Figure 1

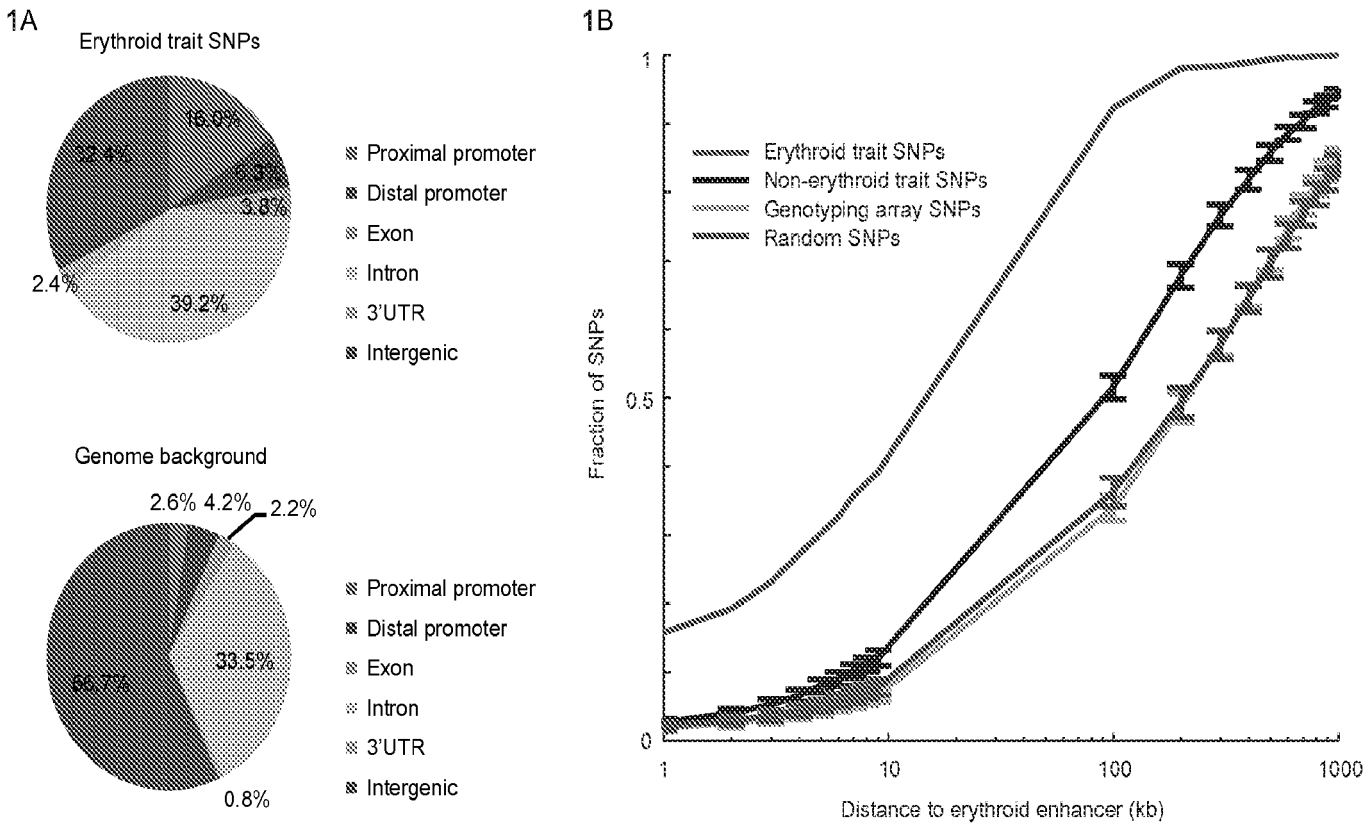

1A
Erythroid trait SNPs
16.0%
32.4%
3.8%
2.4%
39.2%
Proximal promoter
Distal promoter
Exon
Intron
3'UTR
Intergenic
Genome background
2.6%
4.2%
2.2%
33.5%
56.7%
0.8%
Proximal promoter
Distal promoter
Exon
Intron
3'UTR
Intergenic
1B
Erythroid trait SNPs
Non-erythroid trait SNPs
Genotyping array SNPs
Random SNPs
Fraction of SNPs
1
0.5
0
1
10
100
1000
Distance to erythroid enhancer (kb)

