

Supplementary Table S1. Details of Experimental Aims, Loci, Cells, Target Sequences, and Screening Primers

<i>Experiment</i>	<i>Gene</i>	<i>Cell Line</i>	<i>Target sequence</i>	<i>Desired mutation</i>	<i>Genomic location</i>	<i>Screening primers</i>	<i>Size (bp)</i>
1	MLH1	COLO320, colon, adenocarcinoma, hyperdiploid	ATGGCGTAAGCTACAGCTGA (G to A) ATGGCGTAAGCTACAGCTAA (A to G)	Mutation of heterozygous SNP: rs1800734 A/G to homozygous AA and GG	Chr3: 36993437–36993456	F-AGCAACCCACAGAGTTGAGA R-GAATAACCCCTGCCACGAAC	213
2	POLE	HCC2998, colon, adenocarcinoma, diploid	TCAAGTTTCgTGATGCTGAG ATGATTTCCTACATGATCGA	Revertant of a pathogenic point mutation	Chr12: 133253174–133253193 Chr12: 133253139–133253158	F-CTAACAGTGGGGCAGATGCT R-GGTGTTTCAGGGAGGCCTAAT	258
3	NFE2L2	SW1463, rectum, adenocarcinoma, hyperdiploid	ACTGGGCTCGATGTGACC GTGTTCTGGTGATGCCACAC TATTTGACTTCAGTCAGCGA	Indel causing gene knockout	Chr2: 177232522–177232544 Chr2: 177231526–177231548 Chr2: 177234188–177234210	F-AGGCCAAGTAGTGTGTCTCC; R-ATGCCCTCACCTGCTACCTTT F-AGGCCAAGTAGTGTGRTCC; R-ATGCCCTCACCTGCTACTTT F-TGATTGACATACTTTGGAGGCA; R-GCTGGCTGAATTGGGAGAAA	224 224 211

Supplementary Table S2. HDR Template Sequences

<i>Experiment</i>	<i>Gene</i>	<i>HDR template</i>
1	MLH1 A to G	GACTGGCATTCAAGCTGTCCAATCAATAGCTGCCGCTGAAGGGTGGGGCTGGATGGCGTAAGCTACAGCTgAAGGAAGAACGTGAGCACGAGGCACTGA GGTGATTGGCTGAAGGCACTTCCGTTGAGCATCTAGACGTTT
1	MLH1 G to A	GACTGGCATTCAAGCTGTCCAATCAATAGCTGCCGCTGAAGGGTGGGGCTGGATGGCGTAAGCTACAGCTaAAGGAAGAACGTGAGCACGAGGCACTG AGGTGATTGGCTGAAGGCACTTCCGTTGAGCATCTAGACGTTT
2	POLE	ATTTTGTCCCCACAGGACCCTGTGGTTTTGGCATTGACATTGAGACGACCAAACCTGCCCTCAAGTTTCcTGATGCTGAGACAGACCAGATTATGATGATT TCCTACATGATCGATGGCCAGGTGAGCAGGTGGCTTCTG