duplication		MMRC0421	Treated
COL17A1	10	105812026				Missense	G297D	MMRC0425	Untreated
COL19A1	6	70694528				Missense	I91M	MMRC0375	Treated
COL19A1	6	70685545(+)		8	31349810(-)	Translocation		MMRC0309	Untreated
COL1A1	17	45617947				Missense	L1437P	MMRC0216	Untreated
COL21A1	6	56143751				Missense	V259I	MMRC0392	Treated
COL23A1	5	177621343				Missense	P230A	MMRC0375	Treated
COL23A1	5	177760406(-)	HABP4	9	98284071(+)	Translocation		MMRC0309	Untreated
COL3A1	2	189580857				Missense	G1122D	MMRC0338	Untreated
COL4A3	2	227818975				Missense	K129T	MMRC0389	Treated
COL4A6	X	107305075				Missense	G953R	MMRC0335	Treated
COL5A2	2	189673088				Nonsense	L120*	MMRC0191	Treated
COL6A6	3	131768444				Missense	Q497H	MMRC0412	Treated
COL7A1	3	48597513				Missense	R1312H	MMRC0356	Untreated
COL7A1	3	48603939				Missense	G533V	MMRC0427	Treated
COPG	3	130462242				Missense	A344T	MMRC0412	Treated
COPS3	2	84020364(-)		17	17110098(-)	Translocation		MMRC0332	Treated
CORIN	4	47361926				Missense	E490G	MMRC0427	Treated
COX11	17	50400745				Missense	R88W	MMRC0356	Untreated

Supplementary Table 3 (continued)

Gene	Chr	Position (strand)	2nd gene	Chr	Position (strand)	Type	AA change	Sample	Previously treated
CPEB4	5	173309189				Missense	S510F	MMRC0338	Untreated
CPSF3	2	9517178				Missense	S589L	MMRC0390	Treated
CPXM2	10	125584026(-)		10	126067313(+)	Tandem duplication		MMRC0425	Untreated
CRB1	1	195657415				Missense	F612L	MMRC0335	Treated
CREBBP	16	3730528(-)		16	20164701(+)	Long range		MMRC0421	Treated
CRHBP	5	76287446				Splice site	P182_splice	MMRC0387	Untreated
CRIPAK	4	1379363				Missense	T355I	MMRC0284	Untreated
CRYBG3	3	99048698(+)		3	99088815(-)	Deletion		MMRC0392	Treated
CSDE1	1	61119464(-)		1	115075967(+)	Long range		MMRC0408	Untreated
CSMD2	1	33962836				Missense	R878C	MMRC0335	Treated
CSMD2	1	33931142				Missense	E1303K	MMRC0347	Untreated
CSMD3	8	114100564				Missense	P273L	MMRC0308	Treated
CSNK1G3	5	122954080				Missense	L307I	MMRC0390	Treated
CSPG4	15	73769113				Missense	R450W	MMRC0309	Untreated
CSRNP3	2	166244255				Missense	V502I	MMRC0392	Treated
CTCFL	20	55517213				Missense	G510V	MMRC0309	Untreated
CTNNA3	10	67991751(+)	HPSE2	10	100583403(-)	Long range		MMRC0332	Treated
CTNNA3	10	68878041(-)		10	69072547(+)	Tandem duplication		MMRC0319	Untreated
CTNNAL1	9	110794886				Missense	N122K	MMRC0322	Untreated
CTNND1	11	54736581(+)		11	57328220(-)	Long range		MMRC0421	Treated
CTNND2	5	11399603				Nonsense	Y503*	MMRC0347	Untreated
CTTN	11	69940833				Missense	G175A	MMRC0309	Untreated
CUBN	10	17125964				Missense	S1233P	MMRC0322	Untreated
CUEDC2	10	104173261				Missense	R259Q	MMRC0375	Treated
CUL5	11	107418816(+)		11	128642410(+)	Long range		MMRC0375	Treated
CUL7	6	43124247				Nonsense	Q706*	MMRC0322	Untreated
CUX2	12	110213632				Missense	R110H	MMRC0004	Untreated
CUX2	12	110256876				Missense	V1059I	MMRC0216	Untreated
CXorf22	X	35854181				Missense	K126Q	MMRC0284	Untreated
CXorf57	23	105784286(-)		23	125251872(-)	Long range		MMRC0392	Treated
CYC1	8	145223274				Missense	R167Q	MMRC0308	Treated
CYLD	16	49378431(+)		16	49379310(-)	Deletion		MMRC0335	Treated
CYP11B2	8	143996171				Missense	R30W	MMRC0286	Untreated
CYP2F1	19	46319298				Missense	R194C	MMRC0383	Treated
CYP8B1	3	42891855				Missense	T153M	MMRC0381	Untreated
DAPK1	9	89507784				Missense	H964Q	MMRC0282	Treated
DAPK1	9	89511987				Missense	K1394R	MMRC0308	Treated
DAPK1	9	89486233				Missense	G699E	MMRC0335	Treated
DAPK1	9	89409460(+)	FAM70B	13	113629070(-)	Translocation		MMRC0425	Untreated
DAPK1	9	89409470(-)	FAM70B	13	113629456(+)	Translocation		MMRC0425	Untreated
DCAF12L1	X	125512984				Missense	A430E	MMRC0383	Treated
DCC	6	127201041(-)		18	48821684(+)	Translocation		MMRC0338	Untreated
DCC	18	48866177(+)		X	101299697(-)	Translocation		MMRC0387	Untreated
DCHS1	11	6601555				Nonsense	S2643*	MMRC0389	Treated
DCHS2	4	155438464				Missense	N1696S	MMRC0389	Treated
DCHS2	4	155377120				Missense	H2257N	MMRC0392	Treated
DCHS2	4	155377152				Missense	I2246T	MMRC0173	Treated
DCLK2	4	151373029				Missense	E463K	MMRC0322	Untreated
DCT	13	93912536(+)		13	94254023(-)	Deletion		MMRC0356	Untreated
DDX11	12	31129245				Missense	R186W	MMRC0329	Treated
DDX11	12	31133348				Missense	R263Q	MMRC0375	Treated
DDX23	12	47520116				Missense	D121N	MMRC0329	Treated
DDX25	11	125292218				Missense	I300M	MMRC0389	Treated
DENND1B	1	196003820(-)	DENND1A	9	125217126(+)	Translocation		MMRC0332	Treated
DENND4C	9	19336503				Missense	V961I	MMRC0421	Treated
DENND4C	1	201999182(-)		9	19318941(+)	Translocation		MMRC0383	Treated
DHDDS	1	26652949(+)	FHOD3	18	32169734(-)	Translocation		MMRC0191	Treated
DHRS11	17	32022689				Missense	G46D	MMRC0282	Treated
DHX15	4	24159734				Missense	E364K	MMRC0389	Treated
DIAPH2	X	96197114(+)		X	96276850(-)	Deletion		MMRC0356	Untreated
DIAPH2	X	96053996				Missense	F201V	MMRC0406	Untreated
DIS3	13	72244372				Missense	S447R	MMRC0308	Treated
DIS3	13	72234065				Missense	R750K	MMRC0319	Untreated
DIS3	13	72244028				Missense	V474G	MMRC0343	Treated
DIS3	13	72234108				Missense	G736R	MMRC0421	Treated
DISP2	15	38443358				Missense	H120Q	MMRC0389	Treated
DKFZp761E198	11	65303756				Missense	E205K	MMRC0389	Treated
DKK2	4	108175987				Missense	N71D	MMRC0332	Treated
DLG2	11	82850778				Missense	M807I	MMRC0286	Untreated

Supplementary Table 3 (continued)

Gene	Chr	Position (strand)	2nd gene	Chr	Position (strand)	Type	AA change	Sample	Previously treated
DMXL1	5	118513835				Missense	D1472N	MMRC0191	Treated
DMXL2	15	49550868				Missense	D2411E	MMRC0173	Treated
DMXL2	3	39389102(+)		15	49670533(+)	Translocation		MMRC0343	Treated
DNAH11	7	21688701(+)		19	37979626(+)	Translocation		MMRC0376	Untreated
DNAH5	5	13967660				Missense	E430G	MMRC0322	Untreated
DNAH5	5	13897959				Missense	K1753T	MMRC0335	Treated
DNAH9	17	11548440				Missense	D1783N	MMRC0322	Untreated
DNAH9	17	11543776				Nonsense	Q1626*	MMRC0389	Treated
DNAH9	17	11538956(-)	FAM3B	21	41624442(+)	Translocation		MMRC0392	Treated
DNAJA1	9	33020498				Missense	Q159P	MMRC0319	Untreated
DNAJC14	12	54508123				Missense	R196K	MMRC0028	Untreated
DNM2	19	10795538				Missense	S615L	MMRC0387	Untreated
DNMT3B	20	30848280				Missense	K421E	MMRC0191	Treated
DNMT3B	20	30832882				Splice site	Q68_splice	MMRC0173	Treated
DOCK10	2	225389675				Splice site	T1090_splice	MMRC0335	Treated
DOCK3	3	50941199(-)		19	54424331(+)	Translocation		MMRC0383	Treated
DOCK4	7	111330149(-)		7	115106315(+)	Long range		MMRC0191	Treated
DOCK8	9	366301				Missense	T734S	MMRC0356	Untreated
DOLK	9	130748152				Missense	P418A	MMRC0329	Treated
DONSON	21	33878793				Missense	T253N	MMRC0375	Treated
DOPEY2	21	36587690				Missense	Q2283P	MMRC0309	Untreated
DOT1L	19	2167622				Missense	G756S	MMRC0381	Untreated
DPP6	7	153794042(+)		X	95567529(+)	Translocation		MMRC0173	Treated
DPY19L2	12	62343861				Missense	R132C	MMRC0191	Treated
DRD2	4	52583111(-)		11	112796764(+)	Translocation		MMRC0392	Treated
DRD3	3	115341045				Missense	P239T	MMRC0338	Untreated
DSCAM	21	40472889				Missense	S928P	MMRC0308	Treated
DSCAM	17	11861613(+)		21	40946326(+)	Translocation		MMRC0392	Treated
DSCAM	17	14820911(-)		21	40934450(-)	Translocation		MMRC0392	Treated
DSG1	18	27180053				Missense	M665K	MMRC0383	Treated
DSPP	4	88756533				Missense	N1232S	MMRC0332	Treated
DST	6	56491665(+)		6	56692575(-)	Deletion		MMRC0375	Treated
DST	6	56577270				Missense	E2835G	MMRC0390	Treated
DST	6	56505221				Missense	I3544S	MMRC0412	Treated
DSTYK	1	96264245(-)		1	203401185(-)	Long range		MMRC0191	Treated
DYSF	2	71642546				Missense	E804D	MMRC0335	Treated
EED	11	85660516(+)		11	85675554(-)	Deletion		MMRC0421	Treated
EFCAB3	17	57847388				Missense	R428K	MMRC0191	Treated
EFHC1	6	52425580				Missense	T237P	MMRC0216	Untreated
EFNA4	1	153308070				Missense	R196H	MMRC0376	Untreated
EGFR	7	55236444				Missense	D1006Y	MMRC0390	Treated
EGLN3	14	33465977				Missense	V210L	MMRC0244	Untreated
EGR1	5	137829376				Missense	Q9H	MMRC0282	Treated
EHBP1	2	63077366				Missense	A1093T	MMRC0381	Untreated
EHMT1	9	139827373				Missense	A988T	MMRC0423	Treated
EIF3B	7	2385341				Missense	Y760F	MMRC0343	Treated
ELAVL2	9	23694928				Missense	D159N	MMRC0383	Treated
ELF2	4	140200998				Missense	S303P	MMRC0244	Untreated
ELOVL3	10	103976305				Missense	A4T	MMRC0390	Treated
EMID1	22	27940941				Missense	R43L	MMRC0347	Untreated
ENOX1	13	42798568				Missense	R377Q	MMRC0389	Treated
EP400	12	131095428				Missense	K2253R	MMRC0191	Treated
EPB41L3	18	5396904				Missense	T741S	MMRC0284	Untreated
EPHA5	4	66098050(+)	ARHGAP24	4	86845602(-)	Long range		MMRC0344	Treated
EPHA6	3	98850840(+)		3	99018634(-)	Deletion		MMRC0319	Untreated
EPHA6	3	98925845(-)	SRRM4	12	117926083(+)	Translocation		MMRC0389	Treated
EPHA7	6	94025844				Missense	A625T	MMRC0359	Untreated
EPHA7	6	94185719				Missense	F21Y	MMRC0389	Treated
EPHB1	3	136273401(+)		3	136342717(-)	Deletion		MMRC0356	Untreated
EPHB3	3	185777638				Missense	A443T	MMRC0191	Treated
EPHB3	3	185773037				Missense	Q79K	MMRC0282	Treated
EPHB4	7	100241140				Missense	R866H	MMRC0347	Untreated
EPYC	12	89920434				Missense	F14I	MMRC0335	Treated
ERBB2IP	5	65385594				Missense	T898A	MMRC0319	Untreated
ERBB2IP	5	65355987				Missense	D257A	MMRC0421	Treated
ERBB3	12	54760558(+)		12	54941789(-)	Deletion		MMRC0412	Treated
ERC1	12	1215386(+)	WNT5B	12	1619954(-)	Deletion		MMRC0191	Treated
ERLIN1	10	101927910				Missense	E92K	MMRC0389	Treated

Supplementary Table 3 (continued)

Gene	Chr	Position (strand)	2nd gene	Chr	Position (strand)	Type	AA change	Sample	Previously treated
ESR1	6	152457336				Missense	Q498P	MMRC0329	Treated
ESYT1	12	54813701				Missense	L452F	MMRC0359	Untreated
ETNK1	12	22703262				Missense	N244S	MMRC0338	Untreated
EVI5	1	92936075				Missense	L276P	MMRC0356	Untreated
EWSR1	22	27915334(+)		22	28014414(-)	Deletion		MMRC0343	Treated
EWSR1	22	28000740(+)		22	28048145(-)	Deletion		MMRC0343	Treated
EXOC6	10	94633807(+)		10	94748129(-)	Deletion		MMRC0387	Untreated
EXOSC2	9	132568055(-)		9	132569509(-)	Inversion		MMRC0338	Untreated
EYA4	6	133875588				Missense	D417N	MMRC0425	Untreated
EYS	6	66261477				Missense	C183F	MMRC0381	Untreated
F3	1	94774262				Missense	T87S	MMRC0191	Treated
F5	1	167772526				Missense	D1605N	MMRC0389	Treated
FA2H	16	73305596				Missense	T371M	MMRC0173	Treated
FAF1	1	50742413(+)	C1orf185	1	51358905(-)	Deletion		MMRC0408	Untreated
FAF2	5	175842798(-)		23	93410042(-)	Translocation		MMRC0191	Treated
FAM115A	7	143204463				Missense	R58C	MMRC0329	Treated
FAM116A	3	57594099				Missense	S429F	MMRC0286	Untreated
FAM120A	9	95358144(-)	NALCN	13	100726293(+)	Translocation		MMRC0191	Treated
FAM120B	6	170469940				Missense	D513N	MMRC0309	Untreated
FAM12A	14	20285657				Missense	N26K	MMRC0375	Treated
FAM134B	5	16538412(-)	AUTS2	7	68960111(+)	Translocation		MMRC0191	Treated
FAM135A	6	71243741				Missense	H176P	MMRC0309	Untreated
FAM135B	8	139233957				Missense	L648P	MMRC0173	Treated
FAM153B	5	175461190				Missense	L222F	MMRC0406	Untreated
FAM155A	13	107316728				Missense	Q73R	MMRC0381	Untreated
FAM155A	2	58643357(+)		13	106644312(-)	Translocation		MMRC0387	Untreated
FAM174A	5	99925862(+)		14	92957371(-)	Translocation		MMRC0425	Untreated
FAM174A	5	99925884(-)		14	92957369(+)	Translocation		MMRC0425	Untreated
FAM18B2	17	15389837				Missense	T150R	MMRC0412	Treated
FAM190A	4	91312895(+)		4	91455046(-)	Deletion		MMRC0319	Untreated
FAM190A	4	91741790(+)		4	92050647(-)	Deletion		MMRC0421	Treated
FAM190A	4	91838617(+)		4	91993399(-)	Deletion		MMRC0319	Untreated
FAM190B	10	86175545				Missense	P595L	MMRC0390	Treated
FAM38B	18	10670234				Missense	N2525K	MMRC0335	Treated
FAM46C	1	117967150				Frame shift deletion	I46fs	MMRC0412	Treated
FAM46C	1	117967569				In frame deletion	I186del	MMRC0406	Untreated
FAM46C	1	117967621				Missense	S203C	MMRC0216	Untreated
FAM46C	1	117967557				Missense	D182Y	MMRC0390	Treated
FAM46C	1	117967954				Missense	V314G	MMRC0408	Untreated
FAM47B	23	34871321(+)		23	34958336(-)	Deletion		MMRC0319	Untreated
FAM5B	1	175493103				Missense	R210Q	MMRC0332	Treated
FAM5C	1	188458384(+)		1	188673956(-)	Deletion		MMRC0421	Treated
FAM73B	9	130845216(+)	PPP2R4	9	130929149(-)	Deletion		MMRC0191	Treated
FAM82A2	12	14767152(-)		15	38832870(-)	Translocation		MMRC0335	Treated
FAM83H	8	144880320				Missense	G1100E	MMRC0308	Treated
FANCB	X	14793391				Missense	K55Q	MMRC0387	Untreated
FAT3	11	90023454(+)		11	92182626(-)	Long range		MMRC0338	Untreated
FAT3	11	91727410				Missense	S828R	MMRC0191	Treated
FAT3	11	91726190				Missense	I422F	MMRC0376	Untreated
FAT3	11	91726313				Missense	E463K	MMRC0389	Treated
FBN3	19	8102579				Missense	R617C	MMRC0381	Untreated
FBXL13	7	102359616				Missense	S242N	MMRC0329	Treated
FBXL19	16	30860980				Missense	RR468>RW	MMRC0335	Treated
FBXW12	3	48389575(+)		3	48390034(-)	Deletion		MMRC0406	Untreated
FBXW12	3	48391853				Missense	E98Q	MMRC0309	Untreated
FCGBP	19	45060581				Missense	V4203M	MMRC0381	Untreated
FCHSD2	11	72342786(-)	ARHGEF17	11	72707119(+)	Tandem duplication		MMRC0356	Untreated
FCRL2	1	156005059				Missense	E218K	MMRC0389	Treated
FEN1	11	61320050				Missense	Q214R	MMRC0282	Treated
FFAR2	19	40632784				Missense	G110R	MMRC0308	Treated
FGA	4	155726959				Missense	G358R	MMRC0356	Untreated
FGA	4	155726404				Missense	E543K	MMRC0389	Treated
FGF6	12	4413697				Missense	R191Q	MMRC0173	Treated
FGFR2	10	123253372				Missense	T366M	MMRC0356	Untreated
FGG	4	155753196				Missense	H6Y	MMRC0376	Untreated
FGGY	1	59797002(+)	FAM159B	5	64028255(+)	Translocation		MMRC0319	Untreated
FHDC1	4	154083946				Missense	R96Q	MMRC0423	Treated
FHDC1	4	154117155				Nonsense	R1088*	MMRC0383	Treated
FIG4	6	110219423				Missense	P778S	MMRC0286	Untreated

