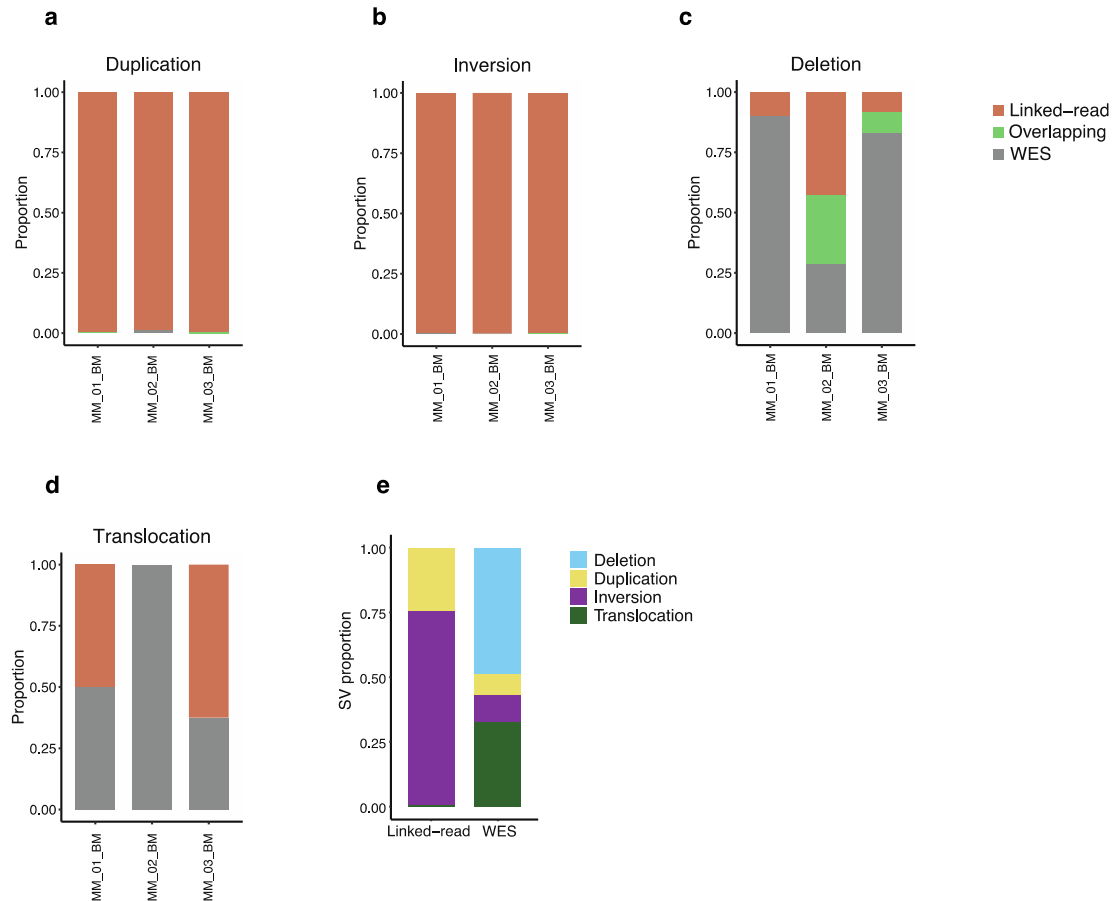# Comparison of structural and short variants detected by linked-read and whole-exome sequencing in multiple myeloma

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Supplementary figures and figure legends

Supplementary Figure 1.
Total SVs detected by linked-read and WES in 3 paired samples.
(a) Duplication; linked-read sequencing detected more than 99% of all duplications across three samples (b) Inversion; linked-read detected more than 99% of inversions called in each sample. (c) Deletions; WES detected a higher proportion of deletions across all the samples. Linked-read sequencing alone detected about 10% of deletions in two samples and more than 40% in one sample. The proportion of overlaps varied across the samples. (d) Translocations; the proportion of translocations varied among the samples. WES detected all the translocations in one sample and 50% in another. (e) The proportion of each type of SV called by each sequencing method.

