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Supplemental Data

Biallelic *BRCA2* Mutations Shape the Somatic Mutational Landscape of Aggressive Prostate Tumors

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Figure S1

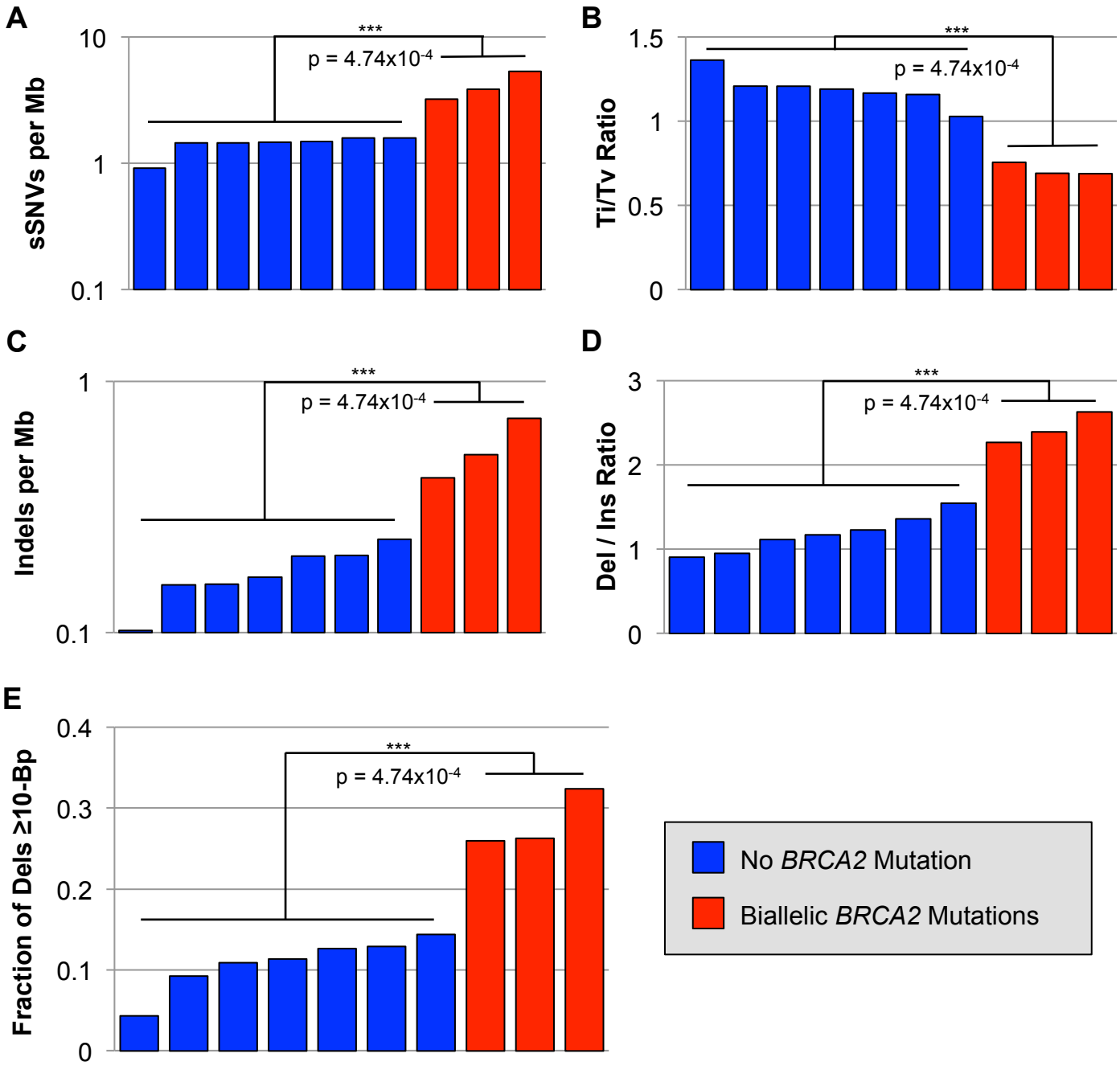
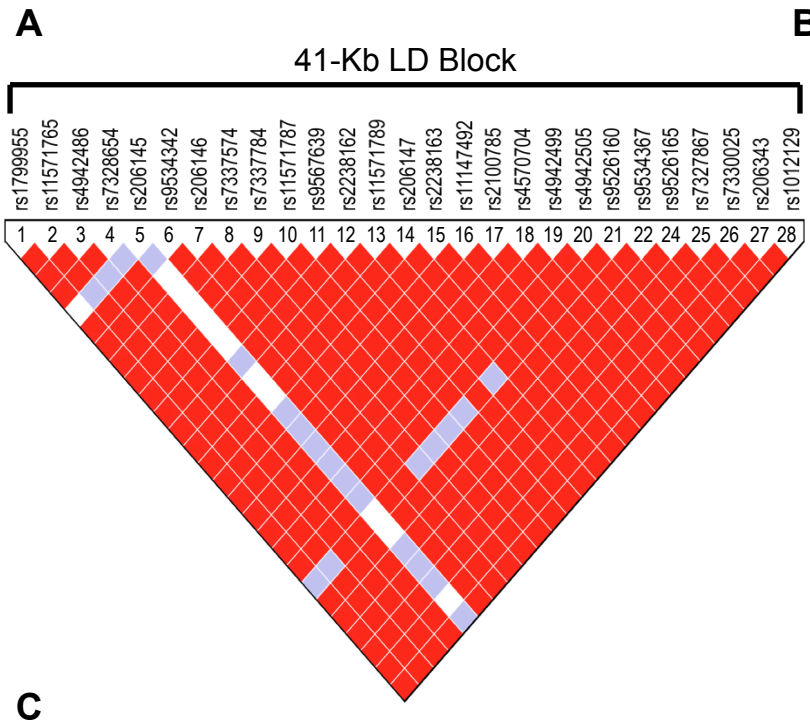


