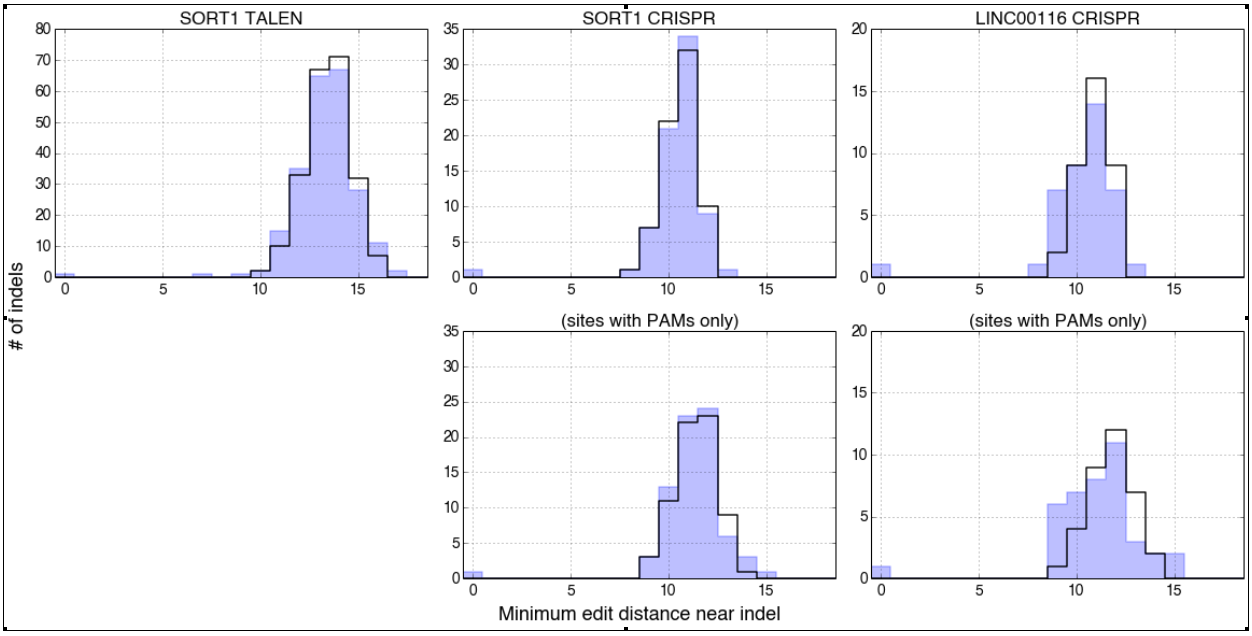
SUPPLEMENTAL DATA

Figure S1, Related to Table 1. Minimal Edit Distances Near Indels



In each panel, the blue shaded area represents the distribution of minimal edit distances for each nuclease's subset of 381 filtered indels, and the black line represents the expected distribution inferred from 50,000 randomly sampled parental HUES 9 line indels. Top row, minimal edit distances across a 100-bp window around a given indel. Bottom row, minimal edit distances across a 100-bp window, retaining only sequences that end in an NGG or NAG PAM sequence.