Supplementary Figure 2. The number of multiple myeloma specific SV hotspots across 8 samples identified by linked-read and WES. (a) The first bar shows the total number of identified SV hotspots. The median number of hotspots per patient is 2. The other bars represent hotspots identified in each sample by linked-read sequencing and WES. Linked-read sequencing detected an exceptionally high number of SVs per patient, with a median number of 41.5. The median number of SVs for WES is 3.5. (b) Overall linked-read sequencing detected more gain of function hotspots. WES detected a higher proportion of loss of function hotspots.

Supplementary Figure 3. The overlapping short variants across all 8 tumor samples identified by GATK tool RNA-seq, WES and linked-read exome sequence data.

a

KRAS, MM_04_BM

Linked-read

```
(133.28Mbp)
57.39%                    █           Number of reads: 959
51.02%                    █              (1123 filtered)
44.64%        █   █       █           Covered bases:   6.3Kbp
38.26%        █   █       █           Percent covered: 13.76%
31.89%        █   █       █           Mean coverage:   1.82x
25.51%        █   █       █       █   Mean baseQ:      30.9
19.13%        █   █       █   █   █   Mean mapQ:       59.8
12.75%        █   █       █   █   █
 6.38%        █   █       █   █   █   Histo bin width: 1.4Kbp
 0.00%      █ █ █ █ █   ███ █ █ █ █   Histo max bin:   63.77%
       25.21M     25.22M   25.23M    25.25M
```

WES

```
(133.28Mbp)
80.22%                  █   █         Number of reads: 2236
71.31%                 ██   ██           (68 filtered)
62.40%      █ ███ █   ███ ██ ██   █   Covered bases:   23.3Kbp
53.48%      ████ ██ █████ █████ █ █   Percent covered: 51.02%
44.57%      ██████ ████████████ ██   Mean coverage:   4.87x
35.66%      ███████████████████ ██   Mean baseQ:      34.9
26.74%      ██████████████████████   Mean mapQ:       60
17.83%      ██████████████████████
 8.91%      ██████████████████████   Histo bin width: 1.4Kbp
 0.00%      ██████████████████████   Histo max bin:   89.138%
       25.21M     25.22M   25.23M    25.25M
```

b

FAM46C; MM_05_BM1

Linked-read

```
(248.96Mbp)
90.00%                   █            Number of reads: 2575
80.00%                   █               (1979 filtered)
70.00%                   ██           Covered bases:   5.7Kbp
60.00%                  ███           Percent covered: 25.46%
50.00%      █   █       ███           Mean coverage:   10x
40.00%      █   █       ███           Mean baseQ:      30.1
30.00%      █  ██       ███           Mean mapQ:       59.9
20.00%      █ ███       ███  █
10.00%      █████     █ ███ ██        Histo bin width: 698bp
 0.00%     ███████   █ ██████████     Histo max bin:   100%
      117.61M  117.61M  117.62M  117.63M
```

WES

```
(248.96Mbp)
90.00%        █  █         █          Number of reads: 3430
80.00%       ██ ██        ██             (104 filtered)
70.00%      ███ ███   █  ███ █        Covered bases:   15.6Kbp
60.00%      █████████  █████ █        Percent covered: 69.81%
50.00%      ██████████ █████ ██       Mean coverage:   15.2x
40.00%      ██████████████████       Mean baseQ:      33.8
30.00%      ███████████████████      Mean mapQ:       60
20.00%      ███████████████████
10.00%      ████████████████████     Histo bin width: 698bp
 0.00%      ████████████████████     Histo max bin:   100%
      117.61M  117.61M  117.62M  117.63M
```

c

FAM46C; MM_07_BM

Linked-read

```
(248.96Mbp)
90.00%                      █         Number of reads: 250
80.00%                      █            (163 filtered)
70.00%                      █         Covered bases:   2.6Kbp
60.00%                      █         Percent covered: 11.85%
50.00%                      █         Mean coverage:   0.983x
40.00%                      █         Mean baseQ:      31.3
30.00%                      █         Mean mapQ:       60
20.00%      █               ██
10.00%      █   █         ████        Histo bin width: 698bp
 0.00%      █  █         █████        Histo max bin:   100%
      117.61M  117.61M  117.62M  117.63M
```