Figure S1. Among the 10 aggressive tumors from the Mayo Clinic discovery set, the three tumors with biallelic *BRCA2* disruptions are clearly significant outliers for numerous measures of the quantity and quality of sSNVs and somatic indels, including **A)** sSNV rate, **B)** transition-transversion ratio, **C)** somatic indel rate, **D)** deletion-to-insertion ratio, and **E)** percent of deletions spanning more than 10-Bp.

Figure S2



B

Hap#	Allele at Informative SNP	Freq.
1	AACAATGGGTGTCTCGCTCTACGAGAC	31.2%
2	AATGACGGGTGCCTATACTCACAGAAG	24.2%
3	AATGACAGGTGCCCATACTCATAGAGG	16.1%
4	GACAATGACGATCTCGCTCTACGAGAC	9.1%
5	GACAATGACGATATCGCTCTACGAGAC	6.4%
6*	GGCAATGACGATATCGCTCTACGAGAC	5.9%
7^	AATGACAGGTGCCCATACTCGTAGAGG	4.8%
8	AACAATGGGTGTCTCGCTTTACGAGAC	0.5%
9	AATGTCGGGTGCCTATACTCACAGAAG	0.3%
10	AATGACAGGTGCCCATACTCACAGAAG	0.3%
11	AATGACGAGTGCCTATACTCACAGAAG	0.3%
12	AACAATGGGTGTCTCGCTCCACGAGAC	0.3%
13	AACAATGGCGATATCGCTCTACGAGAC	0.1%
14	GACAATGGGTGTCTCGCTCTACGAGAC	0.1%
15	GACATTGACGATCTCGCTCTACGAGAC	0.1%
16	GATGACAGGTGCCCATACTCATAGAGG	0.1%