Figure 2

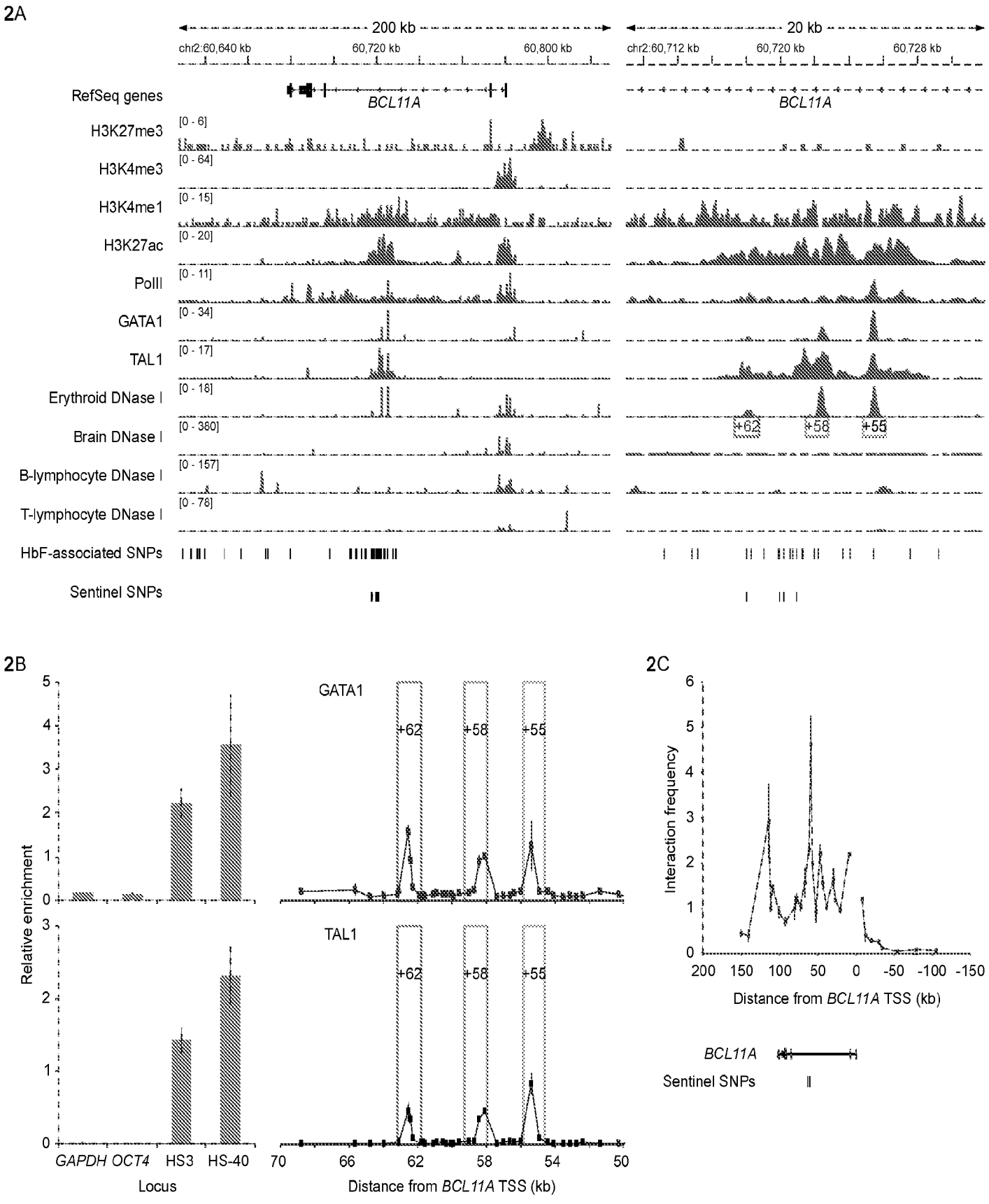
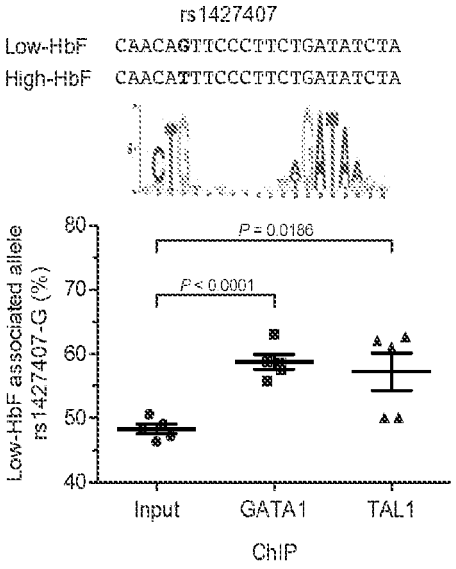
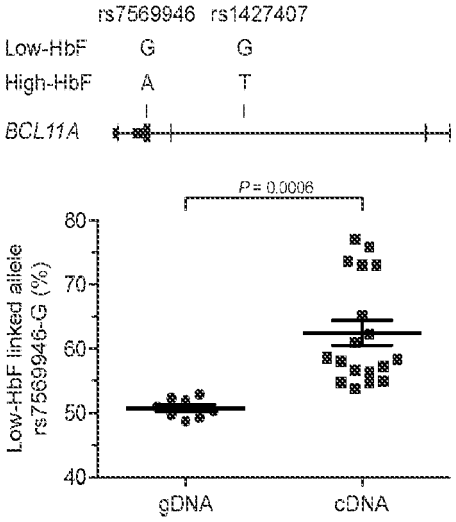

