SUPPLEMENTAL METHODS

FACS antibodies

The majority of samples were stained with an antibody panel containing: CD14 PE-Cy5 (61D3, eBiosciences), CD16 PE-Cy5 (3G8, BD), CD11b PE-Cy5 (ICRF44, BD), CD56 BV421 (HCD56, BioLegend), CD3 Alexa700 (UCHT1, BD), CD19 PeCy7 (HIB19, BioLegend), CD38 BV605 (HB7, BD), CD45 BV786 (HI30, BD), CD138 APC (MI50, BioLegend) and CD319 PE (162.1, BioLegend).

Generation of strand-specific RNAseq

500 or 1000 cells were FACS-sorted into 5 or 10ml Single cell lysis solution (SCLS) respectively (Single cell lysis kit Invitrogen, cat# 4458235) with DNase I according to manufacturer’s instructions with the exception that the lysis reaction was incubated for 15min at RT before adding stop solution. For a few samples, 20k cells were instead sorted into buffer RLT with β-mercaptoethanol and total RNA extracted using RNeasy Micro Kit (Qiagen, cat#74004) with on-column DNase I treatment according to manufacturer’s instructions. Double-stranded cDNA was prepared from 500 lysed cells in SCLS or the RNeasy purified RNA from 7.5-10k cells using NEBNext Ultra II RNA First Strand Synthesis (NEB cat#E7771) and NEBNext Ultra II Directional RNA Second Strand Synthesis (NEB Cat# E7550) modules according to manufacturer’s instructions. In the majority of samples, QIAseq FastSelect rRNA HMR kit (Qiagen cat# 334386) was utilized (according to manufacturer’s instructions) to minimize rRNA contribution to the final library. Stranded libraries were subsequently prepared by adding custom-made i5 containing Tn5 (transposase) and tagmentation buffer (50mM tris Acetate, 25mM Mg Acetate, 50% dimethylformamide) to double-stranded cDNA sample. After 5 min at 55°C, the reaction was stopped by incubating with 5µl 1% SDS for 5min at room temperature and samples were purified using AmPure XP beads at a ratio sample:beads of 1:1.3 and eluted in water. Introduction of indexes through oligo replacement1 was carried out by adding custom-made i7 replacement oligos and gap fill buffer (165mM Tris acetate, 330mM potassium acetate, 50mM Mg acetate, 2.5mM DTT, 1mM beta-NAD, and 1.25mM each of dATP, dCTP, dGTP, and dTTP). After 30min incubation at 37°C, gap fill enzymes were added (1U Sulfolobulus DNA Polymerase IV NEB cat# M0327S and 10U E Coli DNA Ligase NEB cat# M0205L) and incubation continued for an additional 30min at 37°C. Samples were purified using AmPure XP beads at a ratio sample:beads of 1:1.25 and eluted in 12µl water. Libraries were subsequently PCR amplified using Phusion HF PCR Master Mix (Thermo Scientific) with the following PCR program: 95°C 2 min; followed by 16 cycles of 94°C 10 s, 60°C 30 s, and 72°C 1 min. Library cleanup was done using AmPure XP beads at a ratio sample:beads of 1:0.9. DNA concentrations in purified samples were measured using the Qubit dsDNA HS Kit (Invitrogen). Barcoded libraries were pooled and paired-end sequenced (2×41 cycles) using the Illumina platform (NextSeq500, Illumina, San Diego, CA).

ChIPseq and analysis

ChIPseq was performed as previously described with minor modifications to the preparations of input controls2. In brief, a 10µl aliquot was put aside from the sonicated sample. Subsequently, 2µl 50mM MgCl₂ was added to neutralize EDTA before tagmentation was performed by adding 7µl water, 20µl 2x tagment buffer (Illumina cat# 15027866) and 1µl tagment enzyme (Illumina cat#15027865). Tagmented input control samples were split into two reactions containing 20µl sample before 25µl PCR MM (NEB cat# M0541S) and 5µl primer mix was added to each tube. Input control libraries were amplified together with ChIPseq libraries using the following PCR program: 72°C 5 min (adapter extension); 95°C 5 min (reverse crosslinking and denaturation); followed by 11 cycles of 98°C 10 s, 63°C 30 s, and 72°C 3 min.
After PCR amplification, library cleanup was done using Agencourt AmPureXP beads (Beckman Coulter) at a PCR mix to beads ratio of 1:1. Barcoded libraries were pooled and single-end sequenced (50 cycles) using the Illumina platform (NextSeq500, Illumina, San Diego, CA).