*** Chromosome with 37.1-Mb Deletion**
^ Chromosome with Germline Frameshift

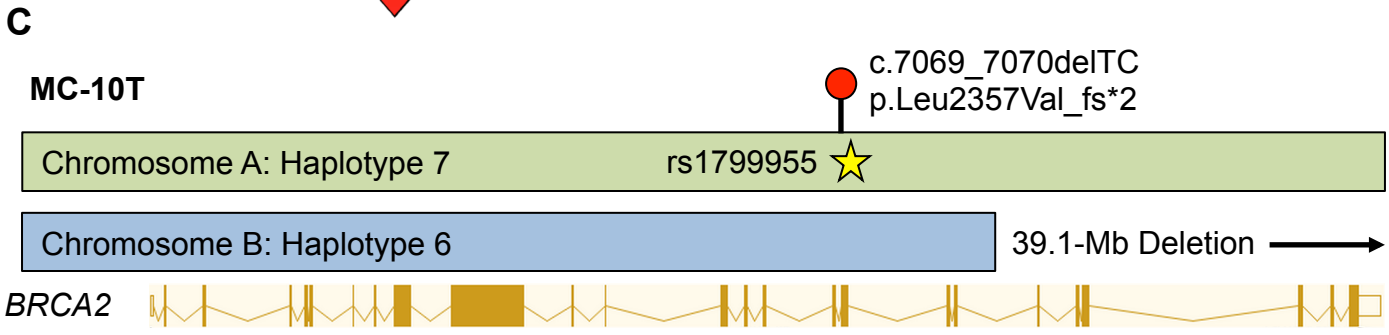


Figure S2. Linkage disequilibrium (LD) and predicted haplotypes at the *BRCA2* locus indicate that in MC-6T, the 39.1-Mb deletion affects one chromosome, while the germline frameshift likely affects the other. **A)** Leveraging 1000 Genomes Project data, we used Haploview[22] to generate haplotypes and calculate LD between rs1799955, a SNP on the same read as the germline c.7069_7070delCT indel, and hemizygous SNPs within the somatic 39.1-Mb deletion interval. Strong LD spans the locus. **B)** We used the genotypes from the normal DNA sample, as well as 26 hemizygous germline variants within the deletion interval, to phase both chromosomes inherited by subject MC-6. The effective phasing that resulted from the 39.1-Mb deletion unambiguously revealed that the deleted chromosome had haplotype #6 (Table S5). We then predicted the genotypes for both chromosomes at rs1799955, and inferred that haplotype #7 most likely harbored the germline frameshift (Table S5). **C)** Haplotype analysis revealed that the germline indel and somatic SV exist on different chromosomes, resulting in two defective copies of *BRCA2* in MC-6T.