Supplementary Table 3 (continued)

Gene	Chr	Position (strand)	2nd gene	Chr	Position (strand)	Type	AA change	Sample	Previously treated
FKBP5	6	35651654				Missense	V437G	MMRC0406	Untreated
FLG	1	150543421				Missense	G3522D	MMRC0389	Treated
FLG2	1	150592174				Missense	R1571K	MMRC0028	Untreated
FLJ20184	4	106028973(+)		4	106757763(-)	Deletion		MMRC0332	Treated
FLJ43860	8	138372705(+)		8	142514381(-)	Long range		MMRC0421	Treated
FLNC	7	128271111				Missense	Y946F	MMRC0191	Treated
FLRT2	14	85157648				Missense	A13S	MMRC0309	Untreated
FMN1	15	31048687				Missense	S613Y	MMRC0389	Treated
FMN1	13	87772249(-)		15	31142435(-)	Translocation		MMRC0191	Treated
FMO1	1	169511175				Missense	M130L	MMRC0332	Treated
FNBP1	9	131710989				Splice site	R432_splice	MMRC0421	Treated
FNDC3A	13	48485221(+)		13	48556445(-)	Deletion		MMRC0375	Treated
FNDC3A	13	48497043(+)		13	48638419(-)	Deletion		MMRC0375	Treated
FNTB	14	64580830				Missense	R291C	MMRC0338	Untreated
FOXK1	7	4763284				Missense	R395Q	MMRC0322	Untreated
FOXO3	6	109021861(-)		17	40800755(+)	Translocation		MMRC0356	Untreated
FOXP1	3	71109797				Missense	P407L	MMRC0004	Untreated
FOXP2	7	113998137				Missense	S100T	MMRC0423	Treated
FRK	6	116370951				Missense	S411C	MMRC0359	Untreated
FRMD3	9	85230753(-)	LIMK2	22	29971364(-)	Translocation		MMRC0387	Untreated
FRMPD1	9	37727115				Missense	S475F	MMRC0322	Untreated
FRYL	4	48303252				Missense	Y234S	MMRC0427	Treated
FSCB	14	44043760				Missense	E727D	MMRC0322	Untreated
FXYD6	11	117218642				Splice site	A20_splice	MMRC0356	Untreated
G6PC2	2	169466275				Missense	I63T	MMRC0286	Untreated
GAA	17	75696270				Missense	L312R	MMRC0028	Untreated
GAB2	11	77761957(-)	NARS2	11	77868861(+)	Tandem duplication		MMRC0356	Untreated
GAB2	11	77609971(+)	CSNK1E	22	37022655(-)	Translocation		MMRC0191	Treated
GABRA1	5	161232700				Splice site	E86_splice	MMRC0329	Treated
GABRB1	3	142881392(-)		4	46802698(-)	Translocation		MMRC0191	Treated
GABRB2	5	160819394				Nonsense	W91*	MMRC0390	Treated
GABRB3	15	24344125				Missense	D444N	MMRC0412	Treated
GABRG1	4	45762306				Missense	K125T	MMRC0322	Untreated
GABRG1	4	45761281				Missense	E187K	MMRC0389	Treated
GABRR3	3	99213914				Missense	R165H	MMRC0356	Untreated
GAL3ST3	11	65567324				Missense	P176A	MMRC0329	Treated
GALNT9	12	131319962(+)		17	67973231(+)	Translocation		MMRC0242	Treated
GALNTL4	11	11271295				Nonsense	Q512*	MMRC0329	Treated
GAS2L3	12	99540293				Splice site	R252_splice	MMRC0406	Untreated
GCET2	3	17806021(-)		3	113325891(-)	Long range		MMRC0343	Treated
GCET2	3	113325271				Nonsense	Y86*	MMRC0408	Untreated
GHR	5	33269949(+)		5	42718868(-)	Long range		MMRC0335	Treated
GIT1	17	24928298				Missense	S368G	MMRC0389	Treated
GJB4	1	35000047				Missense	L202R	MMRC0308	Treated
GJD2	15	32832230				Missense	C236Y	MMRC0329	Treated
GLB1L2	11	133744914				Missense	D345N	MMRC0344	Treated
GLIPR1L2	12	74103057				Missense	M231L	MMRC0284	Untreated
GLP2R	17	9677917				Missense	D86E	MMRC0173	Treated
GLRA1	5	151208817(-)		8	10438247(+)	Translocation		MMRC0387	Untreated
GLT6D1	9	137656168				Missense	W143G	MMRC0359	Untreated
GMCL1	2	69930294				Missense	F284V	MMRC0284	Untreated
GNAL	6	85388419(-)		18	11704387(-)	Translocation		MMRC0389	Treated
GNB3	12	6825177				Missense	Y289S	MMRC0383	Treated
GNMT	6	43038011				Missense	K97R	MMRC0308	Treated
GNPAT	1	229468482				Missense	T291I	MMRC0028	Untreated
GP2	16	20242741(-)	PRKCB	16	23931582(+)	Long range		MMRC0344	Treated
GPATCH2	1	215860109				Missense	G138W	MMRC0359	Untreated
GPATCH2	1	215733075(+)		2	190451622(-)	Translocation		MMRC0343	Treated
GPATCH8	17	39848388(+)		17	39891813(-)	Deletion		MMRC0421	Treated
GPATCH8	17	39863458(+)		17	39902861(-)	Deletion		MMRC0332	Treated
GPC6	13	60893557(-)		13	93655919(-)	Long range		MMRC0392	Treated
GPC6	13	61358472(-)		13	92972239(-)	Long range		MMRC0392	Treated
GPC6	13	61381281(-)		13	93099690(+)	Long range		MMRC0392	Treated
GPD1	12	48785727				Missense	S117A	MMRC0173	Treated
GPI	19	39576490				Missense	Q295K	MMRC0286	Untreated
GPR109A	12	121753516				Missense	R90C	MMRC0356	Untreated
GPR109B	12	121766287				Missense	I317M	MMRC0004	Untreated
GPR112	X	135256213				Missense	S894R	MMRC0173	Treated
GPR115	6	47783927				Missense	D34E	MMRC0173	Treated

Supplementary Table 3 (continued)

Gene	Chr	Position (strand)	2nd gene	Chr	Position (strand)	Type	AA change	Sample	Previously treated
GPR143	X	9667654				Missense	S331T	MMRC0173	Treated
GPR155	2	174551041(+)		2	175014250(-)	Deletion		MMRC0332	Treated
GPR158	10	25901622				Missense	I518T	MMRC0028	Untreated
GPR83	11	93753016				Missense	Q407E	MMRC0332	Treated
GPR98	5	90021565				Missense	E2208K	MMRC0191	Treated
GPR98	5	90086696				Missense	E3840K	MMRC0412	Treated
GPRC6A	6	117220698				Missense	L694S	MMRC0343	Treated
GPRIN2	10	46420033				Nonsense	R383*	MMRC0308	Treated
GRB2	4	89357014(-)		17	70835809(+)	Translocation		MMRC0191	Treated
GRIA2	4	158462134				Missense	K225T	MMRC0282	Treated
GRIA4	11	104659366(+)		11	105191433(-)	Deletion		MMRC0338	Untreated
GRID1	10	87363311				Missense	D812Y	MMRC0284	Untreated
GRID1	10	87618868				Missense	R277M	MMRC0383	Treated
GRID1	10	87369647				Missense	A773S	MMRC0390	Treated
GRID1	8	49728873(-)		10	87939728(-)	Translocation		MMRC0191	Treated
GRIK1	21	29849375				Missense	E826Q	MMRC0286	Untreated
GRIK2	6	101469309(+)		6	102332800(-)	Deletion		MMRC0421	Treated
GRIP1	12	65221917				Missense	D73N	MMRC0286	Untreated
GRM7	3	7163215				Missense	V199A	MMRC0242	Treated
GRM7	3	7588164(+)	C18orf34	18	28973325(+)	Translocation		MMRC0309	Untreated
GRM8	7	126197269				Missense	A415T	MMRC0389	Treated
GSTO2	10	106029219				Missense	E156D	MMRC0309	Untreated
GTF2F2	13	44701741(+)	SIAH3	13	45285735(+)	Inversion		MMRC0392	Treated
GTF3C1	16	19002992(+)		16	27392966(+)	Long range		MMRC0344	Treated
GUCY1A2	11	106354736(-)		11	130034355(+)	Long range		MMRC0338	Untreated
H2AFY2	10	71523528				Missense	T170S	MMRC0028	Untreated
HAO1	20	7814483				Missense	A281V	MMRC0322	Untreated
HAS2	8	122698594				Missense	S221T	MMRC0343	Treated
HCFC2	12	103016264				Nonsense	S585*	MMRC0389	Treated
HCLS1	3	122834005				In frame insertion	P368>PEPEP	MMRC0173	Treated
HCN1	5	19981971(+)		5	45628215(-)	Long range		MMRC0344	Treated
HCN1	5	27587136(-)		5	45627949(+)	Long range		MMRC0344	Treated
HCN2	3	197328869(-)		19	563639(+)	Translocation		MMRC0343	Treated
HDAC9	7	18820223(+)		7	19816336(-)	Deletion		MMRC0392	Treated
HEATR5A	8	13898318(+)		14	30859784(-)	Translocation		MMRC0191	Treated
HECW1	7	43318040				Missense	V61F	MMRC0282	Treated
HECW1	7	43450980				Missense	R562C	MMRC0389	Treated
HEPHL1	11	93458977				Missense	T685K	MMRC0335	Treated
HES3	1	6227248				Nonsense	Y45*	MMRC0335	Treated
HEXB	5	74020966				Missense	Q119H	MMRC0191	Treated
HHIPL2	1	220782114				Missense	I327M	MMRC0216	Untreated
HIPK1	1	114310366				Missense	T403I	MMRC0344	Treated
HIST1H2AC	6	26232749				Missense	A104S	MMRC0282	Treated
HIST1H3A	6	26128983				Missense	A96V	MMRC0425	Untreated
HIST1H4D	6	26297180				Missense	I35T	MMRC0173	Treated
HIVEP1	6	12248762(+)		23	83151704(-)	Translocation		MMRC0335	Treated
HIVEP3	1	41818588				Missense	G1490S	MMRC0408	Untreated
HKDC1	10	70675849				Missense	K295M	MMRC0335	Treated
HLA-A	6	30018667				Missense	I76M	MMRC0427	Treated
HLA-A	6	30018672				Missense	Q78R	MMRC0427	Treated
HMGCL	1	24016623				Missense	D61G	MMRC0191	Treated
HMGCR	5	74682861				Missense	V385A	MMRC0427	Treated
HMGCS2	1	120108530				Missense	R116H	MMRC0387	Untreated
HNF4A	20	42486171				Missense	R331H	MMRC0329	Treated
HNMT	2	138484576(+)		2	138623739(-)	Deletion		MMRC0421	Treated
HNRNPUL2	11	62247643				Missense	E295K	MMRC0389	Treated
HOXD13	2	176667595				Missense	R308H	MMRC0308	Treated
HPD	12	120779655				Missense	S54T	MMRC0322	Untreated
HPSE2	5	40850563(+)		10	100720127(-)	Translocation		MMRC0191	Treated
HRH4	18	20310982				Missense	Q123K	MMRC0004	Untreated
HS2ST1	1	87330920				Nonsense	R190*	MMRC0322	Untreated
HS3ST4	16	17023278(-)		16	25797138(-)	Long range		MMRC0344	Treated
HS3ST4	16	24294544(+)		16	25813970(+)	Long range		MMRC0344	Treated
HS6ST3	13	96283082				Missense	A349P	MMRC0389	Treated
HSD17B1	17	37959117				Missense	G134S	MMRC0389	Treated
HSP90AB1	6	44328839				Missense	R604Q	MMRC0390	Treated
HSPA4	5	132431102				Missense	L87R	MMRC0338	Untreated

Supplementary Table 3 (continued)

Gene	Chr	Position (strand)	2nd gene	Chr	Position (strand)	Type	AA change	Sample	Previously treated
HSPA8	11	122377330(+)		11	122436746(-)	Deletion		MMRC0191	Treated
HTR1A	5	63292924				Missense	L127V	MMRC0308	Treated
HTR3D	3	185239345				Missense	S418L	MMRC0308	Treated
IARS	9	94031231				Splice site	G1095_splice	MMRC0191	Treated
IBTK	6	83006718				Missense	D69N	MMRC0421	Treated
IDE	10	94292538(+)		10	94301591(-)	Deletion		MMRC0389	Treated
IDE	10	94284405				Missense	H134P	MMRC0343	Treated
IDH3A	15	76248382				Nonsense	R361*	MMRC0383	Treated
IFFO2	1	19136695(-)	ST3GAL3	1	44136921(+)	Long range		MMRC0191	Treated
IFI44	1	78898899				Missense	I362T	MMRC0319	Untreated
IFNAR2	21	33541667(+)		21	33543218(+)	Inversion		MMRC0338	Untreated
IFT122	3	130721131				Missense	V1109L	MMRC0389	Treated
IGF1R	15	97283159				Missense	V821I	MMRC0308	Treated
IGF2BP1	17	44470556				Missense	Q143H	MMRC0284	Untreated
IGSF3	1	116923808				Missense	D1021E	MMRC0216	Untreated
IGSF3	1	116923808				Missense	D1021E	MMRC0322	Untreated
IGSF5	21	40059472				Missense	V81I	MMRC0028	Untreated
IHH	2	219628513				Missense	Q299R	MMRC0329	Treated
IKBIP	12	97531523				Missense	E342K	MMRC0319	Untreated
IKBKB	8	42283051				Missense	K171E	MMRC0427	Treated
IL10RA	11	117375238				Missense	T470R	MMRC0309	Untreated
IL1RL2	2	102171968				Missense	D20G	MMRC0390	Treated
IL24	1	205142030				Missense	A176E	MMRC0335	Treated
IL4R	16	27204079(+)		16	27270827(-)	Deletion		MMRC0392	Treated
IL6ST	5	55280693(-)		5	55295034(+)	Tandem duplication		MMRC0191	Treated
ILDR2	1	165161836(+)	USH2A	1	213992413(-)	Long range		MMRC0191	Treated
IMMP2L	7	110426992(-)		7	114862969(-)	Long range		MMRC0191	Treated
IMP5	17	41278774				Missense	K241M	MMRC0322	Untreated
INO80	15	39153881				Missense	N436Y	MMRC0242	Treated
INO80D	2	206615660(-)		11	43948564(-)	Translocation		MMRC0191	Treated
INSR	19	7123394				Missense	S392L	MMRC0308	Treated
INTS12	4	106823393				Missense	M445I	MMRC0389	Treated
INTS4	11	77272573				Missense	R889L	MMRC0343	Treated
IPMK	10	57784079(+)		10	59628825(+)	Long range		MMRC0425	Untreated
IPMK	10	57784853(-)		10	59628838(-)	Long range		MMRC0425	Untreated
IPPK	9	94451674				Missense	S99F	MMRC0392	Treated
IRF4	6	339972				Missense	K123R	MMRC0390	Treated
IRF4	6	339972				Missense	K123R	MMRC0423	Treated
IRF8	16	84504299				Missense	R170Q	MMRC0322	Untreated
IRGC	19	48915458				Missense	R303H	MMRC0347	Untreated
IRX5	16	53522742				Missense	A44V	MMRC0028	Untreated
ISPD	7	16284326				Missense	K296Q	MMRC0332	Treated
ISPD	7	16412368				Missense	R126H	MMRC0387	Untreated
ITFG1	16	46020294				Missense	P193S	MMRC0406	Untreated
ITGA10	1	144239081				Nonsense	W55*	MMRC0389	Treated
ITGAE	17	3611959				Missense	L105W	MMRC0389	Treated
ITGB1	6	129195685(-)		10	33244408(+)	Translocation		MMRC0319	Untreated
ITGB1BP3	19	3890920				Missense	R116C	MMRC0322	Untreated
ITGB6	2	160702875				Missense	G397S	MMRC0406	Untreated
ITGB6	1	99682944(-)		2	160751148(-)	Translocation		MMRC0242	Treated
ITIH5L	X	54798187				Missense	G1064W	MMRC0319	Untreated
ITIH5L	X	54794283				Missense	P1203R	MMRC0173	Treated
IVNS1ABP	1	183536017				Missense	D442N	MMRC0344	Treated
JAG2	14	104683150				Missense	R934H	MMRC0242	Treated
JAK2	9	5067542				Missense	E652K	MMRC0242	Treated
JAKMIP3	10	133816510				Missense	A687V	MMRC0383	Treated
JAM3	11	91489467(+)		11	133499676(+)	Long range		MMRC0338	Untreated
JMJD4	1	225986811				Missense	D433N	MMRC0191	Treated
JUND	19	18252535				Missense	E254K	MMRC0308	Treated
KCNA4	11	29990511				Nonsense	Y97*	MMRC0309	Untreated
KCNC1	11	17750190				Missense	T325A	MMRC0028	Untreated
KCNH1	1	209364145(+)		1	209364915(-)	Deletion		MMRC0408	Untreated
KCNH4	17	37583717				Missense	R171L	MMRC0335	Treated
KCNH5	14	62244770				Missense	Q726E	MMRC0389	Treated
KCNH7	2	163401353				Missense	A83S	MMRC0338	Untreated
KCNJ12	17	21259375				Missense	R43H	MMRC0335	Treated
KCNT2	1	194562479				Missense	L756S	MMRC0322	Untreated
KCTD1	18	22293888				Splice site	D104_splice	MMRC0406	Untreated
KCTD17	22	35785309				Missense	I173T	MMRC0356	Untreated

Supplementary Table 3 (continued)