Fastq files were mapped to hg38 using bowtie2, identification of peaks and quantification of reads in peaks was done using HOMER\(^3\). Identification of elements displaying significantly different signals between different genetic MM subgroups (HRD, t(4;14), t(11;14), and t(14;16)) was done using DESeq2\(^4\). Peaks with a fold change >2 and with an adjusted p-value <0.05 were considered significantly changed. The row-normalized values for the 250 most significant peaks in each comparison were plotted using R. A combination of newly generated and previously published H3K27Ac ChIPseq data\(^5\) was used in the analysis. For visualization, median (± standard deviation) H3K27Ac coverage for each MM genetic group was calculated and visualized in UCSC genome browser\(^6\) using a multiWig hub.

**Analysis of linked-read WGS data**

**Identification of CNVs**

To calculate and visualize copy-number, Long Ranger\(^7\) files were processed using BarCrawler\(^8\) and the output subsequently processed by an in-house developed script that transforms read coverage into chromosome numbers. In brief, to visualize the data and impute chromosomal copy-numbers, the BarCrawler output was binned into 500kb windows and the median total, unphased and haplotype-specific coverage per chromosome was calculated. Then the following rules were used to determine what chromosomes had two copies (normal chromosome numbers):

\[
\frac{\sigma_{1/2}(h_1)}{\sigma_{1/2}(t) - \sigma_{1/2}(u)} > 0.47, \quad \frac{\sigma_{1/2}(h_2)}{\sigma_{1/2}(t) - \sigma_{1/2}(u)} > 0.47 \quad \text{and} \quad \sigma(t) < 1.5 \frac{\sigma_{1/2}(\sigma(t))}{\sigma_{1/2}(t)}
\]

Where:
- Standard deviation of the coverage per chromosome, \(\sigma(t)\)
- Median of the standard deviation of the coverage per chromosome, \(\sigma_{1/2}(\sigma(t))\)
- Median of total coverage, \(\sigma_{1/2}(t)\)
- Median of unphased coverage, \(\sigma_{1/2}(u)\)
- Median of both haplotype specific coverages, \(\sigma_{1/2}(h_1)\) and \(\sigma_{1/2}(h_2)\)

Afterwards, the median coverage of the chromosomes with two copies was calculated, halved and used as a coefficient to transform coverage into number of chromosomes.

When compared to FISH data, the above did not accurately call the chromosomal numbers of samples P13172_106 and P14402_128, likely because of the complex subclonal makeup of copy-number variations in these samples. With chr4 being the only chromosome known to display a normal chromosome number from the FISH analysis, the coefficient to impute the copy-numbers was obtained as described above but only taking into account the data from chr4.

For selected samples, chromosomal copy-numbers were assessed using CNVkit (v0.9.8)\(^9\), ASCAT (v2.5.2)\(^{10}\), and the Battenberg approach (v2.2.9)\(^{11}\). CNVs were called using FindSV\(^{12}\) and Long Ranger. CNVs >30kb overlapping with regions investigated by FISH were further confirmed by visualizing the haplotype specific coverage (10kb bins).
Identification of somatic variants from lrWGS tumor/normal pairs

Somatic variant calling was done using the nf-core/Sarek pipeline (v2.6)\(^\text{13}\). In brief, the BAM files containing the Long Ranger mapping information were used as input for the Sarek pipeline, Strelka2 (v2.9.10)\(^\text{14}\) and Mutect2 (GATK v.4.1.7.0)\(^\text{15}\) were used for variant calling (tumor-normal subtraction analysis) and a combination of VEP (v99.2)\(^\text{16}\) and Snpeff (v4.3t)\(^\text{17}\) was used for variant annotation. Variants in genes recurrently mutated in MM\(^\text{18,19}\) with a PASS filter from both Strelka2 and Mutect2, having a moderate or high predicted impact on gene function according to either variant annotation tool and having a GnomAD allele frequency <1% were considered to affect gene function.

Identification of SVs

SVs involving different chromosomes were identified using GROC-SVs (only considering tumor lrWGS data) and Long Ranger. To exclude obvious artifacts, identified SVs were visually assessed using Loupe (10x Genomics, Loupe Browser 2.1.2). SVs called by Long Ranger and/or GROC-SVs that were not within blacklisted regions and passed visual inspection (using Loupe and IGV\(^\text{20}\) to exclude artifacts) were considered valid.