Figure S3

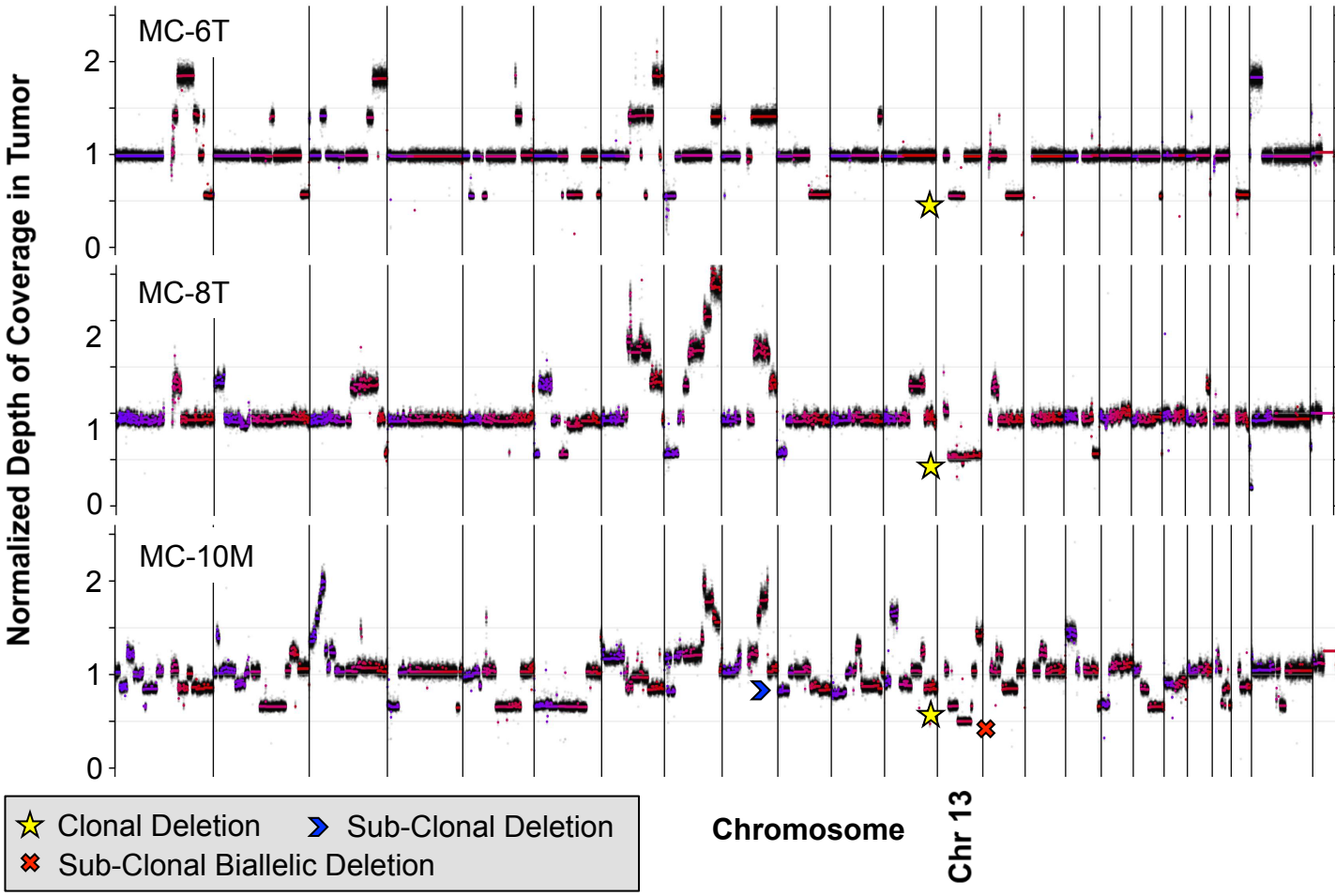


Figure S3. *BRCA2* copy loss was clonal in all three tumors, indicated by the consistent magnitude of decrease in the normalized tumor coverage in each sample, as well as allelic imbalance. Plots were generated with Patchwork.[23]