Gene	Chr	Position (strand)	2nd gene	Chr	Position (strand)	Type	AA change	Sample	Previously treated
KCTD19	16	65885137				Missense	A677S	MMRC0191	Treated
KCTD7	7	65735278(-)		23	20321462(-)	Translocation		MMRC0309	Untreated
KDM3B	5	137765194(+)		8	42489268(+)	Translocation		MMRC0344	Treated
KDM3B	5	137767569(-)		8	42487492(-)	Translocation		MMRC0344	Treated
KDM3B	5	137769281(+)		8	42487795(+)	Translocation		MMRC0344	Treated
KDM6A	X	44834083				Missense	C1234G	MMRC0332	Treated
KHDRBS3	8	136493662(+)		8	136597182(-)	Deletion		MMRC0421	Treated
KIAA0100	17	23990586				Missense	S368L	MMRC0389	Treated
KIAA0125	14	105400359(+)		14	105453725(-)	Deletion		MMRC0408	Untreated
KIAA0182	16	84262123				Missense	V1042G	MMRC0191	Treated
KIAA0319	6	24659718				Missense	K988T	MMRC0329	Treated
KIAA0319L	1	35682448				Missense	I853L	MMRC0332	Treated
KIAA0391	14	34662805				Missense	M201I	MMRC0286	Untreated
KIAA0556	12	91590012(+)		16	27528637(-)	Translocation		MMRC0375	Treated
KIAA0802	18	8815103				Missense	V1199M	MMRC0359	Untreated
KIAA0922	4	154614335(+)		8	28506098(+)	Translocation		MMRC0335	Treated
KIAA1009	6	84909851(+)		6	85035429(+)	Inversion		MMRC0191	Treated
KIAA1009	6	84895756(-)	ADK	10	75782773(-)	Translocation		MMRC0191	Treated
KIAA1024	15	77535890				Missense	E116K	MMRC0381	Untreated
KIAA1109	4	123488211				Missense	T4319I	MMRC0329	Treated
KIAA1244	2	64689541(+)		6	138624939(+)	Translocation		MMRC0343	Treated
KIAA1279	10	70430283				Missense	E175V	MMRC0381	Untreated
KIAA1409	14	93153362				Missense	R1218W	MMRC0338	Untreated
KIAA1467	12	13102703				Missense	R162H	MMRC0308	Treated
KIAA1468	18	58093609				Missense	L964V	MMRC0381	Untreated
KIAA1486	2	226155904				Missense	S509R	MMRC0376	Untreated
KIAA1614	1	179162140(+)		1	179174736(-)	Deletion		MMRC0392	Treated
KIAA1755	20	36285373				Missense	D750G	MMRC0359	Untreated
KIAA1755	13	60129309(-)		20	36297694(+)	Translocation		MMRC0191	Treated
KIF1A	2	241314929				Missense	S1269F	MMRC0383	Treated
KIF3C	2	26032731				Missense	Q544H	MMRC0387	Untreated
KIF6	6	39433094				Missense	T706M	MMRC0335	Treated
KIFC1	6	33479716				Missense	Q196H	MMRC0335	Treated
KIR2DS4	19	60042774				Missense	SS150>ST	MMRC0284	Untreated
KIRREL3	11	126043158(+)		11	126701882(-)	Deletion		MMRC0343	Treated
KLHL6	3	184755845				Missense	F97L	MMRC0308	Treated
KLK15	19	56022207				Missense	E74K	MMRC0389	Treated
KLK9	19	56198824				Missense	S184L	MMRC0381	Untreated
KLRC2	12	10479798				Missense	R19W	MMRC0191	Treated
KRAS	12	25271542				Missense	Q61H	MMRC0004	Untreated
KRAS	12	25269829				Missense	A146T	MMRC0282	Treated
KRAS	12	25271535				Missense	Y64D	MMRC0308	Treated
KRAS	12	25289529				Missense	L19F	MMRC0329	Treated
KRAS	12	25269829				Missense	A146T	MMRC0332	Treated
KRAS	12	25269914				Missense	K117N	MMRC0338	Untreated
KRAS	12	25271542				Missense	Q61H	MMRC0359	Untreated
KRAS	12	25271538				Missense	E63K	MMRC0381	Untreated
KRAS	12	25289548				Missense	G13D	MMRC0406	Untreated
KRAS	12	25269829				Missense	A146T	MMRC0408	Untreated
KRBA2	17	8210763(-)		17	8214067(-)	Inversion		MMRC0392	Treated
KRBA2	17	8214118				Missense	E180K	MMRC0392	Treated
KRT31	17	36805031				Frame shift deletion	E285fs	MMRC0173	Treated
KSR2	12	116519582(+)		17	67520926(-)	Translocation		MMRC0383	Treated
LAMA2	6	129241534(+)		6	129397206(-)	Deletion		MMRC0332	Treated
LAMA4	6	112635034				Missense	C101W	MMRC0322	Untreated
LAMA4	6	112619741				Missense	A170S	MMRC0406	Untreated
LAMA5	20	60345216				Missense	G729V	MMRC0173	Treated
LAMB1	7	107414014				Nonsense	R152*	MMRC0427	Treated
LAMB2	3	49135612				Missense	S1394F	MMRC0286	Untreated
LAMC3	9	132904156				Missense	H354P	MMRC0423	Treated
LARS2	3	45417370(-)		12	99765359(+)	Translocation		MMRC0376	Untreated
LASS3	15	98837769				Missense	R138T	MMRC0389	Treated
LCE3A	1	150862174				Nonsense	C10*	MMRC0173	Treated
LGALS3	14	54674555				Nonsense	Q20*	MMRC0335	Treated
LGR5	12	70123383(-)		19	47133190(+)	Translocation		MMRC0191	Treated
LILRA2	19	59778650				Missense	K257N	MMRC0335	Treated
LINGO2	9	27939072				Missense	T533N	MMRC0343	Treated
LINGO4	1	150041224				Missense	T194I	MMRC0423	Treated
LIPC	15	56640364				Missense	Y354F	MMRC0335	Treated

Supplementary Table 3 (continued)

Gene	Chr	Position (strand)	2nd gene	Chr	Position (strand)	Type	AA change	Sample	Previously treated
LIPC	8	114544567(+)		15	56586588(-)	Translocation		MMRC0309	Untreated
LIX1L	1	144203617				Missense	R161L	MMRC0329	Treated
LMBR1L	12	47778142				Missense	F418L	MMRC0383	Treated
LMO2	11	33842783				Missense	E135D	MMRC0335	Treated
LMOD3	3	69250793				Missense	M468T	MMRC0425	Untreated
LNP1	3	101631363				Missense	R34W	MMRC0344	Treated
LOH12CR1	12	12425720(+)	C12orf11	12	26958462(-)	Long range		MMRC0421	Treated
LOXL2	8	23235653				Missense	G413R	MMRC0308	Treated
LPO	2	34043266(-)		17	53689430(+)	Translocation		MMRC0344	Treated
LRIG3	12	57594383				Missense	D20Y	MMRC0309	Untreated
LRMP	12	25133277(+)	CASC1	12	25165289(+)	Inversion		MMRC0344	Treated
LRMP	12	25134396				Missense	E202Q	MMRC0344	Treated
LRMP	12	25134330				Nonsense	E180*	MMRC0344	Treated
LRMP	12	25133858(-)	PRKCB	16	23889173(+)	Translocation		MMRC0344	Treated
LRMP	12	25135141(+)	PRKCB	16	23867717(+)	Translocation		MMRC0344	Treated
LRP1B	2	141586373(+)		2	141707595(-)	Deletion		MMRC0421	Treated
LRP1B	2	141614994(-)		2	221292668(+)	Long range		MMRC0375	Treated
LRP1B	2	141424323				Missense	N1029K	MMRC0376	Untreated
LRP1B	2	140824905				Missense	F3941L	MMRC0425	Untreated
LRP1B	2	140931690				Missense	V3209A	MMRC0425	Untreated
LRP1B	2	142098906(-)		18	71609703(-)	Translocation		MMRC0191	Treated
LRP2	2	169885550				Missense	A57V	MMRC0406	Untreated
LRP6	12	12208550				Missense	T659I	MMRC0028	Untreated
LRP8	1	53463794(+)		1	53490546(-)	Deletion		MMRC0319	Untreated
LRRC16A	6	25689503				Missense	D955Y	MMRC0343	Treated
LRRC36	16	65941637				Missense	T53A	MMRC0412	Treated
LRRC41	1	46523909				Missense	R403C	MMRC0028	Untreated
LRRC4C	11	40093586				Missense	N278I	MMRC0344	Treated
LRRIQ3	1	74421820				Nonsense	L46*	MMRC0335	Treated
LRRK2	12	38918064				Missense	E155K	MMRC0286	Untreated
LRRK2	12	38994132				Missense	I1543S	MMRC0344	Treated
LRRK2	12	38953506(+)		18	8522903(+)	Translocation		MMRC0376	Untreated
LRRK2	12	38953703(-)		18	8522979(-)	Translocation		MMRC0376	Untreated
LRRN3	7	110551713				Missense	S550C	MMRC0191	Treated
LRRN3	7	110551428				Missense	Y455F	MMRC0322	Untreated
LRTM2	12	1813952				Missense	R306Q	MMRC0347	Untreated
LSM14A	19	39398045				Missense	A239T	MMRC0329	Treated
LSM14A	19	39402623				Splice site	R379_splice	MMRC0412	Treated
LUC7L3	17	46177079				Missense	I200T	MMRC0322	Untreated
LUM	12	90026794				Missense	Q32E	MMRC0322	Untreated
LY6H	8	144311151				Missense	C105Y	MMRC0381	Untreated
LYPD4	19	47033866				Missense	T174I	MMRC0344	Treated
LYST	1	233942040				Missense	D3289N	MMRC0028	Untreated
LZTR1	22	19673082				Missense	P172T	MMRC0329	Treated
MAB21L2	4	151724005				Missense	A125E	MMRC0335	Treated
MACF1	1	39438098(-)	HNF1A	12	119911516(-)	Translocation		MMRC0383	Treated
MAGEC1	X	140821961				Missense	P369S	MMRC0356	Untreated
MAGED1	X	51656630				Nonsense	W380*	MMRC0216	Untreated
MAGED1	X	51655046				Nonsense	S68*	MMRC0173	Treated
MAGEL2	15	21441683				Missense	A767V	MMRC0309	Untreated
MAN1A1	6	119551411				Missense	F526C	MMRC0322	Untreated
MAN1A1	6	119664968				Splice site	G234_splice	MMRC0335	Treated
MAOA	X	43400553				Missense	A7V	MMRC0173	Treated
MAP1LC3B	16	85993288				Missense	I35V	MMRC0390	Treated
MAP2K3	17	21144827				Missense	D81N	MMRC0421	Treated
MAP2K4	17	8032880(+)		17	11869941(-)	Long range		MMRC0392	Treated
MAP2K4	17	11890824(+)		17	14883729(-)	Long range		MMRC0392	Treated
MAP2K4	17	11946633(+)		17	14820955(+)	Long range		MMRC0392	Treated
MAP2K4	17	11956089(+)		17	14900582(-)	Long range		MMRC0392	Treated
MAP2K4	4	33914(+)		17	11909416(-)	Translocation		MMRC0392	Treated
MAP2K4	17	11909171(+)		21	42321425(-)	Translocation		MMRC0392	Treated
MAP2K4	17	11946955(-)	DSCAM	21	40855018(-)	Translocation		MMRC0392	Treated
MAP3K1	5	56209516(-)		8	42575852(+)	Translocation		MMRC0344	Treated
MAP3K14	17	40720277(+)		17	40725216(-)	Deletion		MMRC0319	Untreated
MAP4K4	2	101814695				Missense	P197S	MMRC0343	Treated
MAPK4	18	46444433				Missense	S36L	MMRC0412	Treated
MARK2	11	63428833				Splice site	S559_splice	MMRC0359	Untreated
MASP1	3	188486521				Missense	Y8F	MMRC0412	Treated
MATK	19	3736123				Missense	R4Q	MMRC0286	Untreated

Supplementary Table 3 (continued)

Gene	Chr	Position (strand)	2nd gene	Chr	Position (strand)	Type	AA change	Sample	Previously treated
MBD1	18	46053966				Missense	G471A	MMRC0383	Treated
MCART1	9	37877707				Missense	I281V	MMRC0390	Treated
MCF2L	13	112790041				Missense	T876M	MMRC0392	Treated
MCM4	8	49048122				Missense	A694V	MMRC0338	Untreated
MCTP2	15	92823262				Missense	L878V	MMRC0282	Treated
MCTS1	X	119623420				Missense	D48Y	MMRC0406	Untreated
MDC1	6	30780239				Missense	T1567I	MMRC0173	Treated
MDM4	1	202780399				Missense	Q262H	MMRC0343	Treated
MDN1	6	90458942				Missense	V3510M	MMRC0282	Treated
ME3	11	85914611(-)		12	12973435(-)	Translocation		MMRC0383	Treated
MECOM	3	170697373(-)	TMEM120B	12	120666057(+)	Translocation		MMRC0383	Treated
MED26	19	16557098(+)		19	18275083(-)	Long range		MMRC0392	Treated
MEF2A	15	98070181				Missense	I394M	MMRC0309	Untreated
MEGF9	9	122493555				Missense	A199V	MMRC0406	Untreated
MELK	9	36587286				Missense	K158R	MMRC0004	Untreated
METAP2	12	94392090				Missense	A2S	MMRC0282	Treated
METTL2B	7	108718285(+)		7	127928372(-)	Long range		MMRC0191	Treated
METTL9	16	21531602				Missense	H101Y	MMRC0286	Untreated
MFN1	3	180559326				Missense	S85R	MMRC0389	Treated
MFSD6L	17	8642488				Missense	S226T	MMRC0242	Treated
MGA	15	39775090(+)		15	39784434(-)	Deletion		MMRC0392	Treated
MGA	15	39784934(+)	EHD4	15	40032969(-)	Deletion		MMRC0332	Treated
MID2	X	106970865				Missense	R105H	MMRC0335	Treated
MIPEP	13	23351435				Missense	L171F	MMRC0338	Untreated
MKRN3	15	21363470				Missense	D483V	MMRC0173	Treated
MLKL	16	73286702				Missense	R152K	MMRC0387	Untreated
MLL	11	117875341				Missense	M2022I	MMRC0308	Treated
MLL2	12	47702190				Missense	H5475L	MMRC0343	Treated
MLL2	12	47714190				Missense	F3556S	MMRC0173	Treated
MLL3	7	151557958				Missense	Y987H	MMRC0242	Treated
MLPH	2	238084372				Missense	V112F	MMRC0347	Untreated
MMP16	8	89128127				Missense	Y459D	MMRC0322	Untreated
MMP17	12	130893124(-)	EP400	12	131045475(+)	Tandem duplication		MMRC0387	Untreated
MOGAT3	7	100626060				Missense	E305K	MMRC0173	Treated
MON2	12	61181623				Missense	L223F	MMRC0308	Treated
MOXD1	6	132690948				Splice site	G282_splice	MMRC0392	Treated
MPDZ	9	13128005				Missense	G1384V	MMRC0173	Treated
MPHOSPH9	12	122264308(+)		12	122273615(-)	Deletion		MMRC0335	Treated
MPL	1	43576423				Missense	T49N	MMRC0375	Treated
MPRIP	17	16738425(-)		17	16925310(+)	Tandem duplication		MMRC0332	Treated
MRC2	17	58107608				Nonsense	W606*	MMRC0244	Untreated
MRE11A	11	90023122(-)		11	93829988(-)	Long range		MMRC0338	Untreated
MRPL15	8	55211768				Missense	E85K	MMRC0335	Treated
MRPS27	5	71559926				Missense	A206V	MMRC0376	Untreated
MRVI1	11	10630174				Nonsense	Q58*	MMRC0412	Treated
MSL3	X	11689608				Missense	E92Q	MMRC0332	Treated
MSRB3	12	64010867(-)		12	122274899(+)	Long range		MMRC0335	Treated
MSRB3	12	64004119(-)	MPHOSPH9	12	122264416(-)	Long range		MMRC0335	Treated
MSRB3	12	63992556(+)	TXNRD1	12	103180160(-)	Long range		MMRC0335	Treated
MSRB3	12	64013283(+)	TXNRD1	12	103176369(+)	Long range		MMRC0335	Treated
MT1A	16	55231284				Missense	C36F	MMRC0375	Treated
MTDH	8	53819616(-)		8	98802054(+)	Long range		MMRC0343	Treated
MTDH	8	98802088(-)		8	128868323(-)	Long range		MMRC0343	Treated
MTMR1	X	149649337				Missense	GQ210>GP	MMRC0244	Untreated
MTMR11	1	148169939				Missense	R376H	MMRC0282	Treated
MTMR2	11	95296028(+)		11	134024425(-)	Long range		MMRC0338	Untreated
MTR	1	235053847(+)		1	236285234(-)	Long range		MMRC0406	Untreated
MUC16	19	8863576				Missense	K13414E	MMRC0319	Untreated
MUC16	19	8945925				Missense	S2297N	MMRC0343	Treated
MUC16	19	8925540				Missense	L7636I	MMRC0412	Treated
MUC16	19	8945158				Missense	G2553R	MMRC0412	Treated
MUC17	7	100463930				Missense	T838I	MMRC0392	Treated
MUC2	11	1083295				Missense	T1705I	MMRC0392	Treated
MUC2	11	1083094				Missense	V1638G	MMRC0421	Treated
MUC21	6	31062393				Missense	D154E	MMRC0412	Treated
MUC6	11	1008462				Missense	V1447I	MMRC0329	Treated
MXRA5	6	13686616(-)		X	3244036(+)	Translocation		MMRC0383	Treated
MYH10	17	7970180(+)		17	8377434(-)	Deletion		MMRC0392	Treated
MYH10	17	8406603(+)		17	8849242(+)	Inversion		MMRC0392	Treated

Supplementary Table 3 (continued)