WES

```
(248.96Mbp)
90.00%                     █          Number of reads: 1286
80.00%                     █             (36 filtered)
70.00%      █              █          Covered bases:   9.4Kbp
60.00%      █         █   ██  █       Percent covered: 42.03%
50.00%      █  █      ██ ███ ██       Mean coverage:   5.47x
40.00%      ████ █  █ ██ ███ ██       Mean baseQ:      33.4
30.00%      █████ ████████████        Mean mapQ:       60
20.00%      █████ ████████████
10.00%      ████████████████████     Histo bin width: 698bp
 0.00%      █████████████████████    Histo max bin:   100%
      117.61M  117.61M  117.62M  117.63M
```

d

BRAF; MM_03_BM

Linked-read

```
(159.35Mbp)
39.84%          █                    Number of reads: 3916
35.41%          █                       (2416 filtered)
30.99%        █ █ █                   Covered bases:   23.5Kbp
26.56%        ██ ██                   Percent covered: 11.43%
22.13%        ██ ███                  Mean coverage:   1.67x
17.71%       ███ ███                  Mean baseQ:      31.2
13.28%      █████████     █           Mean mapQ:       59.4
 8.85%      ████████████ ███          
 4.43%      ██████████████████  █     Histo bin width: 6.4Kbp
 0.00%      █████████████████████     Histo max bin:   44.265%
      140.72M  140.78M  140.85M  140.92M
```

WES

```
(159.35Mbp)
33.00%         █                     Number of reads: 7472
29.34%         ██                       (1126 filtered)
25.67%         ██                    Covered bases:   35.4Kbp
22.00%       █ ██                    Percent covered: 17.22%
18.33%      ██ ███                   Mean coverage:   3.63x
14.67%      ████████     █  █        Mean baseQ:      33.1
11.00%      ████████    ███ ██       Mean mapQ:       59.8
 7.33%      █████████   ███████
 3.67%      █████████  ████████      Histo bin width: 6.4Kbp
 0.00%      ███████████████████      Histo max bin:   36.669%
      140.72M  140.78M  140.85M  140.92M
```

e

KRAS; MM_01_BM

Linked-read

```
(133.28Mbp)
60.23%                          Number of reads: 1484
53.54%                              (1440 filtered)
46.85%                          Covered bases:    8.0Kbp
40.15%                          Percent covered: 17.5%
33.46%                          Mean coverage:    2.83x
26.77%                          Mean baseQ:       31.2
20.08%                          Mean mapQ:        59.7
13.38%
 6.69%                          Histo bin width: 1.4Kbp
 0.00%                          Histo max bin:   66.924%
    25.21M   25.22M   25.23M   25.25M
```

WES

```
(133.28Mbp)
60.99%                          Number of reads: 2927
54.21%                              (482 filtered)
47.44%                          Covered bases:    9.9Kbp
40.66%                          Percent covered: 21.74%
33.88%                          Mean coverage:    6.39x
27.11%                          Mean baseQ:       33.2
20.33%                          Mean mapQ:        60
13.55%
 6.78%                          Histo bin width: 1.4Kbp
 0.00%                          Histo max bin:   67.765%
    25.21M   25.22M   25.23M   25.25M
```

f

TP53; MM_01_BM

Linked-read

```
(83.26Mbp)
90.00%                          Number of reads: 1576
80.00%                              (1031 filtered)
70.00%                          Covered bases:    7.8Kbp
60.00%                          Percent covered: 30.11%
50.00%                          Mean coverage:    5.28x
40.00%                          Mean baseQ:       31.1
30.00%                          Mean mapQ:        59.9
20.00%
10.00%                          Histo bin width: 805bp
 0.00%                          Histo max bin:   100%
    7.66M   7.67M   7.68M   7.69M
```