Identification and classification of complex structural variants

To investigate if the SVs described in the paper (affecting the IGH, Myc, Mafa, and Map3k14 loci) were part of more complex rearrangements, we investigated if we had detected additional interchromosomal rearrangements affecting the chromosomes of the described SV. Cases involving >2 chromosomes were considered complex and illustrated using Circos\(^\text{21}\). Further considering copy-number variations and the number of involved chromosomes, the complex SVs were either classified as (unspecified) complex, chromothripsis, chromoplexy, or templated insertion events according to previously published criterion\(^\text{22}\).

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Linked-read whole-genome sequencing resolves common and private structural variants in multiple myeloma

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SUPPLEMENTAL FIGURES
10xWGS

P13756_107 (male) N50=27.8Mbp, mol size=300kbp

P14402_116 (male) N50=15.3Mbp, mol size=195kbp

P11603_109 (female) N50=2.5Mbp, mol size=123kbp
Figure S1. Deletions are associated with poor phasing and shorter phase blocks. Phase block structure of the samples with the highest (top), representative intermediate (middle), and shortest (bottom) N50 phase block size are shown. Phase blocks were drawn by Loupe in green and blue, where alternate colors illustrate phase block boundaries. Patient number, N50 phase block size, and average molecule size are given for each sample above the graphical representations. Known copy number variations are indicated on the left of each chromosome (del, deletion; pdel, partial deletion; and mpd, monoparental disomy).
| Sample ID       | Haplotype 1 (Copy#) | Haplotype 2 (Copy#) | Total (Copy#) |
|-----------------|---------------------|---------------------|---------------|
| P14402_128      | del17p (93%)        |                     |               |
| P13172_101      | no del17p           |                     |               |
| P14402_129      | del17p (14%)        |                     |               |
| P14402_125      | del17p (24%)        |                     |               |
| P18203_1012     | del17p (47%)        |                     |               |
| P13756_105      | del17p (80%)        |                     |               |
| P14402_117      | del17p (77%)        |                     |               |
| P14402_117      | del17p (77%)        |                     |               |
| P13756_105      | del17p (80%)        |                     |               |
| P11603_109      | del17p (95%)        |                     |               |

- **A**
  - Unphased
  - Haplotype 2
  - Haplotype 1
  - Total

- **B**
  - TP53
  - Amplification (identified by lrWGS)
  - Normal TP53 locus
  - Loss of 17p (not identified in lrWGS)
  - Loss of 17p (identified by lrWGS)
Figure S2. Linked-read WGS data allows for the identification of chr17p CNVs. Copy-number (A) and phased read-clouds (B) are shown for eight patients with identified chr17p CNVs. In addition, one patient with a normal chr17p region is displayed for comparison. The percentage of cells with chr17p copy-number aberration (as determined by FISH) is shown above the line graphs. (A) Line graph displaying the copy-number of total, haplotype specific, and unphased reads in the area surrounding the TP53 locus. Median copy-number of the normal control samples (GL, germline) is shown for comparison. Color coding is displayed at the left of the figure. Vertical lines indicate the boundaries of the FISH probes used to identify chr17p/TP53 CNVs. (B) Depiction of the phased read-clouds (drawn by Loupe). Read-clouds constituting haplotype 1 and haplotype 2 are indicated. The localization of the TP53 gene is indicated by the transparent grey box.
Fig. S3

A

[Graph showing mutation types with sample frequencies]