Gene	Chr	Position (strand)	2nd gene	Chr	Position (strand)	Type	AA change	Sample	Previously treated
MYH10	17	8325800(+)	NCOR1	17	15891328(-)	Long range		MMRC0392	Treated
MYH10	17	8413251(+)	PIGL	17	16077806(-)	Long range		MMRC0392	Treated
MYH10	17	8348738				Missense	R1169C	MMRC0390	Treated
MYH10	17	8415436(-)		21	42325724(-)	Translocation		MMRC0392	Treated
MYH10	17	8406802(+)	PDE9A	21	42952931(-)	Translocation		MMRC0392	Treated
MYH11	16	15765375(+)		16	15773834(+)	Inversion		MMRC0344	Treated
MYH11	16	15779710(+)		16	34645650(+)	Long range		MMRC0344	Treated
MYH11	3	77792962(-)		16	15799932(+)	Translocation		MMRC0191	Treated
MYH8	17	10244725				Missense	E1148Q	MMRC0421	Treated
MYO10	5	16754269				Missense	A1079P	MMRC0335	Treated
MYO18B	22	24730698				Missense	I2116N	MMRC0335	Treated
MYO18B	22	24577473				Missense	R1271Q	MMRC0344	Treated
MYO1C	17	1329657				Missense	N298K	MMRC0338	Untreated
MYO1E	15	57437976(+)		15	57475211(+)	Inversion		MMRC0344	Treated
MYO3A	10	26522184				Nonsense	R1495*	MMRC0028	Untreated
MYO5A	14	95299060(+)		15	50550021(-)	Translocation		MMRC0335	Treated
MYO6	6	76614846(+)		6	77319167(-)	Deletion		MMRC0421	Treated
MYO9A	15	69957446				Missense	T1974P	MMRC0286	Untreated
MYOCD	17	12581699(+)	RICH2	17	12716278(-)	Deletion		MMRC0191	Treated
MYOF	10	95073029				Missense	R1770Q	MMRC0242	Treated
MYOM2	8	2064591				Missense	Y1255C	MMRC0427	Treated
MYOM3	1	24261151				Missense	T1269M	MMRC0338	Untreated
MYSM1	1	58920143				Missense	Q387H	MMRC0387	Untreated
MYT1	20	62341567				Missense	M1035T	MMRC0347	Untreated
N4BP1	16	47134504				Missense	A835T	MMRC0392	Treated
NAALADL2	3	176237088(+)	THSD7A	7	11574366(+)	Translocation		MMRC0406	Untreated
NALCN	13	100744950(+)	ITGBL1	13	101001082(-)	Deletion		MMRC0332	Treated
NALCN	13	100734313				Missense	P369H	MMRC0242	Treated
NAV2	11	20034002				Missense	R1585Q	MMRC0322	Untreated
NAV3	12	76924973				Missense	K508N	MMRC0412	Treated
NAV3	12	76912769				Missense	K243E	MMRC0427	Treated
NBAS	2	15224765				Nonsense	W2325*	MMRC0427	Treated
NBEA	13	35118474				Missense	A2566T	MMRC0412	Treated
NBN	8	91018479				Missense	V729L	MMRC0338	Untreated
NBPF16	1	147023078				Missense	L595V	MMRC0344	Treated
NBPF3	1	21679254				Missense	D444E	MMRC0329	Treated
NCAM2	21	21760803				Missense	V554F	MMRC0335	Treated
NCAPD3	11	133595759				Missense	I46L	MMRC0173	Treated
NCKAP1	2	183601903(+)		6	70370171(+)	Translocation		MMRC0309	Untreated
NCLN	19	3143630				Missense	M116T	MMRC0308	Treated
NCOA3	20	45714618				In frame deletion	M1336_S1337>M	MMRC0004	Untreated
NCOR1	17	15910721(-)	PIGL	17	16070205(-)	Inversion		MMRC0392	Treated
NCOR1	17	8172996(-)		17	15909891(+)	Long range		MMRC0392	Treated
NDRG3	20	34726791(+)		20	34733246(-)	Deletion		MMRC0387	Untreated
NDRG3	20	34766752(+)		20	34771458(+)	Inversion		MMRC0412	Treated
NDRG3	20	34757479(+)		20	48734587(-)	Long range		MMRC0387	Untreated
NDST4	4	116064910(+)		4	116233317(-)	Deletion		MMRC0421	Treated
NDUFA5	7	122969429				Nonsense	Q111*	MMRC0308	Treated
NDUFAF2	5	60385870(+)	BAG4	8	38173841(+)	Translocation		MMRC0344	Treated
NEB	2	152092285				Missense	P5553S	MMRC0376	Untreated
NEB	2	152289034				Missense	A200T	MMRC0173	Treated
NEBL	10	21160467				Missense	V501M	MMRC0319	Untreated
NEBL	10	21187262				Missense	D272E	MMRC0421	Treated
NEDD1	12	95835636				Missense	R113Q	MMRC0286	Untreated
NEFH	22	28215638				Missense	V670E	MMRC0390	Treated
NEFM	8	24830678				Missense	M93L	MMRC0335	Treated
NES	1	154910509(-)		1	154942931(+)	Tandem duplication		MMRC0242	Treated
NEURL4	17	7170770				Missense	D359G	MMRC0390	Treated
NFATC3	16	66806021(-)	CDH1	16	67347328(+)	Tandem duplication		MMRC0425	Untreated
NFIA	1	61435759(+)	VAV3	1	108178920(-)	Long range		MMRC0408	Untreated
NFIB	9	14234848(-)	C12orf42	12	102325833(-)	Translocation		MMRC0191	Treated
NID1	1	234278803				Missense	D112G	MMRC0390	Treated
NKAIN2	2	35385997(+)		6	124531546(+)	Translocation		MMRC0421	Treated
NKAIN2	2	35460209(-)		6	124551124(-)	Translocation		MMRC0421	Treated
NKAIN3	8	51306139(-)		8	63764015(+)	Long range		MMRC0344	Treated
NKAIN3	8	56102765(+)		8	63763970(-)	Long range		MMRC0344	Treated
NKAPL	6	28335421				Missense	R98H	MMRC0191	Treated
NLRP2	19	60186564(+)		19	60187365(+)	Inversion		MMRC0383	Treated
NLRP4	19	61061928				Missense	V453M	MMRC0338	Untreated

Supplementary Table 3 (continued)

Gene	Chr	Position (strand)	2nd gene	Chr	Position (strand)	Type	AA change	Sample	Previously treated
NLRP7	19	60104250(+)		19	60135890(-)	Deletion		MMRC0383	Treated
NLRP7	19	60135655(-)		X	136757206(-)	Translocation		MMRC0383	Treated
NLRP8	19	61157859				Missense	I208T	MMRC0028	Untreated
NLRP8	19	61159220				Missense	V662I	MMRC0392	Treated
NNT	2	216780312(+)		5	43687830(-)	Translocation		MMRC0191	Treated
NOLC1	10	103902447(+)	SMPD3	16	66962164(-)	Translocation		MMRC0390	Treated
NOM1	7	156439605				Missense	L387Q	MMRC0425	Untreated
NOS1	12	116194635				Missense	Y593H	MMRC0392	Treated
NOTCH2NL	1	143964034(-)	LCLAT1	2	30594834(-)	Translocation		MMRC0191	Treated
NOTCH4	6	32299637				In frame deletion	L15_L16>L	MMRC0319	Untreated
NPAS3	14	33332866				Missense	G389V	MMRC0356	Untreated
NPFFR2	4	73116661				Missense	R60Q	MMRC0359	Untreated
NPLOC4	17	77184284				Splice site	K177_splice	MMRC0389	Treated
NPR2	9	35784002				Missense	G259R	MMRC0282	Treated
NPY2R	4	156355623				Missense	K361R	MMRC0344	Treated
NR2F2	15	94681737				Missense	S223L	MMRC0389	Treated
NR3C2	4	149400600				Missense	F626C	MMRC0308	Treated
NR3C2	4	149254800				Missense	E785K	MMRC0319	Untreated
NR6A1	9	126511745(+)		11	9633987(-)	Translocation		MMRC0387	Untreated
NRAS	1	115058052				Missense	Q61R	MMRC0244	Untreated
NRAS	1	115058051				Missense	Q61H	MMRC0284	Untreated
NRAS	1	115058053				Missense	Q61K	MMRC0319	Untreated
NRAS	1	115058052				Missense	Q61R	MMRC0343	Treated
NRAS	1	115058052				Missense	Q61R	MMRC0383	Treated
NRAS	1	115058052				Missense	Q61R	MMRC0390	Treated
NRAS	1	115058052				Missense	Q61R	MMRC0412	Treated
NRAS	1	115060268				Missense	G13R	MMRC0423	Treated
NRAS	1	115060268				Missense	G13R	MMRC0173	Treated
NRG1	8	32740315				Missense	H433N	MMRC0425	Untreated
NRG3	10	84384775(+)		10	84709572(-)	Deletion		MMRC0392	Treated
NRG3	10	84734905				Missense	N552T	MMRC0329	Treated
NRP2	2	206336664				Missense	L689R	MMRC0390	Treated
NRXN1	2	50256599(-)		2	70640059(+)	Long range		MMRC0309	Untreated
NRXN1	2	50317592				Missense	S94C	MMRC0322	Untreated
NRXN3	14	78821969(+)		14	79079626(-)	Deletion		MMRC0392	Treated
NRXN3	14	79100435(+)		14	79211468(-)	Deletion		MMRC0392	Treated
NRXN3	14	78959852(-)		14	79205866(-)	Inversion		MMRC0392	Treated
NRXN3	14	78825766(-)		14	78956817(+)	Tandem duplication		MMRC0392	Treated
NRXN3	14	78947069(-)		14	79057415(+)	Tandem duplication		MMRC0392	Treated
NRXN3	14	79101780(-)		14	79201916(+)	Tandem duplication		MMRC0392	Treated
NSMCE2	8	126438008(+)		8	126454670(-)	Deletion		MMRC0392	Treated
NSMCE2	8	126386631(+)		8	128775537(-)	Long range		MMRC0343	Treated
NSMCE2	8	126387784(+)		8	128834720(+)	Long range		MMRC0392	Treated
NSUN2	5	6664174				Missense	F374L	MMRC0389	Treated
NT5C3L	17	37238614				Missense	H166P	MMRC0427	Treated
NTM	8	41188158(-)		11	130987563(+)	Translocation		MMRC0412	Treated
NTN1	17	8874232(-)		17	9062733(-)	Inversion		MMRC0392	Treated
NTN1	17	8931037(-)	GAS7	17	9776265(-)	Inversion		MMRC0392	Treated
NTN1	17	8962987(+)	MAP2K4	17	11890893(-)	Long range		MMRC0392	Treated
NTN1	17	9053236(+)	MAP2K4	17	11958316(-)	Long range		MMRC0392	Treated
NTN1	17	8849351(-)		17	8899501(+)	Tandem duplication		MMRC0392	Treated
NTN1	17	8889896(-)		21	42308631(+)	Translocation		MMRC0392	Treated
NTN1	17	8930086(+)		21	42444746(+)	Translocation		MMRC0392	Treated
NTN1	17	9003033(+)	BACE2	21	41530729(+)	Translocation		MMRC0392	Treated
NTN1	17	8929539(-)	DSCAM	21	40864782(-)	Translocation		MMRC0392	Treated
NTN1	17	8931346(+)	FAM3B	21	41629575(-)	Translocation		MMRC0392	Treated
NUCB2	3	124191567(-)		11	17306312(+)	Translocation		MMRC0191	Treated
NUMA1	11	71407199				Missense	I251L	MMRC0309	Untreated
NUMB	14	72813619				Missense	S448L	MMRC0389	Treated
NUP155	5	37353901				Missense	P751S	MMRC0191	Treated
NUP155	5	37387135				Missense	T213P	MMRC0309	Untreated
NUP160	11	47448402(+)		11	47793673(-)	Deletion		MMRC0408	Untreated
NUP210	3	13402852				Missense	P247L	MMRC0344	Treated
NUP210L	1	152328606				Missense	H759P	MMRC0332	Treated
NUP214	9	133004531				Missense	E350K	MMRC0286	Untreated
NUP93	16	55425591				Missense	R530W	MMRC0376	Untreated
OBFC2A	2	192257253				Missense	T144K	MMRC0376	Untreated
OBSCN	1	226498862				Missense	G1150C	MMRC0338	Untreated
OCM	7	5887105				Missense	R20Q	MMRC0389	Treated

Supplementary Table 3 (continued)

Gene	Chr	Position (strand)	2nd gene	Chr	Position (strand)	Type	AA change	Sample	Previously treated
ODF1	8	103642209				Missense	N225S	MMRC0284	Untreated
ODZ1	X	123633315				Missense	L356Q	MMRC0387	Untreated
ODZ2	5	167421693				Missense	G454C	MMRC0383	Treated
ODZ4	11	78161592(+)		11	78567574(-)	Deletion		MMRC0319	Untreated
OLFM3	1	102042783				Missense	D326Y	MMRC0389	Treated
OPRL1	20	62194608				Missense	L31V	MMRC0381	Untreated
OR12D2	6	29472995				Missense	K180N	MMRC0329	Treated
OR1G1	17	2977247				Missense	V117F	MMRC0356	Untreated
OR1L6	9	124552015				Missense	Q23R	MMRC0344	Treated
OR2A14	7	143458045				Missense	A303T	MMRC0421	Treated
OR2G2	1	245818830				Nonsense	C182*	MMRC0356	Untreated
OR2K2	9	113129840				Missense	G232V	MMRC0387	Untreated
OR2L8	1	246179310				Missense	F176L	MMRC0191	Treated
OR4D5	11	123315982				Missense	V150G	MMRC0425	Untreated
OR4E2	14	21203812				Nonsense	R226*	MMRC0392	Treated
OR4K14	14	19552945				Missense	I83T	MMRC0376	Untreated
OR5AP2	11	56165605				Missense	Y296C	MMRC0282	Treated
OR5D16	11	55363092				Missense	S97P	MMRC0309	Untreated
OR5H14	3	99351494				Missense	S192F	MMRC0309	Untreated
OR5P3	11	7803897				Missense	A67S	MMRC0412	Treated
OR8D1	11	123684960				Missense	L305V	MMRC0381	Untreated
OR8J3	11	55661718				Missense	S18C	MMRC0344	Treated
OR8K3	11	55843058				Missense	Q234E	MMRC0282	Treated
ORAOV1	11	69191913				Missense	F92L	MMRC0244	Untreated
OSBP	11	59100733				Missense	E773Q	MMRC0389	Treated
OSBP2	22	29613453				Missense	R383Q	MMRC0242	Treated
OSBPL6	2	178934702				Missense	E401Q	MMRC0309	Untreated
OSBPL8	12	75308492				Missense	D294N	MMRC0389	Treated
OSR2	8	100030520				Missense	T55M	MMRC0191	Treated
OVCH1	12	29489537				Missense	T941I	MMRC0335	Treated
PAK4	19	44356290				Missense	S300T	MMRC0329	Treated
PANK3	5	167921011				Missense	I301F	MMRC0242	Treated
PAPPA2	1	174887833(+)		6	38796456(+)	Translocation		MMRC0309	Untreated
PARK2	2	34866613(-)		6	161858558(-)	Translocation		MMRC0376	Untreated
PARN	16	11675607(-)		16	14557118(+)	Long range		MMRC0344	Treated
PARN	16	14557020				Missense	G437V	MMRC0344	Treated
PARVG	22	42923414				Missense	N210K	MMRC0383	Treated
PBK	8	27724445				Missense	M241L	MMRC0335	Treated
PBRM1	3	52662877(+)	KRT15	17	36924674(+)	Translocation		MMRC0335	Treated
PBX2	6	32263038				Missense	G328A	MMRC0284	Untreated
PCCA	13	99946892(+)	NALCN	13	100666583(-)	Deletion		MMRC0392	Treated
PCDH10	4	134303621				Missense	A946V	MMRC0343	Treated
PCDH10	4	134293320				Missense	G859C	MMRC0381	Untreated
PCDH15	10	55452774				Missense	T809A	MMRC0376	Untreated
PCDH17	13	57105459				Missense	T260A	MMRC0412	Treated
PCDH18	4	138670955				Missense	A580T	MMRC0344	Treated
PCDH18	4	138672160				Missense	A178V	MMRC0173	Treated
PCDH20	13	60884812				Missense	P474R	MMRC0335	Treated
PCDH7	2	172845896(-)		4	30588059(-)	Translocation		MMRC0191	Treated
PCDHA11	5	140230230				Missense	A453V	MMRC0381	Untreated
PCDHA12	5	140235327				Missense	G29V	MMRC0216	Untreated
PCDHB1	5	140412416				Missense	V393L	MMRC0412	Treated
PCDHB10	5	140552936				Missense	S209R	MMRC0390	Treated
PCDHB13	5	140576140				Missense	C754Y	MMRC0329	Treated
PCDHGA7	5	140743885				Missense	R412Q	MMRC0191	Treated
PCYT1B	X	24503217				Missense	R265K	MMRC0191	Treated
PDE11A	2	178644936				Missense	R159W	MMRC0242	Treated
PDE11A	2	178253862				Missense	F537L	MMRC0329	Treated
PDE3A	12	20681341				Missense	N681I	MMRC0347	Untreated
PDE4D	4	96913100(-)		5	59410132(+)	Translocation		MMRC0309	Untreated
PDE8B	5	76682659				Missense	V344G	MMRC0004	Untreated
PDGFRL	8	17530561				Missense	Y264F	MMRC0338	Untreated
PDIA6	2	10854709				Missense	P99S	MMRC0338	Untreated
PDZD8	10	119124316				Missense	R138H	MMRC0329	Treated
PFAS	17	8105431(-)	MAP2K4	17	11947091(-)	Long range		MMRC0392	Treated
PFAS	17	7936725(-)		17	8110682(+)	Tandem duplication		MMRC0392	Treated
PFAS	17	8110065(-)	MYH10	17	8376370(+)	Tandem duplication		MMRC0392	Treated
PFAS	17	8112256(-)		21	39868238(+)	Translocation		MMRC0392	Treated
PFAS	17	8105593(+)	DSCAM	21	40855116(-)	Translocation		MMRC0392	Treated

Supplementary Table 3 (continued)