Figure S4

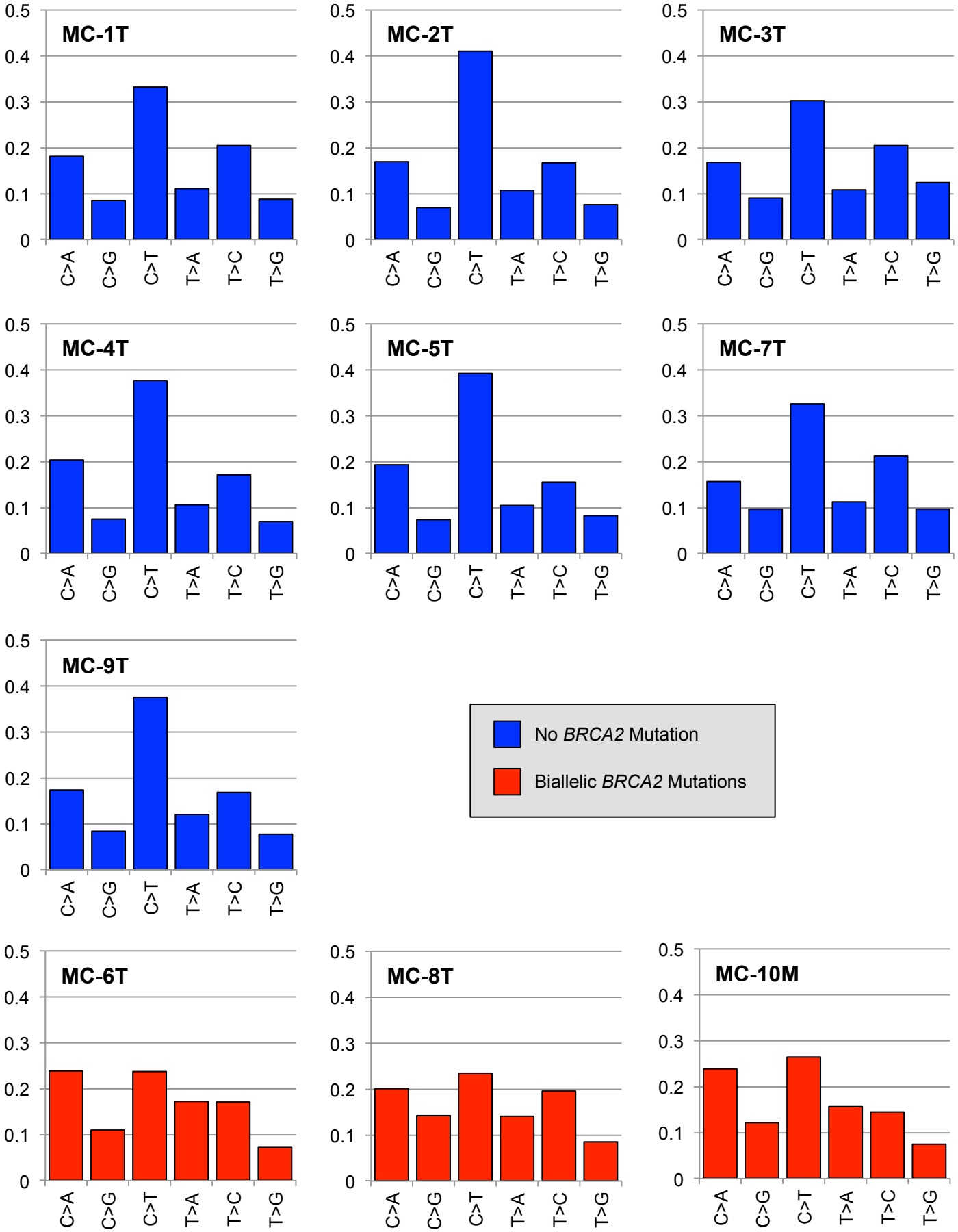


Figure S4. Substitution profiles for all 10 aggressive discovery set samples.