B

[Genetic diagrams with different chromosomes and genes]
Figure S3. Identification and localization of mutations in recurrently mutated genes. (A) Identified mutations in genes recurrently mutated in MM. (B) Localization of mutations identified in the ZFHX4, KRAS, BRAF, NRAS and TP53 gene.
Figure S4. Different structural variants generate distinct patterns in the IrWGS data. (A-E) Heatmaps showing the read-cloud (barcode) overlap between regions involved in different structural variants (SVs) and schematic representations of the SVs. As barcodes are essentially unique to each IrWGS read-cloud (and each read-cloud is generated from a single long DNA molecule), structural variants involving regions from different chromosomes give distinct patterns depending on the orientation and localization of the involved regions within the SVs. The connected green and orange arrows schematically indicate the areas joined by the indicated events. Arrows with blunt ends indicate abrupt stops in read-cloud overlap. (A) Reciprocal translocations (t(r)) can be identified by clusters of read-clouds spanning the involved regions that form distinct arrowhead patterns that point to the translocation breakpoint. Orientation of the arrowhead patterns depend on the orientation of the regions joined by the translocation (compare the left and right heatmap). The right example in addition to the translocation harbors a deletion of large parts of the b region. Non-reciprocal translocations (t(nr)) can be observed in a similar manner by the presence of a single arrowhead pattern. (B) Templated insertions (ti) create patterns with non-overlapping arrowhead patterns that are truncated on one side (read-cloud overlap does not gradually decline but abruptly stops) as only a defined area (the inserted region) can share read-clouds with the surrounding chromosomal region. In the example, the insertion co-occurs with the loss of a small area (the β region) on the chromosome harboring the templated insertion. Both a loss in coverage of the lost β-region and an increase in coverage of the inserted region can be observed. (C) Templated insertions (ti) occurring in the middle of a focal amplification (fa), like templated insertions occurring alone, create signals resembling truncated arrowheads but these are in addition overlapping in the heatmap as the inserted region shares read-clouds with the fa region on either flank. Depending on the orientation of the insertion, the overlapping ‘truncated arrowheads’ will have different orientations (compare the left and right example). The increase in coverage caused by the fa and ti can be observed in both examples though it is more apparent in the case on the right. (D) Translocations occurring in the middle of a fa - similar to the fa with ti events (fa+ti) - can be observed as overlapping arrowheads patterns. However, as the regions are joined, the ‘overlapping arrowheads’ extend in both directions (i.e. truncated arrowheads are not created). Depending on the orientation of the translocation, the overlap of the arrowheads is either direct (left) or only observed in terms of the involved chromosomal regions (right). The increased coverage caused by the fa is most apparent in the case on the left.
Figure S5. Overview of identified t(4;14), t(11;14), and t(14;16) MM cases. Heatmaps displaying the number of read-clouds shared between the IGH locus (chr14) and breakpoint regions on chr4 (MMSET), chr11 (CCND1), and chr16 (MAF) for all patients (n=17) with detected t(4;14), t(11;14), and t(14;16) translocations. Blue, red, and green boxes indicate patients with verified t(4;14), t(11;14), and t(14;16) translocations respectively. The type of SV is indicated next to the read-cloud clusters: t(r), reciprocal translocation; t(nr), non-reciprocal translocation; t(r)+fa, reciprocal translocation with focal amplification of the breakpoint region; and fa+t(r), reciprocal translocation occurring in the middle of a focal amplification. If the SV depicted is part of a more complex SV, this is indicated. The few read-clouds supporting the existence of the subclonal t(11;14) in P10852_102 are indicated by a dotted circle. Percentage (%) of cells found to have the indicated translocation by FISH is shown in parenthesis next to the patient identifier.
Figure S6. Reciprocal t(4;14) translocations juxta- pose IGH enhancers with the MMSET and FGFR3 loci. (A) Heatmaps displaying the number of read-clouds shared between the IGH locus (chr14) and breakpoint regions on chr4 (MMSET) in P14402_121. The connected green and orange arrows schematically indicate the areas joined by the indicated events (i and ii). Position of the IGH VDJ regions and the 3’RR and Eμ enhancers are indicated. (B) Overview of the enhancer landscape surrounding the translocation and schematic representation of derivate chromosomes. Genome browser tracks show the median H3K27Ac signal (red) ±1SD (yellow and black respectively) in normal plasmablasts (PB) and MM samples belonging to the indicated genetic group. (C) Expression of MMSET and FGFR3 in patients with and without t(4;14).
**Fig. S7**

(A) P13756_108 t(14;16) chr16:77.0-80.5 mbp

(B) chr14:104.0-107.5 mbp

(C) MAF expression log10(TPM+1)
Figure S7. Reciprocal t(14;16) translocations juxtapose IGH enhancers with the MAF locus. (A) Heatmaps displaying the number of read-clouds shared between the IGH locus (chr14) and breakpoint regions on chr16 (MAF) in P13756_108. The connected green and orange arrows schematically indicate the areas joined by the indicated events (i and ii). Position of the IGH VDJ regions and the 3’RR and Eµ enhancers are indicated. (B) Overview of the enhancer landscape surrounding the translocation and schematic representation of derivate chromosomes. Genome browser tracks show the median H3K27Ac signal (red) ±1SD (yellow and black respectively) in normal plasmablasts (PB) and MM samples belonging to the indicated genetic group. (C) Expression of MAF in patients with and without t(14;16).
Figure S8. Reciprocal t(11;14) translocations juxtapose IGH enhancers with the CCND1 locus. (A) Heatmaps displaying the number of read-clouds shared between the IGH locus (chr14) and breakpoint regions on chr11 (CCND1) in P20004_1009. The connected green and orange arrows schematically indicate the areas joined by the indicated events (i and ii). Position of the IGH VDJ regions and the 3’RR and Eµ enhancers are indicated. (B) Overview of the enhancer landscape surrounding the translocation and schematic representation of derivate chromosomes. Genome browser tracks show the median H3K27Ac signal (red) ±1SD (yellow and black respectively) in normal plasmablasts (PB) and MM samples belonging to the indicated genetic group. (C) Expression of CCND1 in patients with and without t(11;14).
Figure S9. Complex SVs associated with identified structural aberrations. Circos plots showing all inter-chromosomal events constituting complex SVs involving the indicated IGH and Myc rearrangements. SVs were classified as (unspecified) complex, chromothripsis, or chromoplexy based on the criterion described by Rustad et al.
Fig. S10