Gene	Chr	Position (strand)	2nd gene	Chr	Position (strand)	Type	AA change	Sample	Previously treated
PFAS	17	8111022(-)	SH3BGR	21	39805530(-)	Translocation		MMRC0392	Treated
PFTK1	7	90338499(+)		7	90399548(-)	Deletion		MMRC0356	Untreated
PFTK2	2	202375229(+)		2	202389723(-)	Deletion		MMRC0343	Treated
PGM2L1	11	73762831(-)		11	73765908(+)	Tandem duplication		MMRC0319	Untreated
PHACTR2	6	144169914				Missense	F545I	MMRC0329	Treated
PHC1	12	8974433				Missense	V250L	MMRC0309	Untreated
PHTF1	1	114085790(+)	PTP4A3	8	142501723(+)	Translocation		MMRC0421	Treated
PICK1	22	36789806(-)		22	38770891(+)	Long range		MMRC0375	Treated
PIGK	1	77399662				Missense	A240V	MMRC0356	Untreated
PIGL	17	8067247(+)		17	16149713(-)	Long range		MMRC0392	Treated
PIGL	17	8193111(-)		17	16138288(+)	Long range		MMRC0392	Treated
PIGL	17	8208481(-)		17	16070121(+)	Long range		MMRC0392	Treated
PIGL	17	16070378(+)	DSCAM	21	40918883(+)	Translocation		MMRC0392	Treated
PIGL	17	16107242(+)	SLC37A1	21	42834123(+)	Translocation		MMRC0392	Treated
PIGL	17	16109115(-)	SLC37A1	21	42834251(-)	Translocation		MMRC0392	Treated
PIGZ	3	198158711				Missense	V485G	MMRC0216	Untreated
PIWIL1	12	129408041				Missense	D552V	MMRC0390	Treated
PKD1L1	7	47496004(-)		7	47846579(+)	Tandem duplication		MMRC0356	Untreated
PKHD1	6	1322688(-)		6	51697366(+)	Long range		MMRC0389	Treated
PKHD1	6	51693456(+)		6	76546987(+)	Long range		MMRC0389	Treated
PKHD1	6	51592193				Missense	R3957H	MMRC0309	Untreated
PKHD1	6	52018871				Missense	Y828N	MMRC0347	Untreated
PKHD1L1	8	110546210				Missense	K2658R	MMRC0343	Treated
PKHD1L1	8	110536259				Splice site	G2292_splice	MMRC0338	Untreated
PKP1	1	199556104				Missense	C461S	MMRC0319	Untreated
PLA2G2D	1	20315541				Missense	Q19H	MMRC0412	Treated
PLA2G2D	1	20314693				Nonsense	W62*	MMRC0242	Treated
PLA2G2E	1	20121737				Missense	G47S	MMRC0244	Untreated
PLA2G6	22	36842102				Missense	Y602C	MMRC0329	Treated
PLA2R1	2	160542111				Nonsense	Y777*	MMRC0242	Treated
PLCB4	20	9336667				Missense	A572D	MMRC0308	Treated
PLD2	17	4668580				Nonsense	S648*	MMRC0389	Treated
PLEKHA2	8	38946121				Missense	S314C	MMRC0389	Treated
PLEKHA7	8	52121898(+)		11	16790987(-)	Translocation		MMRC0191	Treated
PLEKHG2	19	44604700				Missense	P537A	MMRC0356	Untreated
PLK1S1	20	21154716(+)		20	21201650(-)	Deletion		MMRC0421	Treated
PLK4	4	129031759				Missense	E631D	MMRC0329	Treated
PLLP	15	50379143(-)		16	55866315(+)	Translocation		MMRC0383	Treated
PMP22	17	8857645(-)		17	15084210(-)	Long range		MMRC0392	Treated
PMP22	17	15075518(+)	DSCAM	21	40854640(+)	Translocation		MMRC0392	Treated
PNLIP	10	118308665				Missense	F314L	MMRC0387	Untreated
PNPLA3	22	42673444				Missense	S432Y	MMRC0286	Untreated
PNRC1	6	89847473				Frame shift deletion	D47fs	MMRC0286	Untreated
PNRC1	6	89847360				Missense	E10K	MMRC0286	Untreated
PODN	1	53320264				Missense	S610F	MMRC0421	Treated
POLE	12	131730180				Missense	V1444L	MMRC0309	Untreated
POLH	6	43689516				Missense	K462N	MMRC0359	Untreated
POLQ	3	122684928				Missense	P1989S	MMRC0389	Treated
POLR1C	6	43595460				Missense	N96K	MMRC0383	Treated
POLR3A	10	79455508				Missense	D66H	MMRC0376	Untreated
POLR3C	1	144305508				Missense	I471V	MMRC0356	Untreated
POLR3G	5	89838223				Missense	E187D	MMRC0392	Treated
PON3	7	94854641(+)		12	37672207(-)	Translocation		MMRC0242	Treated
POT1	7	124286335				Missense	G205D	MMRC0242	Treated
PPAP2A	5	54779768(+)	NDUFAF2	5	60346427(+)	Long range		MMRC0344	Treated
PPFIA1	11	69878106				Missense	E739K	MMRC0389	Treated
PPFIA4	1	201291220				Missense	A117T	MMRC0191	Treated
PPFIBP1	12	27732507				Missense	A794T	MMRC0242	Treated
PPP1R12B	1	200661436				Missense	L221F	MMRC0421	Treated
PPRC1	10	103897851(+)	NEURL	10	105267915(-)	Long range		MMRC0390	Treated
PPRC1	10	103897926(-)	ZDHHC1	16	65992199(+)	Translocation		MMRC0390	Treated
PPTC7	12	109468207				Missense	N155H	MMRC0284	Untreated
PRDM1	6	106661791				In frame deletion	A739_V754del	MMRC0309	Untreated
PRDM1	6	106661497				Missense	S641R	MMRC0282	Treated
PRG4	1	184543900				Missense	G809E	MMRC0383	Treated
PRICKLE2	3	64108038				Missense	R390W	MMRC0387	Untreated
PRIM2	6	57537913(-)		7	30116221(-)	Translocation		MMRC0191	Treated
PRIMA1	14	93272541(+)		14	93301882(-)	Deletion		MMRC0332	Treated
PRKAG2	7	151109276				Missense	M121L	MMRC0389	Treated

Supplementary Table 3 (continued)

Gene	Chr	Position (strand)	2nd gene	Chr	Position (strand)	Type	AA change	Sample	Previously treated
PRKCB	12	24644411(+)		16	23905687(-)	Translocation		MMRC0344	Treated
PRKCB	12	24646241(-)		16	23880041(-)	Translocation		MMRC0344	Treated
PRKCZ	1	2056602				Missense	Y126D	MMRC0322	Untreated
PRKD2	19	51885761				Missense	I425T	MMRC0376	Untreated
PRKD3	2	37350314				Missense	Q575H	MMRC0338	Untreated
PRKDC	8	48869437				Missense	S3546F	MMRC0389	Treated
PRKG1	10	52873989(+)		10	52904191(-)	Deletion		MMRC0191	Treated
PRPF38B	1	109042827				Missense	W213R	MMRC0308	Treated
PRPF8	17	1503632				Missense	K2108M	MMRC0389	Treated
PRR21	2	240630178				Missense	P299S	MMRC0308	Treated
PRR4	12	11022945(+)	ETV6	12	11854448(-)	Deletion		MMRC0332	Treated
PRSS16	6	27331050				Missense	S508G	MMRC0329	Treated
PRSS16	6	27331057				Missense	I510T	MMRC0329	Treated
PRSS22	16	2843909				Missense	M225I	MMRC0343	Treated
PRSS45	3	46761162				Missense	V30L	MMRC0376	Untreated
PRUNE2	9	78457362				Missense	A2805V	MMRC0173	Treated
PSEN1	14	72739859(+)	TDRD9	14	103564330(-)	Long range		MMRC0335	Treated
PSMC6	14	52254707				Missense	S215N	MMRC0308	Treated
PSMD1	2	231738241				Missense	E855D	MMRC0375	Treated
PTDSS1	8	97376525				Frame shift deletion	V155fs	MMRC0332	Treated
PTK2	8	126684555(-)		8	141913260(+)	Long range		MMRC0343	Treated
PTK2	8	127893075(+)		8	141913284(-)	Long range		MMRC0343	Treated
PTPLA	10	17676236				Missense	L253R	MMRC0242	Treated
PTPN11	12	111411271				Missense	G503V	MMRC0387	Untreated
PTPRD	9	8661723(+)		9	9161382(-)	Deletion		MMRC0332	Treated
PTPRG	3	62253880				Missense	Q1399R	MMRC0375	Treated
PUS7	7	104910053				Missense	Q331K	MMRC0412	Treated
PUS7L	12	42434859				Missense	E153Q	MMRC0347	Untreated
QRICH2	17	71800016				Missense	I630T	MMRC0375	Treated
RAB25	1	154304773				Missense	L110F	MMRC0347	Untreated
RAB27B	18	50695888				Missense	F25C	MMRC0329	Treated
RAB28	4	12992253				Missense	G152V	MMRC0329	Treated
RAB2A	1	100586426(-)		8	61652655(-)	Translocation		MMRC0383	Treated
RAB3GAP1	2	135636644				Missense	L780Q	MMRC0322	Untreated
RAB5B	12	54667069				Missense	Q20E	MMRC0329	Treated
RABL3	3	121907629				Missense	L97F	MMRC0383	Treated
RAD54L2	3	51628225(-)		3	66857717(+)	Long range		MMRC0344	Treated
RAG1	11	36554291				Missense	G954D	MMRC0347	Untreated
RAG2	11	36572180				Nonsense	R39*	MMRC0376	Untreated
RALGAPA1	14	35194796				Missense	E1316K	MMRC0286	Untreated
RALGAPA2	20	20433355(-)		21	9840160(-)	Translocation		MMRC0191	Treated
RALGAPB	20	36635398(+)		20	37118142(-)	Deletion		MMRC0392	Treated
RALGPS1	9	128997310				Missense	G344S	MMRC0383	Treated
RALYL	8	83529322(+)		8	85616029(+)	Long range		MMRC0421	Treated
RALYL	8	83664628(-)		8	85606481(-)	Long range		MMRC0421	Treated
RANBP17	5	170600740				Missense	S876G	MMRC0216	Untreated
RANBP3L	5	36307144				Missense	F40I	MMRC0309	Untreated
RANBP9	6	13749808(+)		6	13781392(-)	Deletion		MMRC0191	Treated
RAP1GAP2	17	2691527(-)		20	31926923(+)	Translocation		MMRC0387	Untreated
RAP1GAP2	17	2711029(+)		20	31915944(-)	Translocation		MMRC0387	Untreated
RASAL2	1	176483017(+)		6	85586756(-)	Translocation		MMRC0191	Treated
RASAL2	1	176460940(-)	FAM19A5	22	47448413(-)	Translocation		MMRC0309	Untreated
RASGRF1	15	77110902				Missense	P386H	MMRC0338	Untreated
RB1	13	47937490				Missense	M825K	MMRC0329	Treated
RBKS	2	27925174(-)		8	95015910(-)	Translocation		MMRC0343	Treated
RBM25	14	72647499				Missense	T634S	MMRC0383	Treated
RBM33	7	155186794(+)		7	155286244(-)	Deletion		MMRC0356	Untreated
RBM33	7	155186274				Missense	S205L	MMRC0356	Untreated
RBM39	20	33760560				Missense	A409T	MMRC0322	Untreated
RBM5	3	50126409				Missense	W547L	MMRC0173	Treated
RBM9	22	34315726(+)		22	34572420(-)	Deletion		MMRC0392	Treated
RBM9	22	28567428(-)		22	34692913(-)	Long range		MMRC0392	Treated
RBMS3	3	29960341(+)	ZC3H7B	22	40052405(-)	Translocation		MMRC0343	Treated
RBP4	10	95343722				Missense	R139H	MMRC0375	Treated
RC3H1	1	172187745				Splice site	M841_splice	MMRC0387	Untreated
RCOR1	14	102220649(+)	TRAF3	14	102424705(-)	Deletion		MMRC0319	Untreated
RD3	1	209721280				Missense	T34M	MMRC0308	Treated
RDH16	12	55635173				Missense	T119M	MMRC0284	Untreated
RELN	7	103177146				Missense	D207N	MMRC0421	Treated

Supplementary Table 3 (continued)

Gene	Chr	Position (strand)	2nd gene	Chr	Position (strand)	Type	AA change	Sample	Previously treated
REPS1	6	139311624(+)		18	50712621(+)	Translocation		MMRC0335	Treated
RERE	1	8494310(-)		8	57670917(+)	Translocation		MMRC0191	Treated
RETSAT	2	85424368				Missense	A533V	MMRC0191	Treated
RFX1	19	13940433				Missense	P559L	MMRC0381	Untreated
RGL1	1	182162007				Missense	K790N	MMRC0319	Untreated
RGNEF	5	73081472				Missense	A30P	MMRC0242	Treated
RIMS2	8	104967063				Missense	R354W	MMRC0332	Treated
RIMS2	8	105056901				Missense	P973L	MMRC0389	Treated
RIPK4	21	42034912				Missense	Q504K	MMRC0347	Untreated
RMI1	9	85807333				Missense	T538S	MMRC0343	Treated
RNASEN	5	31485209				Missense	N919K	MMRC0412	Treated
RNF168	3	197714230				Missense	L71H	MMRC0343	Treated
RNF19A	8	101340094				Missense	I795V	MMRC0387	Untreated
RNF213	17	75931631				Missense	E2081K	MMRC0389	Treated
RNF26	11	118712253				Missense	C404F	MMRC0309	Untreated
ROBO2	3	77709336				Missense	S737G	MMRC0216	Untreated
ROBO2	3	77696952				Missense	R614C	MMRC0319	Untreated
ROPN1	3	125178495				Missense	G47E	MMRC0322	Untreated
RORB	9	76470227				Missense	C299F	MMRC0347	Untreated
RPA4	X	96026003				Missense	S13Y	MMRC0356	Untreated
RPGR	X	38030561				Missense	E879K	MMRC0338	Untreated
RPL10	X	153281344				Missense	E66G	MMRC0282	Treated
RPS6KA1	1	26754634				Nonsense	Q283*	MMRC0335	Treated
RRM1	11	4113032				Missense	N716H	MMRC0425	Untreated
RRN3	16	15077660(+)		16	26381218(-)	Long range		MMRC0344	Treated
RTCD1	1	100506393				Missense	E82K	MMRC0286	Untreated
RTN1	14	59282905				Missense	S97T	MMRC0375	Treated
RUFY2	3	12692826(-)		10	69806115(+)	Translocation		MMRC0356	Untreated
RUNDC3B	7	87190924(+)	RB1	13	47872217(-)	Translocation		MMRC0421	Treated
RUNDC3B	7	87190950(-)	RB1	13	47872099(+)	Translocation		MMRC0421	Treated
RWDD2A	6	83962573				Missense	E248Q	MMRC0389	Treated
RXFP1	4	159787750				Nonsense	S568*	MMRC0343	Treated
RXFP2	13	31254863				Nonsense	S303*	MMRC0347	Untreated
RYR1	19	43688832				Missense	A2864V	MMRC0322	Untreated
RYR2	1	235881425				Splice site	K2608_splice	MMRC0389	Treated
RYR3	15	31805910				Missense	R2315H	MMRC0242	Treated
RYR3	15	31627672				Missense	W264R	MMRC0412	Treated
S100PBP	1	33094122				Missense	R375C	MMRC0381	Untreated
SACM1L	3	45760070				Missense	G557R	MMRC0309	Untreated
SAMD13	1	84587998				Missense	H88Y	MMRC0335	Treated
SAMHD1	20	34989013				Missense	E228Q	MMRC0282	Treated
SAMHD1	20	34989043				Missense	D218H	MMRC0282	Treated
SART1	11	65502882				Missense	V769M	MMRC0347	Untreated
SCG5	15	30776098				Missense	E211A	MMRC0412	Treated
SCGB1A1	11	61946352				Missense	E47T	MMRC0282	Treated
SCN10A	3	38805490				Missense	C144F	MMRC0347	Untreated
SCN11A	3	38867004				Missense	D1433E	MMRC0191	Treated
SCN2A	2	165918977				Missense	L983F	MMRC0389	Treated
SCYL2	12	99253596				Missense	N642I	MMRC0308	Treated
SDF2	17	24000392				Missense	E126D	MMRC0338	Untreated
SDR16C5	8	57377504(-)		10	4626076(+)	Translocation		MMRC0343	Treated
SEC13	3	10317980(-)	CD300LD	17	70089089(-)	Translocation		MMRC0421	Treated
SEC14L2	22	29141994				Missense	Q277K	MMRC0242	Treated
SEC14L5	16	4969295(-)	SDK2	17	69031684(+)	Translocation		MMRC0421	Treated
SEC63	6	108357369				Missense	C56Y	MMRC0376	Untreated
SEL1L3	4	25378497				Missense	S908L	MMRC0389	Treated
SEMA3A	7	83430493				Missense	W608C	MMRC0216	Untreated
SEMA3E	7	82885676				Missense	F172L	MMRC0242	Treated
SEMG1	20	43269993				Missense	H214P	MMRC0408	Untreated
SENP1	12	46726474				Missense	D601H	MMRC0191	Treated
SEPT14	7	55869681				Missense	S217R	MMRC0343	Treated
SERPINB3	18	59475182				Missense	Q211K	MMRC0329	Treated
SERPINB6	6	2900828				Missense	K81E	MMRC0191	Treated
SERPINE2	2	224548839				Missense	N407Y	MMRC0425	Untreated
SERPINH1	11	74955575				Missense	A178V	MMRC0392	Treated
SERTAD4	1	208481863				Missense	V210A	MMRC0390	Treated
SETBP1	18	40785677				Missense	P792A	MMRC0308	Treated
SETD2	3	47138966				Nonsense	Q722*	MMRC0319	Untreated

Supplementary Table 3 (continued)

Gene	Chr	Position (strand)	2nd gene	Chr	Position (strand)	Type	AA change	Sample	Previously treated
SETD4	21	36339866				Missense	V204I	MMRC0344	Treated
SETX	9	134129739				Missense	H2581L	MMRC0244	Untreated
SF3A3	1	38222466				Missense	D144Y	MMRC0173	Treated
SFMBT1	3	52978163				Missense	D8N	MMRC0381	Untreated
SFRP4	7	37922289				Missense	D126N	MMRC0381	Untreated
SFRP4	7	37913675				Missense	K324N	MMRC0406	Untreated
SFTPD	10	81696391				Missense	L2R	MMRC0322	Untreated
SFXN4	10	120902700(+)	IL1RAPL2	23	104703794(+)	Translocation		MMRC0309	Untreated
SGCZ	8	15134428(+)	KIF13B	8	29107152(-)	Long range		MMRC0421	Treated
SGCZ	8	14517910(+)		10	44054930(+)	Translocation		MMRC0421	Treated
SH2D2A	1	155050293				Frame shift deletion	E162fs	MMRC0308	Treated
SHANK2	11	69976211(+)		11	70022000(+)	Inversion		MMRC0421	Treated
SHISA6	17	8032858(+)		17	11114064(+)	Long range		MMRC0392	Treated
SHISA6	17	11118073(-)		17	14865882(-)	Long range		MMRC0392	Treated
SHKBP1	19	45781433				Missense	A379T	MMRC0322	Untreated
SHOC2	10	112757286				Missense	Q390R	MMRC0406	Untreated
SHROOM2	X	9874732				Missense	R1536G	MMRC0347	Untreated
SI	3	166233893				Missense	T850I	MMRC0284	Untreated
SI	3	166208477				Missense	M1395L	MMRC0375	Treated
SI	3	166182883				Missense	T1753S	MMRC0406	Untreated
SIAH3	13	45285451(-)		13	61419069(+)	Long range		MMRC0392	Treated
SIGLEC1	20	3622990				Missense	V1045G	MMRC0028	Untreated
SIPA1	11	65173679				Missense	P866Q	MMRC0389	Treated
SIPA1L2	1	230709105(-)		1	230748579(+)	Tandem duplication		MMRC0344	Treated
SIX1	14	60183029				Missense	N194Y	MMRC0173	Treated
SKIV2L2	5	54717998(-)	CDC25C	5	137687474(+)	Long range		MMRC0344	Treated
SKP2	5	36219832				Missense	C399G	MMRC0282	Treated
SLC10A7	4	147583367				Missense	L151F	MMRC0389	Treated
SLC12A2	5	127477875				Missense	I317L	MMRC0425	Untreated
SLC14A1	18	41401542(+)		18	41562328(-)	Deletion		MMRC0319	Untreated
SLC16A9	10	61094075				Missense	G118R	MMRC0383	Treated
SLC17A4	6	25878738(-)		19	52519405(-)	Translocation		MMRC0191	Treated
SLC1A5	19	51972473				Missense	C363Y	MMRC0375	Treated
SLC1A5	19	51973890				Missense	A314T	MMRC0387	Untreated
SLC1A7	1	53330870				Missense	I325M	MMRC0338	Untreated
SLC23A2	20	4814509				Nonsense	R177*	MMRC0412	Treated
SLC25A13	7	95613829				Missense	D476G	MMRC0425	Untreated
SLC26A4	7	107102699				Missense	T225K	MMRC0381	Untreated
SLC27A5	19	63701835				Missense	M644I	MMRC0286	Untreated
SLC27A5	19	63702771				Missense	V523L	MMRC0308	Treated
SLC2A5	1	9029487(-)		11	59089279(-)	Translocation		MMRC0191	Treated
SLC35C1	11	45789155				Missense	S263N	MMRC0359	Untreated
SLC35F3	1	232390531(+)		7	44883921(-)	Translocation		MMRC0383	Treated
SLC37A1	17	8859523(+)		21	42834577(+)	Translocation		MMRC0392	Treated
SLC38A9	5	55010931(+)		5	55155068(-)	Deletion		MMRC0421	Treated
SLC45A4	8	136489024(-)		8	142304138(-)	Long range		MMRC0421	Treated
SLC4A5	2	74303586				Missense	P1099L	MMRC0173	Treated
SLC5A12	11	26661948				Missense	G414S	MMRC0329	Treated
SLC6A12	12	176245				Missense	W380C	MMRC0412	Treated
SLC8A3	14	69703977				Missense	G306R	MMRC0421	Treated
SLC9A3R1	17	70276277				Missense	D322H	MMRC0286	Untreated
SLC9A5	16	65843898(-)	MAP3K3	17	59078175(-)	Translocation		MMRC0425	Untreated
SLC9A6	X	134932475				Missense	R440K	MMRC0389	Treated
SLCO1B3	12	20905295				Missense	Q146R	MMRC0427	Treated
SLCO2A1	3	134296237(-)		3	135161012(+)	Tandem duplication		MMRC0383	Treated
SLITRK2	X	144711747				Nonsense	K38*	MMRC0322	Untreated
SLITRK4	X	142546379				Frame shift deletion	L71fs	MMRC0387	Untreated
SLITRK6	13	85266568				Missense	P693T	MMRC0309	Untreated
SLMAP	3	57825386				Missense	I346M	MMRC0308	Treated
SMAP2	1	40653559				Missense	N200K	MMRC0381	Untreated
SMARCB1	22	22464037				Missense	I63T	MMRC0282	Treated
SMARCC1	3	47297417(-)		3	47610784(+)	Tandem duplication		MMRC0344	Treated
SMC5	9	72083263				Missense	E194K	MMRC0286	Untreated
SMC5	9	72102771				Missense	N375D	MMRC0322	Untreated
SMEK1	14	91006961				Missense	A532T	MMRC0383	Treated
SMOC2	6	168687183				Missense	E165K	MMRC0387	Untreated
SMOX	20	4111429				Missense	V382I	MMRC0322	Untreated
SMPDL3A	6	123166517				Missense	Y193F	MMRC0319	Untreated
SNAP25	20	10225646				Missense	R119C	MMRC0338	Untreated