Figure S5

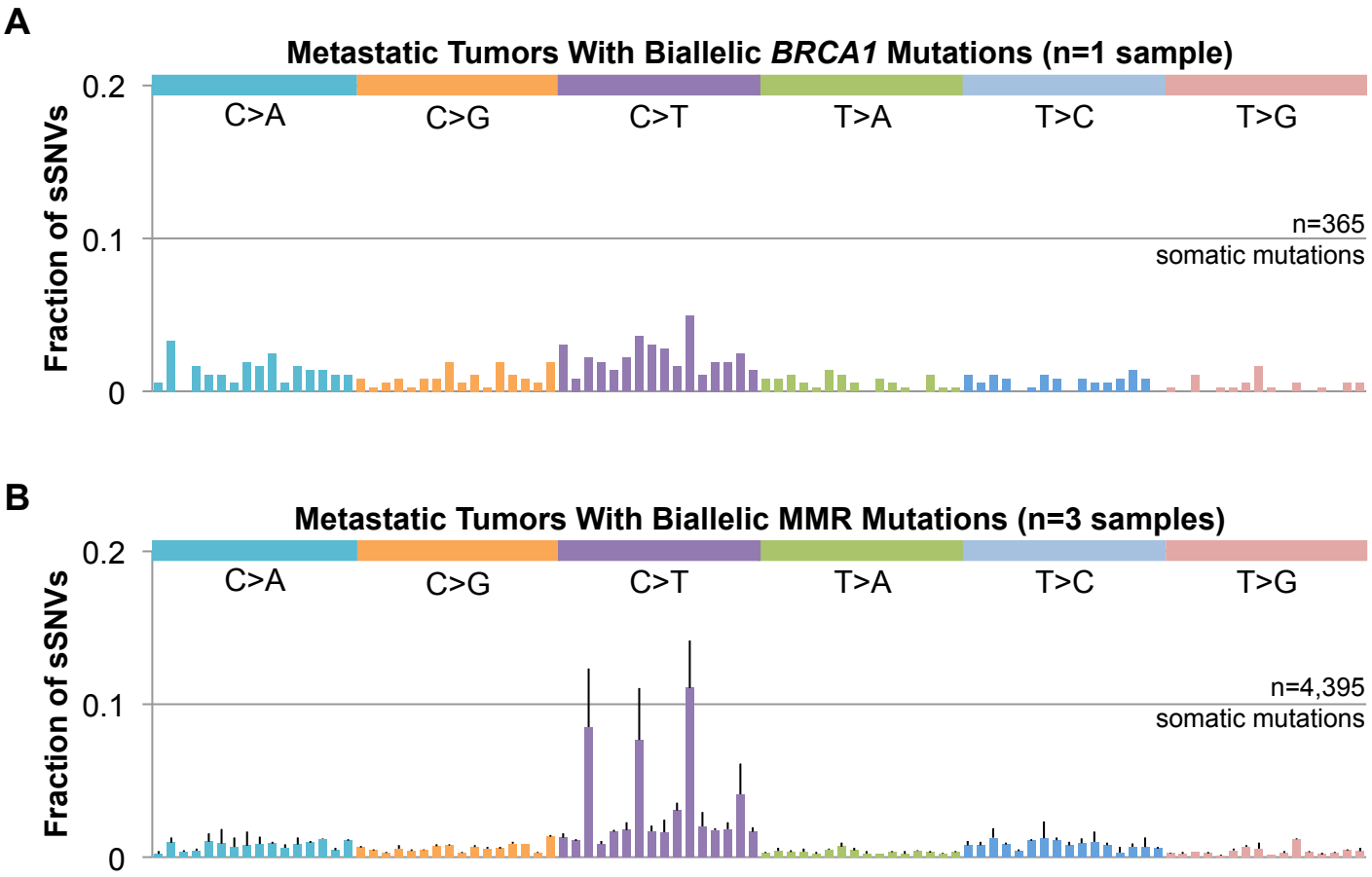


Figure S5. Mutation signatures for additional samples of interest. **A)** The metastatic dataset contained one tumor with a germline plus somatic mutation in *BRCA1*, and the mutation signature more closely resembled the *BRCA2*-deficient tumors than HR-competent samples (Compare to Figure 4B,C). **B)** In contrast, samples with biallelic MMR mutations were indistinguishable from the samples without *BRCA2* mutations (compare to Figure 4C).