A

chr11

P14402_120 t(11;14)

fa+t(r)

CCND1

B

chr14

α β γ

a b c
Figure S10. The t(11;14) in P14402_120 carries duplications on both sides of the breakpoint. (A) Heatmaps displaying the shared read-clouds on chr11 (top left), chr11 to chr14 (top right), and chr14 (bottom right) in P14402_120. The connected green and orange arrows schematically indicate the areas joined by the indicated events (i and ii). (B) Schematic representation of the derivative chromosomes generated by the t(11;14).
Figure S11. The amplification of focal and flanking region in t(11;14) results in the duplication of the CCND1 and 3’RR enhancer regions. (A) Heatmaps showing the number of shared read-clouds between chr11 and chr14 for the indicated patients. Tracks flanking the heatmaps (above and left) show the median H3K27Ac signal (red) ±1SD (yellow and black respectively) in normal plasmablasts (PB) and MM samples belonging to the indicated genetic group. The boundaries of the breakpoints, the CCND1 locus, and the IGHA-1/2 loci are indicated with light grey lines. The position of the IGH VDJ elements as well as the 3’RR and E_{μ} enhancers (flanking the IGHA and IGHJ regions respectively) are indicated on chr14. (B) Expression of CCND1 in MM with the indicated genetic aberrations.
Figure S12. The read-clouds supporting the existence of MYC SV are highly specific to the affected MMs. Heatmaps displaying the number of read-clouds shared between the MYC locus and indicated genomic locations in MMs with (columns 1, 3, and 5) or without the detected SV (columns 2, 4, and 6). The type of SV is indicated next to the read-cloud clusters: t(r), reciprocal translocation; t(nr), non-reciprocal translocation; fa+ti, templated insertion occurring in a focal amplification; and fa+t(r), reciprocal translocation occurring in a focal amplification. Red vertical/horizontal lines show the position of indicated genes.
Figure S13. Overview of the genomic regions involved in the SVs affecting the MYC locus. (A) Schematic representation of more complex SVs involving the MYC locus and tracks showing the median H3K27Ac signal (red) ±1SD (yellow and black respectively) in the involved regions in indicated types of MM and PBs. (B) Representation of the regions involved in simple translocations (reciprocal or non-reciprocal) affecting the MYC locus and tracks showing the H3K27Ac signals (median±SD) in the involved regions in indicated types of MM and PBs. The regions joined on the derivate chromosome containing the MYC locus are indicated by black lines. The type of SV is indicated next to the read-cloud clusters: t(r), reciprocal translocation; t(nr), non-reciprocal translocation; fa+ti, templated insertion occurring in a focal amplification; and fa+t(r), reciprocal translocation occurring in a focal amplification. (C) Expression of MYC in patients with and without SVs involving the MYC locus.
Figure S14. Analysis of the read-clouds in the t(1;8) MAFA and t(6;17) MAP3K14 breakpoint regions. (A) Localization of read-clouds involving the breakpoint regions of the t(1;8) involving the MAFA locus in MM P13172_104. VAF at either breakpoint site (indicated by black dotted lines) were calculated by dividing the number of read-clouds spanning chr1 to chr8 with the total number of read-clouds involving ±10kb of the breakpoint. (B) Copy-number of chr8 and chr1 on patient P13172_104. Considering the amplification of the chr8 c and chr1 γ regions (with 3 copies or more), the VAF of γ to c spanning read-clouds suggests that the SV is clonal. (C) Localization of the read-clouds involving the breakpoint regions constituting the t(6;17) near the MAP3K14 locus in MM P13172_101. VAF at either breakpoint site (indicated by black dotted lines) were calculated by dividing the number of read-clouds spanning chr6 to chr17 with the total number of read-clouds involving ±10kb of the breakpoint. Considering the normal copy-number of both involved chromosomes (data not shown), the VAF calculated at both breakpoints suggests that the SV is subclonal.