Supplementary Table 3 (continued)

Gene	Chr	Position (strand)	2nd gene	Chr	Position (strand)	Type	AA change	Sample	Previously treated
SNAP47	1	226021352				Missense	H398R	MMRC0216	Untreated
SNAPC3	9	15441331				Missense	S249L	MMRC0389	Treated
SNTB2	8	108036097(-)		16	67821681(-)	Translocation		MMRC0344	Treated
SNTG2	2	1253754				Missense	L372M	MMRC0390	Treated
SNX15	11	64559001				Missense	E121D	MMRC0191	Treated
SNX19	11	130278478				Missense	E819K	MMRC0356	Untreated
SOBP	6	108061474				Missense	R245G	MMRC0329	Treated
SOCS2	12	92492809				Missense	D107G	MMRC0425	Untreated
SOHLH2	13	35645870				Missense	S320Y	MMRC0004	Untreated
SORCS2	4	7749870				Missense	I546N	MMRC0335	Treated
SP100	2	230693320(-)		2	231008958(-)	Inversion		MMRC0242	Treated
SP140	2	230842889				Missense	S474T	MMRC0344	Treated
SP8	7	20791710				Missense	S84F	MMRC0308	Treated
SPATA17	1	216085951(-)	KLHL14	18	28583975(+)	Translocation		MMRC0343	Treated
SPATS2	2	11711670(+)		12	48193920(-)	Translocation		MMRC0375	Treated
SPDYE1	7	44013468				Missense	R237C	MMRC0425	Untreated
SPEF2	5	35487987(-)		5	35733151(-)	Inversion		MMRC0335	Treated
SPEG	2	220062795				Missense	E2937D	MMRC0389	Treated
SPOCK1	5	136431326				Missense	P189L	MMRC0244	Untreated
SPOP	17	45051467				Missense	S119R	MMRC0421	Treated
SPRED1	15	36430666				Missense	F282I	MMRC0387	Untreated
SPTA1	1	156876080				Missense	M1632I	MMRC0412	Treated
SPTBN1	2	54709582				Missense	P603A	MMRC0383	Treated
SRD5A3	4	55920272				Missense	Y75C	MMRC0392	Treated
SRRM1	1	24850690				Missense	S242N	MMRC0383	Treated
SRRM2	16	2752059				Missense	S510F	MMRC0356	Untreated
SSX4	X	48129002				Missense	S42F	MMRC0282	Treated
ST13	13	71857552(+)		22	39578062(+)	Translocation		MMRC0335	Treated
ST14	11	129564854				Missense	V151I	MMRC0381	Untreated
ST18	8	53289361				Missense	E4K	MMRC0421	Treated
ST3GAL3	1	44136263(+)		23	61647996(-)	Translocation		MMRC0191	Treated
ST5	11	8708638				Missense	R259W	MMRC0322	Untreated
ST7	7	116592004(+)	RASAL3	19	15434289(+)	Translocation		MMRC0191	Treated
STAB2	12	102588022(+)	MTM1	23	149582976(-)	Translocation		MMRC0191	Treated
STAC	3	36501488				Missense	R169C	MMRC0412	Treated
STAG1	3	137673970				Missense	I394V	MMRC0392	Treated
STARD8	X	67859013				Missense	L787M	MMRC0359	Untreated
STAT2	12	55034851				Missense	N204S	MMRC0244	Untreated
STK17A	7	43614462				Nonsense	R168*	MMRC0406	Untreated
STK38L	12	27342037				Missense	H39Q	MMRC0308	Treated
STK4	20	43137104				Missense	K446R	MMRC0412	Treated
STRN3	14	30457961				Missense	T401I	MMRC0383	Treated
STX8	17	9219719(+)		17	14654365(-)	Long range		MMRC0392	Treated
SULT2B1	19	53782366				Missense	V80M	MMRC0216	Untreated
SVIL	10	29810637				Missense	A1661V	MMRC0375	Treated
SVIL	10	29861680				Missense	R541H	MMRC0389	Treated
SVIL	10	29855698(-)	RNF169	11	74209206(-)	Translocation		MMRC0412	Treated
SYDE2	1	85416527				Missense	R854Q	MMRC0406	Untreated
SYNE2	14	63695234				Missense	E5311Q	MMRC0329	Treated
SYNJ1	21	32933263				Frame shift deletion	F1286fs	MMRC0309	Untreated
SYT17	4	87142950(+)		16	19128527(-)	Translocation		MMRC0338	Untreated
SYT3	19	55821002				Missense	S456T	MMRC0389	Treated
SYTL2	11	85114687				Missense	T154N	MMRC0338	Untreated
TAAR8	6	132916334				Nonsense	W270*	MMRC0412	Treated
TAC4	17	45280282				Missense	E33Q	MMRC0389	Treated
TACR3	4	104860263				Missense	A7S	MMRC0329	Treated
TADA2A	17	32857793				Missense	E33K	MMRC0286	Untreated
TAGAP	6	159377187				Missense	T441K	MMRC0347	Untreated
TAPBPL	12	6414085(-)		12	6433311(+)	Tandem duplication		MMRC0387	Untreated
TAS2R38	7	141319243				Missense	L239Q	MMRC0412	Treated
TBC1D1	4	37800191(-)		13	80893772(-)	Translocation		MMRC0191	Treated
TBC1D9	4	141809523				Nonsense	S529*	MMRC0389	Treated
TCERG1L	10	132834859				Missense	H363Q	MMRC0343	Treated
TECPR1	7	97708386				Missense	L255P	MMRC0173	Treated
TEPP	16	56569422				Missense	Q122H	MMRC0335	Treated
TET1	10	70096986				Missense	H1547P	MMRC0286	Untreated
TET1	10	70096858				Missense	Q1504H	MMRC0383	Treated
TEX2	17	59613101(-)		17	59840409(+)	Tandem duplication		MMRC0425	Untreated
TFAM	10	59824131				Missense	L182P	MMRC0412	Treated

Supplementary Table 3 (continued)

Gene	Chr	Position (strand)	2nd gene	Chr	Position (strand)	Type	AA change	Sample	Previously treated
TFAP2D	6	50791110				Missense	A121V	MMRC0421	Treated
TFPI	2	188069997				Missense	D59N	MMRC0322	Untreated
TG	8	133990689(-)		8	134015290(+)	Tandem duplication		MMRC0387	Untreated
TGFBR2	3	30661282				Missense	V70G	MMRC0408	Untreated
THRB	3	24163230				Nonsense	R158*	MMRC0335	Treated
THSD7B	2	138137602				Missense	Q1517H	MMRC0392	Treated
TIMP2	17	74365323				Missense	G114E	MMRC0286	Untreated
TINAG	6	54296777(+)		19	14493841(-)	Translocation		MMRC0191	Treated
TJP3	19	3684871				Missense	P299A	MMRC0329	Treated
TLE4	9	81392014(+)		9	81481975(-)	Deletion		MMRC0356	Untreated
TLL1	4	167144015				Nonsense	R219*	MMRC0359	Untreated
TLN2	15	60729590				Missense	L51P	MMRC0335	Treated
TLR4	9	119515407				Missense	S394C	MMRC0308	Treated
TLR8	X	12847393				Missense	G105R	MMRC0308	Treated
TMC5	16	19359529				Missense	P223Q	MMRC0344	Treated
TMCC1	3	130853105				Missense	T510S	MMRC0347	Untreated
TMCO6	5	140003570				Missense	C314R	MMRC0381	Untreated
TMED6	16	67934963				Missense	F191L	MMRC0412	Treated
TMEM132B	12	99791634(-)		12	124412138(+)	Long range		MMRC0335	Treated
TMEM150A	2	85680611				Missense	Q51K	MMRC0343	Treated
TMEM19	12	70366801				Missense	I25S	MMRC0421	Treated
TMEM195	7	15437260				Splice site	E137_splice	MMRC0390	Treated
TMEM38A	3	195841914(+)		19	16641397(-)	Translocation		MMRC0343	Treated
TMEM63B	6	44229895				Missense	N740D	MMRC0242	Treated
TMEM63B	6	44210804				Missense	A78T	MMRC0387	Untreated
TMPRSS11B	4	68776271				Nonsense	R402*	MMRC0359	Untreated
TMPRSS13	11	117294552				Missense	Q78R	MMRC0423	Treated
TMX3	18	64495382				Missense	G378A	MMRC0282	Treated
TNC	9	116888162				Missense	D557H	MMRC0335	Treated
TNFRSF1A	12	6310138				Missense	G209D	MMRC0427	Treated
TNKS1BP1	11	56837122				Missense	G539V	MMRC0173	Treated
TNNI3K	1	74623325(+)		2	122720643(+)	Translocation		MMRC0309	Untreated
TNNI3K	1	74623456(-)		8	35156775(-)	Translocation		MMRC0309	Untreated
TNPO1	5	72182866				Missense	Y49H	MMRC0375	Treated
TNPO2	19	12685276(+)	EMR3	19	14613995(-)	Long range		MMRC0344	Treated
TNPO2	19	12686754				Splice site	Y258_splice	MMRC0191	Treated
TNRC6B	22	38991755				Missense	W525C	MMRC0383	Treated
TNS4	17	35906149				Missense	A19P	MMRC0387	Untreated
TOPBP1	3	134847794(+)		3	134851517(+)	Inversion		MMRC0376	Untreated
TOPBP1	3	134847856(-)		3	134851208(-)	Inversion		MMRC0376	Untreated
TOPBP1	3	134858357				Missense	G133A	MMRC0191	Treated
TOX3	16	51041857				Missense	P166T	MMRC0376	Untreated
TP53	17	7517839				Missense	C275S	MMRC0335	Treated
TP53	17	7518961				Missense	Y205D	MMRC0343	Treated
TP53	17	7518988				Nonsense	R196*	MMRC0347	Untreated
TP53AIP1	11	128312908				Nonsense	E6*	MMRC0308	Treated
TRABD	22	38702388(+)		22	48977497(-)	Long range		MMRC0421	Treated
TRAF3	14	102433378				Frame shift insertion	E283fs	MMRC0309	Untreated
TRAF3	14	102441819				Missense	D551V	MMRC0173	Treated
TRAFD1	12	111074265				Missense	N519K	MMRC0322	Untreated
TRAM1L1	4	118225955				Missense	S15G	MMRC0173	Treated
TRAPPC10	21	44303484				Missense	A251T	MMRC0387	Untreated
TRAPPC10	21	44332122				Nonsense	L885*	MMRC0329	Treated
TRAPPC5	19	7653611				Missense	A158T	MMRC0329	Treated
TRIM10	6	30236494				Missense	T41P	MMRC0412	Treated
TRIM17	1	226669003				Missense	V132L	MMRC0338	Untreated
TRIM29	11	119503486				Missense	S301N	MMRC0408	Untreated
TRIM47	17	71382742				Missense	G445E	MMRC0329	Treated
TRIM6	11	5588711				Missense	V372I	MMRC0319	Untreated
TRIO	5	14534728				Splice site	D2155_splice	MMRC0344	Treated
TRPM3	9	72651243				Missense	L183F	MMRC0286	Untreated
TSC1	9	134770859				Missense	T643A	MMRC0383	Treated
TSHR	14	80679476				Missense	T441P	MMRC0344	Treated
TSHZ2	20	51305306				Missense	F634L	MMRC0244	Untreated
TSHZ2	20	51305674				Missense	L757Q	MMRC0427	Treated
TSHZ3	19	36462367				Missense	S58G	MMRC0344	Treated
TSHZ3	19	36459529				Missense	R1004W	MMRC0421	Treated
TSPO2	6	41118876				Splice site	G58_splice	MMRC0322	Untreated
TTC21A	3	39134592				Missense	D249N	MMRC0381	Untreated
TTC21B	2	166493767(+)		2	166524174(-)	Deletion		MMRC0332	Treated

Supplementary Table 3 (continued)

Gene	Chr	Position (strand)	2nd gene	Chr	Position (strand)	Type	AA change	Sample	Previously treated
TTF1	9	134267207				Missense	S275T	MMRC0332	Treated
TTLL6	17	44202102				Missense	M799I	MMRC0286	Untreated
TTN	2	179178424				Missense	P9075L	MMRC0356	Untreated
TTN	2	179224655				Missense	E10715V	MMRC0376	Untreated
TTN	2	179190751				Nonsense	IE6984>M*	MMRC0335	Treated
TUBAL3	10	5432910				Missense	K48N	MMRC0421	Treated
TUFT1	1	149813382				Missense	R203W	MMRC0425	Untreated
TUSC3	8	15650266				Missense	V317L	MMRC0381	Untreated
TUSC3	8	15666088				Nonsense	L345*	MMRC0408	Untreated
TXK	4	47773181				Missense	M411I	MMRC0319	Untreated
TXNDC5	6	7841537(-)		20	17758553(-)	Translocation		MMRC0406	Untreated
TXNRD1	12	103173371(-)	MPHOSPH9	12	122265505(+)	Long range		MMRC0335	Treated
TYK2	19	10338202				Missense	E174K	MMRC0319	Untreated
UBA2	19	39651878				Missense	R612K	MMRC0308	Treated
UBASH3A	21	42321723(+)		21	42733664(+)	Inversion		MMRC0392	Treated
UBASH3A	21	42444576(-)		21	42734587(-)	Inversion		MMRC0392	Treated
UBASH3A	17	7969619(-)		21	42733404(-)	Translocation		MMRC0392	Treated
UBASH3A	17	14645553(+)		21	42734883(+)	Translocation		MMRC0392	Treated
UBE2G1	17	4145739(+)	METTL2A	17	57876474(+)	Long range		MMRC0376	Untreated
UBE2K	4	39415510				Missense	P47S	MMRC0286	Untreated
UBE3A	15	23152179				Missense	L673I	MMRC0332	Treated
UBN1	16	4850931				Missense	D313N	MMRC0392	Treated
UBN2	7	138619193				Missense	S1001F	MMRC0286	Untreated
UBTD2	1	148783772(-)		5	171603083(+)	Translocation		MMRC0392	Treated
UBTF	17	39603224(-)		17	39647441(-)	Inversion		MMRC0319	Untreated
UGGT1	2	128612876				Missense	A567P	MMRC0389	Treated
UMOD	16	20265062				Missense	V357F	MMRC0421	Treated
UMODL1	21	42404245				Missense	G615D	MMRC0282	Treated
UNC5B	10	72728987				Missense	E929K	MMRC0286	Untreated
UNC5C	4	96594518(+)	OLFML2A	9	126610291(-)	Translocation		MMRC0191	Treated
UNC5D	8	35658077(+)	IDO2	8	39919674(-)	Long range		MMRC0309	Untreated
UNC5D	2	122721177(-)		8	35672344(+)	Translocation		MMRC0309	Untreated
UPF1	19	18832645				Missense	A771T	MMRC0425	Untreated
UPP1	7	48113195				Missense	F213V	MMRC0347	Untreated
USH2A	1	213890739				Missense	A4721S	MMRC0347	Untreated
USP10	16	83370008				Missense	Y739C	MMRC0406	Untreated
USP19	3	49127775				Missense	N535Y	MMRC0319	Untreated
USP22	17	20865096				Missense	L114V	MMRC0389	Treated
USP26	X	131988659				Missense	Q419P	MMRC0389	Treated
USP32	17	55615523				Missense	R1303Q	MMRC0359	Untreated
USP34	2	61303929				Missense	L2534F	MMRC0389	Treated
USP6	17	5012036				Missense	T1041N	MMRC0389	Treated
USP7	16	8916653				Missense	D346A	MMRC0392	Treated
USP9X	X	40945333				Missense	K1560N	MMRC0344	Treated
UTP20	12	100262507				Missense	G1485R	MMRC0308	Treated
UVRAG	11	75396263				Missense	R317C	MMRC0004	Untreated
VAT1L	16	76467830				Missense	G262V	MMRC0242	Treated
VAV3	1	107945904(+)		1	107954405(-)	Deletion		MMRC0332	Treated
VCAN	5	82853306				Missense	T1142R	MMRC0381	Untreated
VCAN	5	82853255				Missense	R1125H	MMRC0387	Untreated
VDAC3	8	42382102				Missense	H273Y	MMRC0338	Untreated
VEPH1	3	158581637				Splice site	R376_splice	MMRC0332	Treated
VGLL3	3	87100694				Missense	V225M	MMRC0389	Treated
VIM	10	17315685				Missense	E240K	MMRC0421	Treated
VPS13D	1	12255030(+)		2	236016644(+)	Translocation		MMRC0389	Treated
VPS13D	1	12255177(-)		2	236016671(-)	Translocation		MMRC0389	Treated
VPS45	1	148315338(-)	HCN2	19	559235(-)	Translocation		MMRC0383	Treated
VPS45	1	148307193(-)	PACS2	14	104856122(-)	Translocation		MMRC0383	Treated
VSIG1	X	107206989				Missense	A296T	MMRC0216	Untreated
VWA2	10	116039167				Missense	S684F	MMRC0191	Treated
VWA2	10	116035876				Missense	P396S	MMRC0359	Untreated
WDR1	4	9725369(+)		4	9732688(-)	Deletion		MMRC0191	Treated
WDR25	14	99917161				Missense	D49E	MMRC0421	Treated
WDR5	9	135996944				Missense	S106L	MMRC0319	Untreated
WDR54	2	74504525				Missense	P148T	MMRC0308	Treated
WDR59	16	73477148				Missense	C865S	MMRC0335	Treated
WDR66	12	120890395				Missense	G903D	MMRC0381	Untreated
WDR7	18	52575176				Nonsense	S785*	MMRC0392	Treated
WDR74	11	62357109				Missense	A350V	MMRC0242	Treated
WHSC1	4	1835231(+)		4	1872509(-)	Deletion		MMRC0421	Treated