WES

```
(83.26Mbp)
90.00%                          Number of reads: 2549
80.00%                              (352 filtered)
70.00%                          Covered bases:    8.9Kbp
60.00%                          Percent covered: 34.5%
50.00%                          Mean coverage:    9.86x
40.00%                          Mean baseQ:       33.4
30.00%                          Mean mapQ:        59.9
20.00%
10.00%                          Histo bin width: 805bp
 0.00%                          Histo max bin:   100%
    7.66M   7.67M   7.68M   7.69M
```

g

NRAS; MM_02_BM

Linked-read

```
(248.96Mbp)
90.00%                          Number of reads: 566
80.00%                              (227 filtered)
70.00%                          Covered bases:    3.3Kbp
60.00%                          Percent covered: 27.03%
50.00%                          Mean coverage:    4.03x
40.00%                          Mean baseQ:       30.6
30.00%                          Mean mapQ:        60
20.00%
10.00%                          Histo bin width: 384bp
 0.00%                          Histo max bin:   100%
    114.70M  114.71M  114.71M  114.72M
```

WES

```
(248.96Mbp)
90.00%                          Number of reads: 1757
80.00%                              (321 filtered)
70.00%                          Covered bases:    4.3Kbp
60.00%                          Percent covered: 34.55%
50.00%                          Mean coverage:    14.4x
40.00%                          Mean baseQ:       32.3
30.00%                          Mean mapQ:        60
20.00%
10.00%                          Histo bin width: 384bp
 0.00%                          Histo max bin:   100%
    114.70M  114.71M  114.71M  114.72M
```

h

FAM46C, MM_05_BM2

Linked-read

```
(248.96Mbp)
90.00%                          Number of reads: 435
80.00%                              (201 filtered)
70.00%                          Covered bases:    2.6Kbp
60.00%                          Percent covered: 11.85%
50.00%                          Mean coverage:    1.67x
40.00%                          Mean baseQ:       30.6
30.00%                          Mean mapQ:        60
20.00%
10.00%                          Histo bin width: 698bp
 0.00%                          Histo max bin:   100%
    117.61M  117.61M  117.62M  117.63M
```

WES

```
(248.96Mbp)
90.00%                          Number of reads: 3053
80.00%                              (147 filtered)
70.00%                          Covered bases:    12.0Kbp
60.00%                          Percent covered: 53.85%
50.00%                          Mean coverage:    13.6x
40.00%                          Mean baseQ:       34.4
30.00%                          Mean mapQ:        60
20.00%
10.00%                          Histo bin width: 698bp
 0.00%                          Histo max bin:   100%
    117.61M  117.61M  117.62M  117.63M
```

i

NRAS; MM_05_BM2

Linked-read

```
(248.96Mbp)
90.00%                                    Number of reads: 411
80.00%                                         (191 filtered)
70.00%                                    Covered bases:   2.9Kbp
60.00%                                    Percent covered: 23.26%
50.00%                                    Mean coverage:   2.93x
40.00%                                    Mean baseQ:      30.6
30.00%                                    Mean mapQ:       59.8
20.00%
10.00%                                    Histo bin width: 384bp
 0.00%                                    Histo max bin:   100%
      114.70M  114.71M  114.71M  114.72M
```

WES

```
(248.96Mbp)
90.00%                                    Number of reads: 2735
80.00%                                         (152 filtered)
70.00%                                    Covered bases:   5.2Kbp
60.00%                                    Percent covered: 42.48%
50.00%                                    Mean coverage:   22.2x
40.00%                                    Mean baseQ:      34.5
30.00%                                    Mean mapQ:       60
20.00%
10.00%                                    Histo bin width: 384bp
 0.00%                                    Histo max bin:   100%
      114.70M  114.71M  114.71M  114.72M
```

j

KRAS; MM_07_BM

Linked-read

```
(133.28Mbp)
55.44%                                    Number of reads: 970
49.28%                                         (1247 filtered)
43.12%                                    Covered bases:   7.0Kbp
36.96%                                    Percent covered: 15.37%
30.80%                                    Mean coverage:   1.85x
24.64%                                    Mean baseQ:      31.4
18.48%                                    Mean mapQ:       59.8
12.32%
 6.16%                                    Histo bin width: 1.4Kbp
 0.00%                                    Histo max bin:   61.598
      25.21M   25.22M   25.23M   25.25M
```