Figure S6

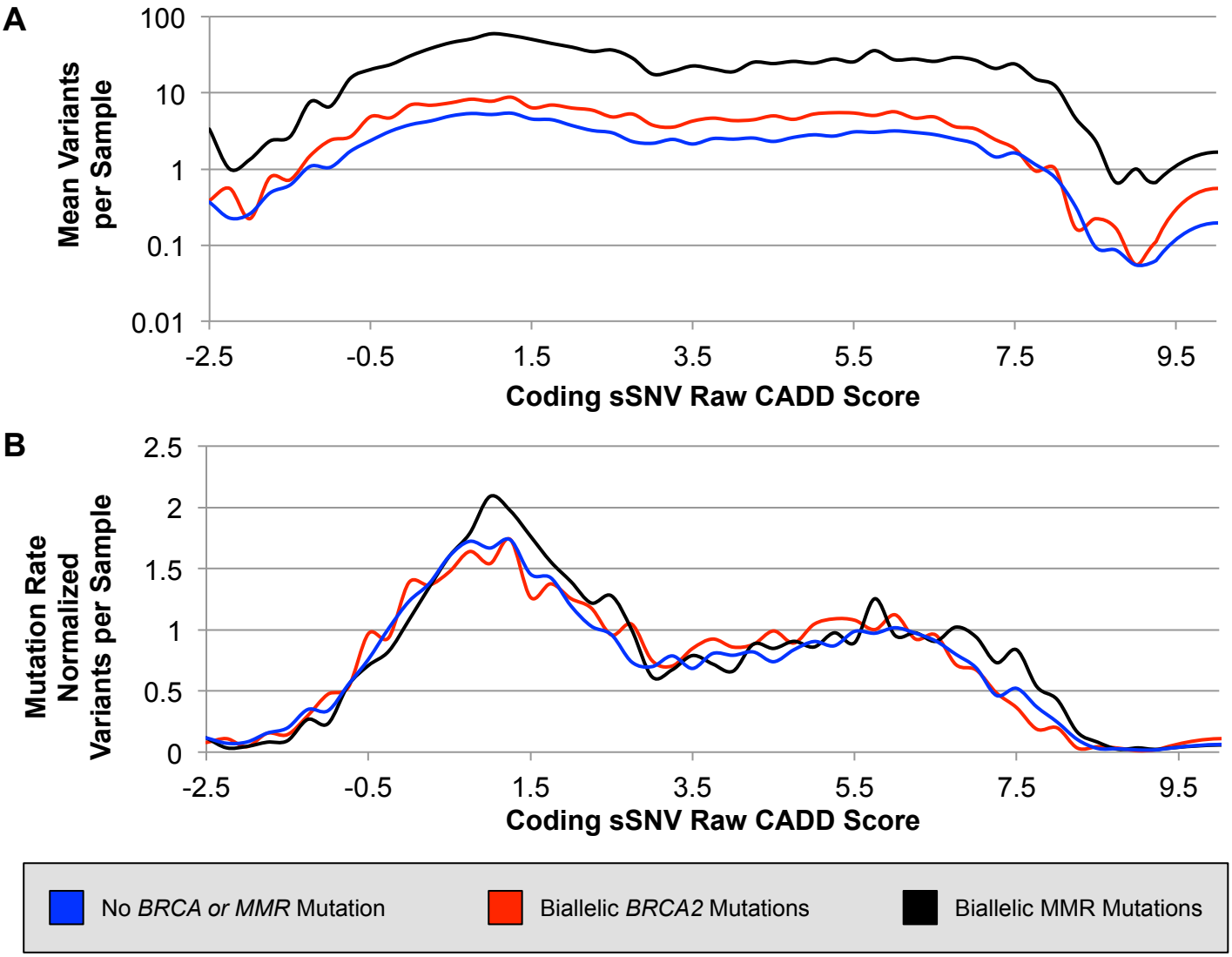


Figure S6. Raw CADD scores for sSNVs in metastatic tumors with and without biallelic *BRCA2* disruption. **A)** Samples with *BRCA2* mutations had more somatic coding mutations at every CADD-projected level of protein damage. **B)** After correcting for the mutation rate, this trend is attributable solely to the elevated mutation burden, and not to any predilection towards generation of more damaging mutations.