Supplementary Table 3 (continued)

Gene	Chr	Position (strand)	2nd gene	Chr	Position (strand)	Type	AA change	Sample	Previously treated
WHSC1	4	1946876				Missense	C1191F	MMRC0282	Treated
WHSC1	4	1889733				Missense	A332D	MMRC0332	Treated
WHSC1	4	1873834(+)		14	105247118(+)	Translocation		MMRC0376	Untreated
WHSC1	4	1885576(-)		14	105397012(-)	Translocation		MMRC0319	Untreated
WHSC1L1	8	38276217				Missense	Y887C	MMRC0332	Treated
WHSC1L1	8	38276213				Missense	K888N	MMRC0309	Untreated
WHSC2	4	1966247(-)		6	14321056(-)	Translocation		MMRC0332	Treated
WHSC2	4	1966507(+)		6	14321021(+)	Translocation		MMRC0332	Treated
XBP1	22	27521317				Missense	P326R	MMRC0191	Treated
XBP1	22	27522135				Missense	L167I	MMRC0383	Treated
XPO4	13	20294410				Missense	E287K	MMRC0191	Treated
ZAN	7	100185303(+)		11	102426910(-)	Translocation		MMRC0191	Treated
ZBTB16	2	30876558(+)		11	113611495(+)	Translocation		MMRC0191	Treated
ZBTB3	11	62276356				Missense	R503C	MMRC0191	Treated
ZBTB33	23	119271466(-)		23	119729737(-)	Inversion		MMRC0392	Treated
ZBTB33	23	119272900(+)		23	119715889(+)	Inversion		MMRC0392	Treated
ZBTB33	X	119272483				Missense	I395M	MMRC0173	Treated
ZBTB45	19	63719702				Missense	P384L	MMRC0381	Untreated
ZC3H11A	1	111118279(+)		1	202075934(+)	Long range		MMRC0332	Treated
ZC3H14	14	88110943				Missense	E339K	MMRC0389	Treated
ZC3H15	2	187078496				Missense	Q264R	MMRC0242	Treated
ZC3H18	16	87192225				Frame shift deletion	A276fs	MMRC0347	Untreated
ZC3H18	16	87171190				Missense	S53T	MMRC0216	Untreated
ZCCHC5	X	77799925				Missense	E217K	MMRC0390	Treated
ZCWPW2	3	28484449(-)		3	28577758(-)	Inversion		MMRC0421	Treated
ZFP36L1	14	68327402(+)		14	105397362(-)	Long range		MMRC0309	Untreated
ZFPM2	8	106883425				Missense	S647P	MMRC0242	Treated
ZFYVE1	14	72512119				Missense	M152V	MMRC0322	Untreated
ZKSCAN3	6	28441507				Missense	Q361H	MMRC0286	Untreated
ZKSCAN5	7	98961878				Missense	E427K	MMRC0389	Treated
ZMYM4	1	35643226				Missense	I1182V	MMRC0406	Untreated
ZNF148	3	126434489				Missense	S591A	MMRC0344	Treated
ZNF193	6	28308679				Missense	Y310C	MMRC0406	Untreated
ZNF319	16	56588088				Missense	H528R	MMRC0359	Untreated
ZNF329	19	63331980				Nonsense	E235*	MMRC0319	Untreated
ZNF416	19	62775520				Missense	Y522N	MMRC0383	Treated
ZNF417	19	63115314				Missense	C30Y	MMRC0389	Treated
ZNF423	16	48229288				Missense	E426Q	MMRC0375	Treated
ZNF430	19	21007307(+)		19	33223164(-)	Long range		MMRC0376	Untreated
ZNF431	19	21122980(+)		19	22703537(+)	Long range		MMRC0421	Treated
ZNF431	19	21123381(-)		19	23120617(-)	Long range		MMRC0421	Treated
ZNF462	9	108728245				Missense	P744L	MMRC0408	Untreated
ZNF483	9	113344664				Missense	R543Q	MMRC0344	Treated
ZNF484	9	94649470				Missense	G474R	MMRC0376	Untreated
ZNF492	19	22639285				Missense	T325N	MMRC0412	Treated
ZNF492	19	22639569				Missense	P420T	MMRC0423	Treated
ZNF527	19	42571695				Missense	Y302N	MMRC0347	Untreated
ZNF530	19	62809897				Missense	Q398E	MMRC0329	Treated
ZNF559	19	9314103				Missense	E326K	MMRC0389	Treated
ZNF569	19	42595854				Missense	H516Y	MMRC0389	Treated
ZNF595	4	45633(+)	DSCAM	21	40865053(+)	Translocation		MMRC0392	Treated
ZNF630	X	47803595				Missense	Q394K	MMRC0375	Treated
ZNF646	16	30999336				Missense	Q1397R	MMRC0421	Treated
ZNF667	19	61645539				Missense	T213A	MMRC0242	Treated
ZNF700	19	11920239				Missense	V134F	MMRC0344	Treated
ZNF749	19	62647400				Missense	E358Q	MMRC0286	Untreated
ZNF761	19	58644701				Missense	P47L	MMRC0309	Untreated
ZNF804A	2	185509380				Missense	E338K	MMRC0389	Treated
ZNF83	19	57808751				Missense	E293V	MMRC0383	Treated
ZNF830	17	30313793				Missense	W365C	MMRC0308	Treated
ZNF878	19	12015828				Missense	S510C	MMRC0389	Treated
ZNRF3	22	27776888				Missense	A807P	MMRC0191	Treated
ZP1	11	60398998				Missense	S530N	MMRC0425	Untreated
ZP3	7	75907862				Missense	H302R	MMRC0191	Treated
ZRANB3	2	135824102				Missense	R171S	MMRC0242	Treated
ZSCAN4	19	62881934				Missense	R384Q	MMRC0322	Untreated
ZSWIM7	17	15835324(-)	DSCAM	21	40354174(-)	Translocation		MMRC0392	Treated
ZZEF1	17	3901057				Missense	H1877P	MMRC0332	Treated
ZZEF1	17	3864229				Missense	D2773H	MMRC0389	Treated
ZZEF1	17	3858960				Missense	T2924N	MMRC0412	Treated

Supplementary Table 3 (continued)

Sample	Chromosome	Position	Wild-type allele	Mutated allele	Gene	Mutation type	Residue change	Genotyping result
MMRC0338	8	39644716	G	A	ADAM18	Missense	p.E457K	True positive
MMRC0383	11	129780757	C	T	ADAMTS8	Missense	p.C859Y	True positive
MMRC0319	3	127356171	G	T	ALDH1L1	Missense	p.N212K	True positive
MMRC0282	2	231835342	A	T	ARMC9	Missense	p.Y369F	False positive
MMRC0335	5	159982131	C	T	ATP10B	Missense	p.V554I	True positive
MMRC0344	17	38510440	C	A	BRCA1	Missense	p.C91F	True positive
MMRC0322	14	92830943	C	T	BTBD7	Missense	p.R59K	True positive
MMRC0308	7	81480722	G	C	CACNA2D1	Missense	p.I421M	False positive
MMRC0322	11	69165273	A	G	CCND1	Missense	p.Q4R	True positive
MMRC0335	11	69165400	A	T	CCND1	Missense	p.K46N	True positive
MMRC0339	16	67421112	C	T	CDH1	Missense	p.R784C	True positive
MMRC0347	16	74120718	G	A	CHST5	Missense	p.R356C	Assay failed
MMRC0375	5	79066681	A	G	CMYA5	Missense	p.I2113V	True positive
MMRC0335	8	3244433	C	T	CSMD1	Missense	p.V766I	True positive
MMRC0343	8	2810771	T	A	CSMD1	Missense	p.S3073C	True positive
MMRC0347	1	33931142	C	T	CSMD2	Missense	p.E1303K	True positive
MMRC0335	1	33962836	G	A	CSMD2	Missense	p.R878C	True positive
MMRC0308	8	114100564	G	A	CSMD3	Missense	p.P313L	True positive
MMRC0004	12	110213632	G	A	CUX2	Missense	p.R110H	True positive
MMRC0216	12	110256876	G	A	CUX2	Missense	p.V1059I	True positive
MMRC0282	9	89507784	C	A	DAPK1	Missense	p.H964Q	True positive
MMRC0335	9	89486233	G	A	DAPK1	Missense	p.G699E	True positive
MMRC0308	9	89511987	A	G	DAPK1	Missense	p.K1394R	True positive
MMRC0329	12	47520116	C	T	DDX23	Missense	p.D121N	True positive
MMRC0319	13	72234065	C	T	DIS3	Missense	p.R750K	True positive
MMRC0308	13	72244372	T	G	DIS3	Missense	p.S447R	True positive
MMRC0343	13	72244028	A	C	DIS3	Missense	p.V474G	True positive
MMRC0376	1	153308070	G	A	EFNA4	Missense	p.R196H	True positive
MMRC0359	6	94025844	C	T	EPHA7	Missense	p.A625T	True positive
MMRC0191	1	94774262	T	A	F3	Missense	p.T87S	True positive
MMRC0319	17	77630632	C	T	FASN	Missense	p.A2430T	True positive
MMRC0284	19	44213752	A	C	FBXO27	Missense	p.V138G	False positive
MMRC0309	3	48391853	G	C	FBXW12	Missense	p.E98Q	True positive
MMRC0356	4	155726959	C	T	FGA	Missense	p.G358R	True positive
MMRC0375	17	7286827	T	A	FGF11	Missense	p.L200H	True positive
MMRC0338	14	64580830	C	T	FNTB	Missense	p.R291C	True positive
MMRC0322	7	4763284	G	A	FOXK1	Missense	p.R395Q	True positive
MMRC0004	3	71109797	G	A	FOXP1	Missense	p.P407L	True positive
MMRC0423	7	113998137	T	A	FOXP2	Missense	p.S100T	True positive
MMRC0329	11	65567324	G	C	GAL3ST3	Missense	p.P176A	Assay failed
MMRC0173	12	48785727	T	G	GPD1	Missense	p.S117A	True positive
MMRC0028	10	25901622	T	C	GPR158	Missense	p.I518T	True positive
MMRC0322	10	87474414	C	A	GRID1	Splice site		False positive
MMRC0383	10	87618868	C	A	GRID1	Missense	p.R277M	True positive
MMRC0284	10	87363311	C	A	GRID1	Missense	p.D812Y	True positive
MMRC0216	1	220782114	G	C	HHIPL2	Missense	p.I327M	True positive
MMRC0344	1	114310366	C	T	HIPK1	Missense	p.T777I	True positive
MMRC0322	1	87330920	C	T	HS2ST1	Nonsense	p.R190*	True positive
MMRC0338	5	132431102	T	G	HSPA4	Missense	p.L87R	True positive
MMRC0028	21	40059472	G	A	IGSF5	Missense	p.V81I	True positive

Supplementary Table 4 – Validation of point mutations. Genotyping was performed using a mass spectrometry-based method (Sequenom).

Sample	Chromosome	Position	Wild-type allele	Mutated allele	Gene	Mutation type	Residue change	Genotyping result
MMRC0423	6	339972	A	G	IRF4	Missense	p.K123R	True positive
MMRC0339	6	339972	A	G	IRF4	Missense	p.K123R	True positive
MMRC0028	16	53522742	C	T	IRX5	Missense	p.A44V	True positive
MMRC0339	5	52254425	A	C	ITGA1	Missense	p.E785A	True positive
MMRC0423	1	150041224	G	A	LINGO4	Missense	p.T194I	True positive
MMRC0308	8	23235653	C	G	LOXL2	Missense	p.G413R	True positive
MMRC0344	12	25134396	G	C	LRMP	Missense	p.E202Q	True positive
MMRC0347	12	1813952	G	A	LRTM2	Missense	p.R306Q	True positive
MMRC0173	X	43400553	C	T	MAOA	Missense	p.A7V	Assay failed
MMRC0173	7	100626060	C	T	MOGAT3	Missense	p.E305K	True positive
MMRC0375	1	43576423	C	A	MPL	Missense	p.T49N	True positive
MMRC0335	22	24730698	T	A	MYO18B	Missense	p.I2116N	True positive
MMRC0344	22	24577473	G	A	MYO18B	Missense	p.R1271Q	Assay failed
MMRC0376	2	152092285	G	A	NEB	Missense	p.P5553S	True positive
MMRC0173	2	152289034	C	T	NEB	Missense	p.A200T	Assay failed
MMRC0319	10	21160467	C	T	NEBL	Missense	p.V501M	True positive
MMRC0319	4	149254800	C	T	NR3C2	Missense	p.E902K	True positive
MMRC0308	4	149400600	A	C	NR3C2	Missense	p.F626C	True positive
MMRC0309	5	37387135	T	G	NUP155	Missense	p.T154P	True positive
MMRC0191	5	37353901	G	A	NUP155	Missense	p.P692S	True positive
MMRC0356	1	245818830	C	A	OR2G2	Nonsense	p.C182*	True positive
MMRC0309	2	178934702	G	C	OSBPL6	Missense	p.E401Q	True positive
MMRC0216	5	140235327	G	T	PCDHA12	Missense	p.G29V	True positive
MMRC0329	10	119124316	C	T	PDZD8	Missense	p.R138H	True positive
MMRC0329	4	129031759	A	C	PLK4	Missense	p.E631D	True positive
MMRC0322	2	135636644	T	A	RAB3GAP1	Missense	p.L780Q	True positive
MMRC0343	3	197714230	A	T	RNF168	Missense	p.L71H	True positive
MMRC0282	X	153281344	A	G	RPL10	Missense	p.E66G	Assay failed
MMRC0347	X	153281355	A	C	RPL10	Missense	p.I70L	Assay failed
MMRC0282	20	34989013	C	G	SAMHD1	Missense	p.E228Q	True positive
MMRC0282	20	34989043	C	G	SAMHD1	Missense	p.D218H	True positive
MMRC0216	7	83430493	C	A	SEMA3A	Missense	p.W608C	True positive
MMRC0284	3	166233893	G	A	SI	Missense	p.T850I	True positive
MMRC0375	3	166208477	T	A	SI	Missense	p.M1395L	Assay failed
MMRC0173	2	74303586	G	A	SLC4A5	Missense	p.P1099L	True positive
MMRC0356	11	130278478	C	T	SNX19	Missense	p.E819K	True positive
MMRC0356	16	2752059	C	T	SRRM2	Missense	p.S510F	True positive
MMRC0359	4	167144015	C	T	TLL1	Nonsense	p.R219*	True positive
MMRC0335	15	60729590	T	C	TLN2	Missense	p.L51P	True positive
MMRC0191	19	12686754	C	T	TNPO2	Splice site		True positive
MMRC0376	2	179224655	T	A	TTN	Missense	p.E10715V	True positive
MMRC0335	2	179190751	C	A	TTN	Nonsense	p.E6793*	True positive
MMRC0335	2	179190752	A	C	TTN	Missense	p.I6792M	True positive
MMRC0356	2	179178424	G	A	TTN	Missense	p.P8883L	True positive
MMRC0319	3	49127775	T	A	USP19	Missense	p.N535Y	True positive
MMRC0004	11	75396263	C	T	UVRAG	Missense	p.R317C	True positive
MMRC0359	10	116035876	C	T	VWA2	Missense	p.P396S	True positive
MMRC0191	10	116039167	C	T	VWA2	Missense	p.S684F	True positive
MMRC0383	19	62775520	A	T	ZNF416	Missense	p.Y522N	True positive
MMRC0173	17	3954844	T	G	ZZEF1	Missense	p.T469P	False positive

Supplementary Table 4 (continued)

Sample	Chromosome	Position	Insertion or deletion	Inserted/deleted sequence	Gene	Genotyping result
MMRC0427	2	9562800	Deletion	TTCAGATACATGATGCCAGGATCACACTCTTCTCC	ADAM17	True positive
MMRC0381	3	56764144	Insertion	G	ARHGEF3	True positive
MMRC0286	1	52926231	Insertion	G	C1orf163	True positive
MMRC0412	1	117967150	Deletion	TAAC	FAM46C	True positive
MMRC0244	2	14692207	Deletion	G	FAM84A	False positive
MMRC0381	2	239674222	Deletion	G	HDAC4	False positive
MMRC0387	X	142546379	Deletion	A	SLITRK4	True positive
MMRC0309	21	32933263	Deletion	A	SYNJ1	True positive
MMRC0309	14	102433378	Insertion	A	TRAF3	True positive
MMRC0347	16	87192225	Deletion	C	ZC3H18	True positive

Supplementary Table 5 – Validation of small indels. Genotyping was performed using a mass spectrometry-based method (Sequenom). Only assays that could successfully be designed are shown.

Gene	Chr	Position (strand)	Chr	Position (strand)	Type	AA change	Sample	Previously treated
EIF3B	7	2385341			Missense	Y760F	MMRC0343	Treated
LRRK2	12	38918064			Missense	E155K	MMRC0286	Untreated
LRRK2	12	38994132			Missense	I1543S	MMRC0344	Treated
LRRK2	12	38953506(+)	18	8522903(+)	Translocation		MMRC0376	Untreated
LRRK2	12	38953703(-)	18	8522979(-)	Translocation		MMRC0376	Untreated
RPL10	X	153281344			Missense	E66G	MMRC0282	Treated
RPS6KA1	1	26754634			Nonsense	Q283*	MMRC0335	Treated
XBP1	22	27521317			Missense	P326R	MMRC0191	Treated
XBP1	22	27522135			Missense	L167I	MMRC0383	Treated

Supplementary Table 6 – Mutations in genes involved in protein translation, stability, and the unfolded protein response. These mutations were not significant on their own, but are considered in conjunction with the statistically significant *DIS3* and *FAM46C* mutations.