Table S1, Related to Table 1. Unique Indels Detected by Whole-genome Sequencing

						SORT1 TALENs			*SORT1* CRISPR-Cas9			*LINC00116* CRISPR-Cas9		
Chr	Pos	5' flanking sequence	Ref	Alternate	3' flanking sequence	A	B	C	D	E	F	G	H	I
1	81390259	ATAGCCTAAGAAGATATTCC	CATATGGTG	C	TTCTCAGAGCTCTTAGTGTG									25,11
1	**109910034**	**GTGTTATTGATCTCACCTTC**	**G**	**GA**	**ATATAGCTTGGACTGTCCAA**					**0,13**	**1,54**			
1	**109910041**	**GATCTCACCTTCGATATAGC**	**TTGGACT**	**TG**	**GTCCAAAAGTCATAATTACC**		**9,4***							
1	**109910043**	**ATCTCACCTTCGATATAGCT**	**TG**	**T**	**GACTGTCCAAAAGTCATAAT**			**7,17***						
1	**109910044**	**TCTCACCTTCGATATAGCTT**	**GGACT**	**G**	**GTCCAAAAGTCATAATTACC**		**5,8***							
1	**109910046**	**TCACCTTCGATATAGCTTGG**	**ACTGTC**	**A**	**CAAAAGTCATAATTACCAGT**			**20,8***						
1	170931870	AATTTGTGCCTAATTTGAGC	TG	T	TTTTTTTTAATTCATTTAAA					8,17				
2	9705788	CGAGAGACTGAAAGAAAAGC	AGCAAAGCCCTGGGT	A	AATCAAGGCCCTAAACGGAA		8,5							
2	76409962	ACAAGTTGAAGATGACAATC	TG	T	TGGCAATTCTACAATATTGT				14,7					
2	**110970046**	**TGCCAGCCCAGGAGTACTCC**	**AGAAGC**	**A**	**GAAGGCTACTAGCACGGACA**									**4,58**
2	**110970049**	**CAGCCCAGGAGTACTCCAGA**	**A**	**AG**	**GCGAAGGCTACTAGCACGGA**								**1,34**	
2	136347377	GACTTGGATAATATATCTGT	CACATTATATAATATATATTATGC AAATCTGTT	C	ACATTATATAATATATATGA			12,10						
3	138374851	TATGTACTTCCCAGATTCTT	TC	T	CCTCCTGGCTAAGAACCATC				16,11					
3	195706577	CCACACGCTTACAAGACACA	C	CAT	GAGCCGAACGCTTTCCGGGC						5,3			
4	65647862	TATTAGTAAGCAAAACATGC	TG	T	TTTGAGTAGTTATGATTTTG	11,12								
4	67241317	TGACAATCATAACTTTTTTA	G	GCCT	CCTCTATGCACACAGAAAAG			11,10						
4	117364346	TTTAAAATATTATCTATGAG	GAATATTTTC	G	TATATTTTTACCTTGAATAT						9,5			
4	**126910474**	**TTCACAGGAAAGATACTTGT**	**GACTTTGGTGATACAGA**	**G**	**ACAAGGATTGAATGTGTTAT**		**8,4**							
5	**850612**	**CTGGAAGTAGTGCAGGGGTA**	**AC**	**A**	**GACCAGCCGTTCACTCTGGA**									**43,15**
5	32712655	CCAGGCCAGTGAGAGAGGTG	A	AG	GCAGGGGCGCGTCCCGGGCC								30,35	
6	156267271	TTTAAAGCCATGTGTTTTAG	TA	T	ACTAAATGTTGCTGCTTTAG					13,12				
7	23212217	GTGTGAAGAAAGAAAAAAGA	ATTAT	A	TTATCTTCGAAGCATCTTCC					19,16				
8	127961691	ATTGATTTGCTATGGGCAAA	A	AAG	AAAAAAAAAAAAAAGAGGAA				4,5					
8	132181273	AAATCCCTTCAAATTTTGTT	TCTAC	TGAAGGGATTTA	ATTTTCTAAACCTAATATTG								6,11	
9	33682336	TGAGTCTTGGAAACATTTGT	GAA	G	ATTCTTATTCTGAGTTTGCC	18,14								
10	30327724	ATACAAATGAAGGAAGAAGG	G	GTA	TATAGGTCCATGTGGAAGGA							34,7		
10	82813787	TAGAAAAGCAGAAAGACTGA	GTCTC	G	TATGAGAGATGTGTTATCGT								18,25	
10	131460181	TGCTACACCCTTTCCATAGG	CT	C	TCACTGTCATCTACCCTCAT								33,8	
11	85267884	CCTCATACAAAGTTTATTCT	CTCT	C	TCTAGTTATCCAAATATAGA								13,15	
12	30161597	TTGTGGAGTCCACCTCATGA	CCTTGTATGGACAGATAGACAT	C	CTAACCTGTTCTTGTGAACT				34,12					
13	71581221	AAAAACACTATGAATTCACA	CATATTTT	C	ATATCTGAAAACATTACCAT							11,3		
14	68143591	AAAAAATAATCAAAAAGAAT	TTTTA	T	TTTGTCATTGACAGTTCAAT					12,6				
17	5015438	GCGGGTGACTTCATCAAGTT	TG	T	GGGGGTCTCTTGTGGAATTG									29,11
18	39827854	CTTGTGATGACAGCAACCAC	C	CAAAT	AAATAACTTGATAGAATTTT							21,6		
22	28415750	TTCGCCCTGGCTGACTTCTC	TTTGCC	T	TCAGCTCTCTGGGCTCTAGA									50,35