Figure S7

OR	Fisher P-Value	Overall Percent	*BRCA2* Percent	Other Percent	Gene
0.25	**0.0198**	**41.1%**	**16.7%**	**44.5%**	***PTEN***
0.28	0.2224	7.5%	0.0%	8.6%	*APC*
0.28	0.2224	7.5%	0.0%	8.6%	*RB1*
0.28	0.2224	7.5%	0.0%	8.6%	*ZFHX3*
0.38	0.3394	5.5%	0.0%	6.3%	*USP28*
0.44	0.3899	4.8%	0.0%	5.5%	*ATM*
0.44	0.3899	4.8%	0.0%	5.5%	*NCOR1*
0.48	0.4197	10.3%	5.6%	10.9%	*ZBTB16*
0.71	0.3290	57.5%	50.0%	58.6%	ETS Fusion
0.94	0.6504	62.3%	61.1%	62.5%	*AR*
1.21	0.4501	51.4%	55.6%	50.8%	*TP53*
2.54	0.1970	5.5%	11.1%	4.7%	*VPS13B*
3.08	0.1670	4.8%	11.1%	3.9%	*PIK3CB*
3.46	0.0872	6.8%	16.7%	5.5%	*KMT2C*
3.88	0.1346	4.1%	11.1%	3.1%	*BMPR1B*
3.88	0.1346	4.1%	11.1%	3.1%	*KDM6A*
4.07	0.0685	6.2%	16.7%	4.7%	*CDH1*
4.29	**0.0355**	**8.2%**	**22.2%**	**6.3%**	***OPHN1***
5.21	0.1013	3.4%	11.1%	2.3%	*MAST2*
5.21	0.1013	3.4%	11.1%	2.3%	*PRKDC*
8.86	**0.0085**	**5.5%**	**22.2%**	**3.1%**	***PVT1***

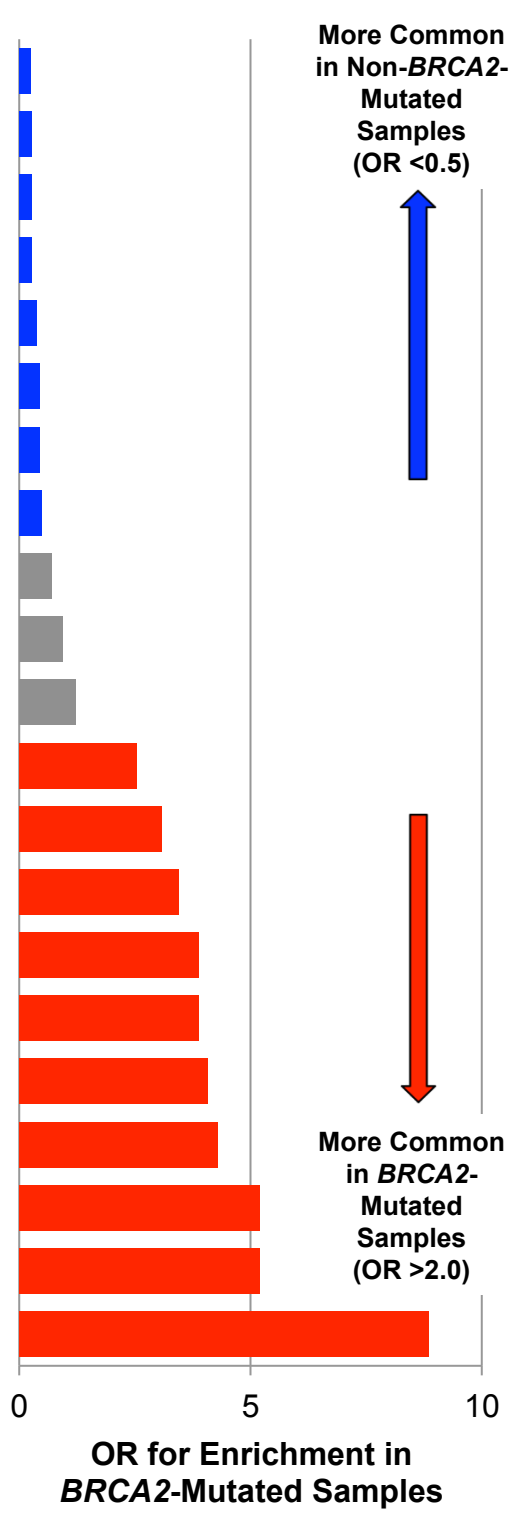


Figure S7. Difference in frequency of damaging mutations between *BRCA2*-mutated and non-*BRCA2*-mutated tumors in the metastatic tumor set. For all genes, truncating sSNVs, truncating indels, biallelic deletions, and fusion-inducing structural variants were included. In addition, for *PTEN*, *AR*, and *TP53*, samples were counted as mutated when one or more alleles was affected by potentially damaging non-truncating somatic mutations.