Gene	Chr	Position (strand)	Chr	Position (strand)	Type	AA change	Sample	Previously treated	Effect of gene on NF-κB	Likely effect of mutation on gene function
BTRC	10	103288069			Missense	A536G	MMRC0286	Untreated	Activation	
CARD11	7	2930442			Missense	Y631H	MMRC0375	Treated	Activation	
CARD11	7	2925677			Missense	D789N	MMRC0425	Untreated	Activation	
CYLD	16	49378431(+)	16	49379310(-)	Deletion		MMRC0335	Treated	Inactivation	Loss (deletion)
IKBIP	12	97531523			Missense	E342K	MMRC0319	Untreated	Unknown	
IKBKB	8	42283051			Missense	K171E	MMRC0427	Treated	Activation	
MAP3K1	5	56209516(-)	8	42575852(+)	Translocation		MMRC0344	Treated	Activation	
MAP3K14	17	40720277(+)	17	40725216(-)	Deletion		MMRC0319	Untreated	Activation	
RIPK4	21	42034912			Missense	Q504K	MMRC0347	Untreated	Activation	
TLR4	9	119515407			Missense	S394C	MMRC0308	Treated	Activation	
TNFRSF1A	12	6310138			Missense	G209D	MMRC0427	Treated	Activation	
TRAF3	14	102433378			Insertion (FS)	E283fs	MMRC0309	Untreated	Inactivation	Loss (frame-shift)
TRAF3	14	102441819			Missense	D551V	MMRC0173	Treated	Inactivation	Loss (high FI mutation affecting MATH, i.e. NIK-interacting, domain)

Supplementary Table 7 – Point mutations and re-arrangements of genes affecting activation of NF-κB. Point mutations achieved significance as part of a gene set (p = 0.016).

Gene	Chr	Position (strand)	Type	AA change	Sample	Previously treated
F3	1	94774262	Missense	T87S	MMRC0191	Treated
F5	1	167772526	Missense	D1605N	MMRC0389	Treated
FGA	4	155726959	Missense	G358R	MMRC0356	Untreated
FGA	4	155726404	Missense	E543K	MMRC0389	Treated
FGG	4	155753196	Missense	H6Y	MMRC0376	Untreated
TFPI	2	188069997	Missense	D59N	MMRC0322	Untreated

Supplementary Table 8 – Mutations in genes involved in generation of the fibrin clot. These mutations achieved significance as part of a gene set in an unbiased search of the MSigDB (q = 0.0054 after correction for multiple hypothesis testing).

Chr	Start	End	Length	Muts	Samples	p-value	q-value
2	88908630	88909380	750	3	2	1.55E-06	4.00E-02
2	88939740	88939930	190	4	3	2.21E-11	1.70E-06
2	88940090	88940430	340	5	3	1.62E-13	1.68E-08
2	88940600	88940670	70	2	2	3.41E-06	7.05E-02
2	88940800	88941190	390	9	6	1.85E-14	4.42E-09
2	88941490	88941690	200	6	6	7.22E-15	4.42E-09
2	88941840	88942340	500	18	7	1.28E-14	4.42E-09
2	88946120	88946140	20	2	1	1.66E-07	6.57E-03
2	88946300	88946650	350	5	4	4.02E-13	3.83E-08
2	89027740	89028620	880	3	2	5.70E-07	1.86E-02
2	89276310	89277630	1320	5	2	6.89E-12	5.65E-07
2	89400240	89401200	960	3	3	1.87E-05	2.41E-01
3	188944110	188948430	4320	23	10	1.33E-13	1.43E-08
14	105121160	105122380	1220	2	2	6.09E-06	1.13E-01
14	105122930	105129920	6990	3	3	1.77E-05	2.34E-01
14	105178690	105186230	7540	11	6	6.67E-14	8.35E-09
14	105246120	105250860	4740	25	11	2.76E-14	4.42E-09
14	105277850	105285620	7770	10	5	2.20E-14	4.42E-09
14	105309360	105313440	4080	12	7	9.33E-15	4.42E-09
14	105394150	105395580	1430	8	5	6.55E-15	4.42E-09
14	105395780	105398150	2370	34	14	2.44E-14	4.42E-09
14	105398300	105398980	680	25	13	2.72E-14	4.42E-09
14	105399330	105399630	300	4	3	1.46E-09	8.70E-05
14	105399840	105403470	3630	102	21	2.70E-14	4.42E-09
14	105420980	105421100	120	1	1	1.33E-05	1.87E-01
14	105565150	105565450	300	2	1	1.71E-05	2.31E-01
14	105657690	105657780	90	2	1	3.19E-06	6.84E-02
14	105861960	105862770	810	4	2	2.53E-10	1.72E-05
14	105876070	105876860	790	3	2	1.30E-06	3.55E-02
14	106240900	106241490	590	6	4	6.00E-13	5.49E-08
14	106249830	106250300	470	34	19	2.35E-14	4.42E-09
14	106330320	106330790	470	3	2	9.04E-07	2.69E-02
22	21359460	21359930	470	4	2	3.00E-09	1.74E-04
22	21376460	21377500	1040	6	1	2.38E-12	2.02E-07
22	21528380	21529390	1010	7	5	2.94E-14	4.42E-09
22	21553070	21553180	110	5	5	1.55E-15	3.70E-09
22	21553290	21553620	330	23	10	7.77E-15	4.42E-09
22	21556900	21558010	1110	7	6	2.98E-14	4.42E-09
22	21559860	21560570	710	4	3	8.56E-11	6.36E-06
22	21560700	21560820	120	3	2	7.64E-10	4.66E-05
22	21561130	21561410	280	4	4	1.15E-10	8.26E-06
22	21571780	21573590	1810	3	3	2.77E-07	1.02E-02
22	21576990	21579030	2040	6	3	3.05E-13	3.02E-08
22	21607620	21608750	1130	3	2	3.18E-06	6.84E-02

Supplementary Table 9 – Non-coding regulatory potential analysis identifies multiple sites that exhibit somatic hypermutation. Regions are Igκ (chromosome 2), BCL6 promoter/intron (chromosome 3), IgH (chromosome 14), and Igλ (chromosome 22).

Chr	Position	Gene	Ref	Mut	Sample	Putative binding sites
1	554731	AK125248 (IGR)	T	C	MM-0343	GATA-1/stress-response element
1	555225	AK125248 (IGR)	G	A	MM-0425	none
1	555269	AK125248 (IGR)	C	T	MM-0309	STAT5a
1	82793242	TTLL7/LPHN2 (IGR)	G	A	MM-0375	HOXA3
1	82793250	TTLL7/LPHN2 (IGR)	G	T	MM-0343	deltaEF1
1	147333845	NBPFA (IGR)	C	T	MM-0387	STAT4
1	147334295	NBPFA (IGR)	A	G	MM-0408	paired box factor 2/STAT4/STAT5a
1	147334296	NBPFA (IGR)	C	G	MM-0408	paired box factor 2/STAT4/STAT5a/Dof3
1	147334380	NBPFA (IGR)	T	C	MM-0425	HOXA3/STAT5a
2	40865609	SLC8A1/PKDCC (IGR)	C	A	MM-0387	alcohol dehydrogenase gene regulator 1
2	40865611	SLC8A1/PKDCC (IGR)	A	C	MM-0389	Dof2/Dof3/paired box factor 2/alcohol dehydrogenase gene regulator 1
3	149273928	ZIC4/AGTR1 (IGR)	A	G	MM-0335	CdxA
3	149274006	ZIC4/AGTR1 (IGR)	A	G	MM-0332	engrailed 1
3	189142836	BCL6/LPP (IGR)	A	C	MM-0421	paired box factor 2/Dof3/STAT4/STAT5a
3	189143134	BCL6/LPP (IGR)	T	C	MM-0343	none
3	189143142	BCL6/LPP (IGR)	G	C	MM-0387	STAT1/STAT3/STAT4/STAT5a/STAT6/paired box factor 2/Ikaros 2
3	189143159	BCL6/LPP (IGR)	A	C	MM-0242	STAT1/STAT3/STAT4/STAT5a/STAT6
3	189143285	BCL6/LPP (IGR)	A	G	MM-0242	Dof2/Dof3/paired box factor 2
3	189143311	BCL6/LPP (IGR)	T	G	MM-0343	none
3	189143391	BCL6/LPP (IGR)	A	C	MM-0376	none
3	189143392	BCL6/LPP (IGR)	T	G	MM-0376	none
3	189440883	LPP (Intron)	G	C	MM-0335	paired box factor 2/Dof1
3	189440884	LPP (Intron)	G	T	MM-0344	Dof1
3	189441175	LPP (Intron)	G	A	MM-0412	Ikaros 2/GATA-2/GATA-6/RAV1 (AP2 interacting)/deltaEF1
4	157902239	PDGFC (3'-UTR)	T	C	MM-0387	STAT5a/heat-shock factor/paired box factor 2/Dof1/Dof3
4	157903235	PDGFC (3'-UTR)	A	T	MM-0408	Hunchback
4	157903658	PDGFC (3'-UTR)	C	G	MM-0309	none
4	157904101	PDGFC (Intron)	T	G	MM-0191	GATA-1/GATA-1/GATA-6
4	39875936	RHOH (Intron)	C	T	MM-0191	Ikaros 2/STAT1/STAT3/STAT4/STAT5a/STAT6/GATA-1
4	39876045	RHOH (Intron)	A	G	MM-0387	GATA-1/GATA-2
4	39876457	RHOH (Intron)	A	G	MM-0387	heat shock factor/STAT5a
4	62180565	LPHN3 (Intron)	T	G	MM-0389	none
4	62180776	LPHN3 (Intron)	T	A	MM-0390	paired box 2/Dof3
4	62181208	LPHN3 (Intron)	T	G	MM-0425	Deformed/HOXA3/octamer factor 1
4	7819489	AFAP1 (Intron)	G	A	MM-0242	none
4	7819515	AFAP1 (Intron)	C	T	MM-0309	none
7	92754257	CCDC132 (Intron)	T	A	MM-0343	none
7	92754258	CCDC132 (Intron)	A	T	MM-0387	none
9	16564622	BNC2 (Intron)	C	A	MM-0412	paired box factor 2/STAT3/STAT4/STAT5a/STAT6
9	16564872	BNC2 (Intron)	C	G	MM-0335	none
9	16564948	BNC2 (Intron)	A	G	MM-0412	paired box factor 2/Dof1/GATA-6
12	120943427	BCL7A (Promoter)	C	G	MM-0412	engrailed 1
12	120943444	BCL7A (Promoter)	T	G	MM-0390	HOXA3/deltaEF1
12	120943453	BCL7A (Promoter)	A	C	MM-0406	deltaEF1/STAT4/GATA-1
12	120943777	BCL7A (Promoter)	T	G	MM-0390	cap signal for transcription initiation
12	120945822	BCL7A (Intron)	C	T	MM-0390	c-Myc/AhR nuclear translocator/USF
12	120946479	BCL7A (Intron)	A	C	MM-0421	paired box factor 2/sex-determining region Y gene product/GATA-1/GATA-2
12	120946774	BCL7A (Intron)	T	C	MM-0309	STAT5a/heat shock factor/HOXA3
14	68328421	ZFP36L1 (Intron)	A	G	MM-0344	CCAAT-enhancer binding factor/Ultrabithoraz
14	68328818	ZFP36L1 (Intron)	G	C	MM-0191	STAT5a/heat shock factor
14	68328974	ZFP36L1 (Intron)	T	C	MM-0392	none
14	68329209	ZFP36L1 (Intron)	C	G	MM-0412	paired box factor 2
17	8108665	PFAS (Intron)	C	T	MM-0356	none
17	8110148	PFAS (Intron)	C	A	MM-0392	alcohol dehydrogenase gene regulator 1
17	8110537	PFAS (Intron)	C	G	MM-0392	Meis1
17	8110620	PFAS (Intron)	C	G	MM-0392	GATA-2
20	60329271	LAMA5 (Synonymous)	G	A	MM-0447	STAT4
20	60329391	LAMA5 (Intron)	G	C	MM-0356	STAT5a

Supplementary Table 10 – Potential transcription factor binding sites targeted by mutations in significantly mutated regulatory regions. Binding sites were predicted using the publicly-available version of the TRANSFAC database (ref.).

Amplicon	Primer sequence (sense)	Primer sequence (antisense)	Annealing temperature (°C)
chr1:554202-555412	TCG TTT GAA ATG GTC ATC CA	TGC GTA GTT GGG TTT GGT TT	55
chr1:82793145-82793343	TGT TAC AAT GGC TGT GCT AAA	AAA GGC CAA TCA TGA TGA GAA	55
chr3:149273859-149274108	TGA AGC TAC AAA AGC TCT AAG AAA A	TGC AAA ATA GGC CAA CAA CA	55
chr3:189142479-189143663	CGC TCA GAG AGA TCA ATG GAC	TGT GTG TGG TGA GTA GGA AAG G	55
chr3:189440767-189441356	GCT TAC AGC TTG CCT AAC AAG G	TTT AAT ATA GCC AAT AGG GAG GTT C	55
chr4:7819353-7819601	AGC AGA GCC ACA GTT TCC AT	TCT GAC GTA TTC CGG ATG TG	55
chr4:62180499-62181471	AGG AAA TGA GTT TTT CGT TTT G	TGC TCC AAT AGT CAG CTC CA	55
chr4:157901940-157902946	CCA CCT ATC ACC AAG CAT TTC	TGT TGG CTT TTC TAA TCT TGT TAA A	55
chr4:157902805-157903743	TCA TCT TTG TTC CTC TGG CTA	GAG CAC CAT GAG GAG TGT GA	55
chr9:16564308-16565147	CAT GCA AAA AGA CAG GTG TGA	CTG TTC TGT CAT CTG TGA AAT GTG	55
chr12:120942955-120943524	CCC GGC CAG TAT TTG TTC T	GCC CCC AGA AGT TCT CTT GT	55
chr20:60328896-60329577	CCT GCA CTG ACA CAT GTA CG	GTG CTG GCC CTA CCT TCT C	55

Supplementary Table 11 – Primer sequences and annealing temperatures for PCR of RP regions. All reactions comprised 35 cycles of PCR.

Gene	OSS	Permutation score
TSPY6P	6291.512653	0.018
LOC283352	5226.686439	0
HOXA9	3217.111381	0.012
PTPRZ1	2705.699055	0
F2R	2321.240087	0.006
KIAA0125	2315.404911	0
COL4A6	2260.239257	0.006
FSTL5	1650.941992	0.012
POPDC3	1611.195061	0.036
NRN1	1266.903751	0
ELMOD1	1219.562329	0.008
TRPM3	1108.72542	0.01
TMPRSS11E	1106.40036	0.016
SAMD3	1032.63057	0.01
GABRR1	873.944921	0.008
SYNPO2	820.740759	0.008
PRSS21	788.115356	0.01
GBA3	763.936377	0
HES1	754.020388	0.044
GNG11	750.429829	0

Supplementary Table 12 – Top 20 outliers by OSS analysis. Only genes with a permutation score less than 0.05 are shown.

Gene	Primer sequence (sense)	Primer sequence (antisense)	Annealing temperature (°C)
F3	CCA AAC CCG TCA ATC AAG TC	TGT ATA AAT TAA GTC CTT GCC AAA AA	54.5
TFPI	TGA AAG TCT GGA AGA GTG CAA A	GCT GGA GTG AGA CAC CAT GA	54.5
FGA	CAT CAA TCT GCC TGC AAA GA	TCT GCA GAA GCT GGA TAT GCT	53.5
FGG	TGC TAC CAG AGA CAA CTG CTG	TTC AAA GTA GCA GCG TCT ATC A	53
LDHA	GAC CTA CGT GGC TTG GAA GA	AAT CTC CAT GTT CCC CAA GG	53

Supplementary Table 13 – Primer sequences and annealing temperatures for RT-PCR of coagulation factors. All reactions comprised 35 cycles of PCR.

Amplicon	Primer sequence (sense)	Primer sequence (antisense)	Annealing temperature (°C)
DIS3 RNB	CCTCTTCTGGCTGATTCTTGA	TGCAGGAAAAAGAAATGTGG	55
DIS3 RNB	CAAAAGCCGATGAACAATGA	GCCGAATCTCCTACTTTTCCA	56
FAM46C	TTGAGTCCTCATGGCAACAC	CGTACATGCTCTCCCCAATC	56
FAM46C	TGAAGGACATCGTCCAGACC	AGACACACGGTGCTCTCGTT	56
FAM46C	TGAAGGAGGCATATGTGCAG	TTTCCAACGTGGCACTGTAA	56
FAM46C	CCCACAGACCAGGAAGAAAT	CAGCACAACTTTCATGTAACTGC	56

Supplementary Table 14 – Primer sequences and annealing temperatures for PCR of DIS3 (RNB domain) and FAM46C. All reactions comprised 35 cycles of PCR.

Cell line	DNA change	Protein change	Del 13q21 at other allele?
H929	c.G1570C	p.A524P	Yes
INA6	None		
JIM3	None		
KMS11	None		
KMS12-BM	None		
KMS12-PE	None		
L363	None		
MM.1S	None		
OCI-My5	None		
OCI-My7	None		
OPM2	None		
RPMI8226	None		
SKMM1	c.A2533G	p.I845V	Yes
U266	None		
XG6	None		

Supplementary Table 15 – *DIS3* RNB domain mutations in cell lines. PCR and Sanger sequencing was used to detect mutations in the cell lines shown.

Cell line	DNA change	Protein change	Del 1p12 at other allele?
H929	c.278_279insC	p.L93fsX15	Yes
INA6	None		
JIM3	None		
KMS11	None		
KMS12-BM	None		
KMS12-PE	None		
L363	None		
LP1	Hom. del. exon 1*		
MM.1S	c.A808G	p.M270V	Yes
OCI-My1	None		
OCI-My5	None		
OCI-My7	None		
OPM2	c.A533C	p.E178A	Yes
RPMI8226	None		
SKMM1	c.519delT	p.I173fsX36	No
U266	None		
XG6	None		

*Determined by aCGH

Supplementary Table 16 – *FAM46C* mutations in cell lines. PCR and Sanger sequencing was used to detect mutations in 16 of the cell lines shown. In addition, aCGH profiles of cell lines were examined for larger re-arrangements and the homozygous deletion in LP1 was identified (FAM46C expression is zero in this cell line).