WES

```
(133.28Mbp)
73.85%                                    Number of reads: 3422
65.65%                                         (73 filtered)
57.44%                                    Covered bases:   21.9Kbp
49.24%                                    Percent covered: 47.95%
41.03%                                    Mean coverage:   7.23x
32.82%                                    Mean baseQ:      33.4
24.62%                                    Mean mapQ:       59.9
16.41%
 8.21%                                    Histo bin width: 1.4Kbp
 0.00%                                    Histo max bin:   82.06%
      25.21M   25.22M   25.23M   25.25M
```

k

TP53; MM_07_BM

Linked-read

```
(83.26Mbp)
90.00%                                    Number of reads: 884
80.00%                                         (699 filtered)
70.00%                                    Covered bases:   7.0Kbp
60.00%                                    Percent covered: 27.18%
50.00%                                    Mean coverage:   3.01x
40.00%                                    Mean baseQ:      31.3
30.00%                                    Mean mapQ:       59.8
20.00%
10.00%                                    Histo bin width: 805bp
 0.00%                                    Histo max bin:   100%
      7.66M    7.67M    7.68M    7.69M
```

WES

```
(83.26Mbp)
90.00%                                    Number of reads: 3266
80.00%                                         (78 filtered)
70.00%                                    Covered bases:   14.5Kbp
60.00%                                    Percent covered: 56.18%
50.00%                                    Mean coverage:   12x
40.00%                                    Mean baseQ:      33.3
30.00%                                    Mean mapQ:       59.9
20.00%
10.00%                                    Histo bin width: 805bp
 0.00%                                    Histo max bin:   100%
      7.66M    7.67M    7.68M    7.69M
```
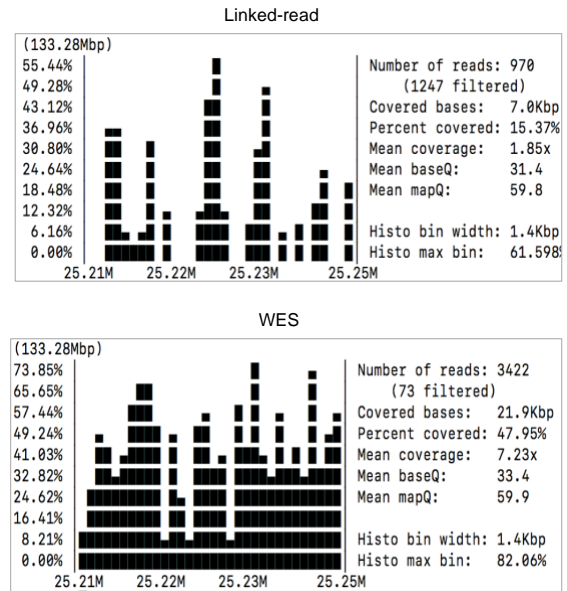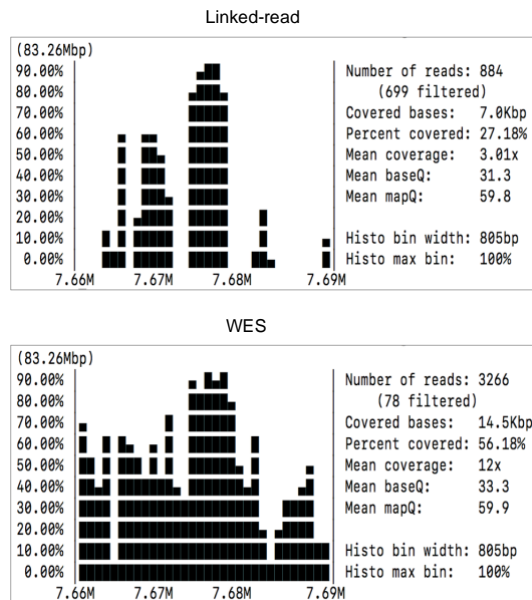
Supplementary Figure 4. Gene coverage plots depicting mutations in myeloma-specific genes in linked-read and WES data.