Indels at on-target sites are indicated in red bold. A likely nuclease-mediated off-target indel is indicated in blue bold. An indel that lies in the coding sequence of *ZDHHC11* is indicated in magenta bold. Underlines indicate potential PAMs (NGG or NAG) within five bases upstream of the indel. Columns A–I indicate reference allele counts (x) and alternate allele counts (y) in the format (x,y) for any of the clones A–I in which the called genotype included at least one copy of the alternate allele. Note: the reference allele counts for the on-target indels in clones B and C marked in red bold and with (*) do **not** indicate wild-type alleles—rather, due to the nature of the calling algorithm, they indicate counts of alleles that do not match the alternate alleles; because clones B and C are compound heterozygotes, the reference allele counts actually represent the indels on the other alleles. All on-target and off-target indels in this Table were confirmed with Sanger sequencing.

Table S2, Related to Table 1. Unique Structural Variants (SVs) Detected by Whole-genome Sequencing

SV class	Clone	Treatment group	Chr	Start	End	Size	Split-read consensus
Translocation[a]	**H**	***LINC00116* CRISPR-Cas9**	**4**	**183998625**	**183998885**	**261 bp**	**chr2 | chr4: CTGCCAGCCCAGGAGTACTCCAGAA | G | CTTACATTTGGGGTTGTGATTCTGG** **chr4 | chr2: CTGGAGGATCCCTTGAGCACAGGAGT | GCGAAGGCTACTAGCACGGACAACT**
Deletion[b]	F	*SORT1* CRISPR-Cas9	6	18754456	18760023	5568 bp	N/A

A structural variant at an on-target site is indicated in red bold. Split-read consensus sequences represent the consensus of all split reads that span the breakpoint. Vertical lines denote precise breakpoint positions.

[a] Translocation represents a duplicated insertion from chromosome 4 that inserted into the on-target chromosome 2 site. The underlined base in the split-read consensus indicates an additional inserted basepair at the breakpoint.

[b] As no split-reads spanned this event, there is not precise refinement of the coordinates.

Table S3, Related to Table 1. Numbers of Indels and Single Nucleotide Variants (SNVs) Detected by Whole-genome Sequencing

		HUES 9	A	B	C	D	E	F	G	H	I
Raw indel calls	Total	881063	879305	878638	886519	867987	889297	873304	874320	875199	873847
	Missed[a]		39191	43335	43159	35729	43211	36810	36181	35699	34666
	De novo		40949	45760	37703	48805	34977	44569	42924	41563	41882
Post low-complexity filter	Total	198172	198325	198116	198923	197398	199108	197898	197542	197589	197436
	Missed[a]		3518	4051	3910	3198	3953	3325	3006	2968	2885
	De novo		3365	4107	3159	3972	3017	3599	3636	3551	3621
Post homopolymeric filter	Total	119573	119899	119710	119980	119555	120026	119735	119486	119563	119513
	Missed[a]		1220	1457	1334	1007	1359	1074	881	878	852
	De novo		894	1320	927	1025	906	912	968	888	912
De novo, nuclease-specific indels			69	195	146	25	57	30	22	20	17
Sample-specific indels			8	78	39	9	29	9	13	12	13
Called reads in only one sample, > 2 reads[b]			3	10	10	4	6	2	3	6	7
Confirmed by Sanger sequencing			2	4	4	4	4	2	3	6	5
		HUES 9	A	B	C	D	E	F	G	H	I
Raw SNV calls	Total	3698888	3707753	3705830	3714888	3695767	3713222	3704487	3695231	3697396	3697034
	Missed[a]		35795	47106	45002	28291	40247	33049	25713	26172	26165
	De novo		26930	40164	29002	31412	25913	27450	29370	27664	28019
Post low-complexity filter	Total	1531069	1533920	1531422	1534449	1531074	1534452	1533074	1530709	1531112	1530978
	Missed[a]		7984	9645	9401	6064	8694	7238	5313	5349	5280
	De novo		5133	9292	6021	6059	5311	5233	5673	5306	5371
De novo, nuclease-specific SNVs			670	1593	1513	195	472	344	235	269	206
Sample-specific SNVs			165	595	538	110	269	163	159	192	147
Called reads in only one sample, > 2 reads			64	115	142	55	94	74	111	127	112

[a] Calls in the parental HUES 9 line that were not called in the individual clone.

[b] Not included in this tally is an on-target indel shared by clones E and F.