2A
200 kb
20 kb
chr2:60,640 kb
60,720 kb
60,800 kb
chr2:60,712 kb
60,720 kb
60,728 kb
RefSeq genes
BCL11A
BCL11A
H3K27me3
H3K4me3
H3K4me1
H3K27ac
PolII
GATA1
TAL1
Erythroid DNase I
Brain DNase I
B-lymphocyte DNase I
T-lymphocyte DNase I
HbF-associated SNPs
Sentinel SNPs
+62
+58
+55
2B
GATA1
TAL1
Relative enrichment
GAPDH
OCT4
HS3
HS-40
Locus
Distance from BCL11A TSS (kb)
2C
Interaction frequency
Distance from BCL11A TSS (kb)
BCL11A
Sentinel SNPs

Figure 3

3A



3B



3C

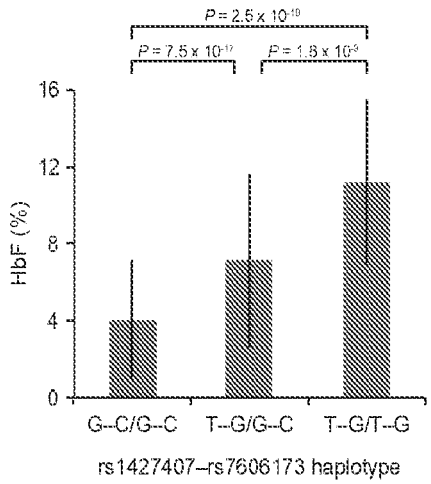
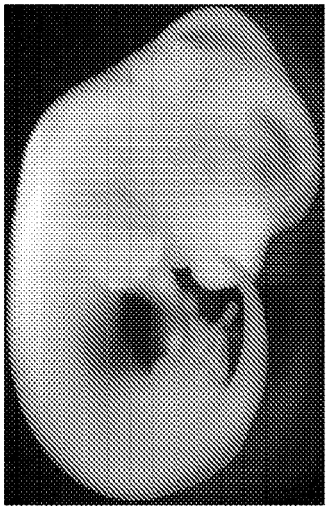


Figure 4

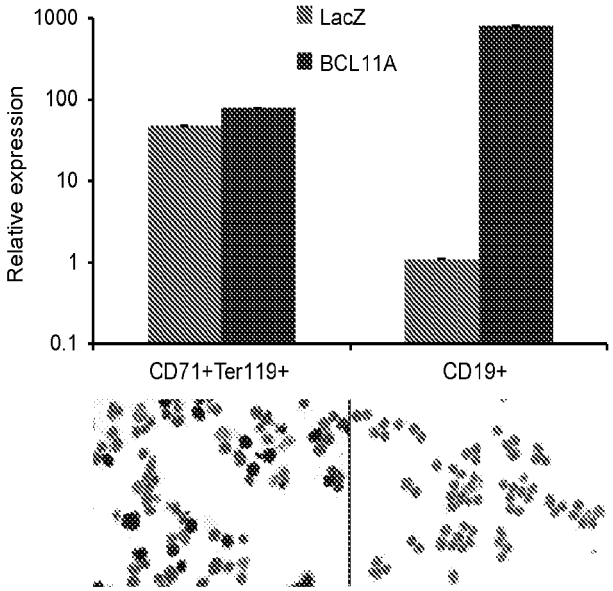
4A



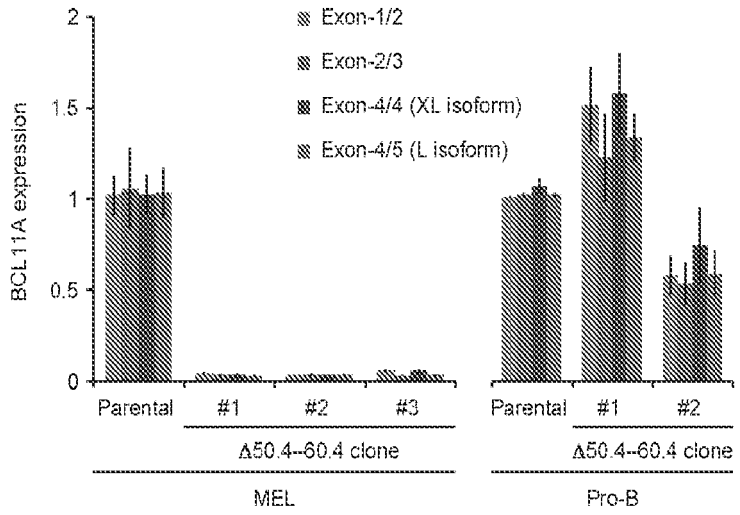
4B



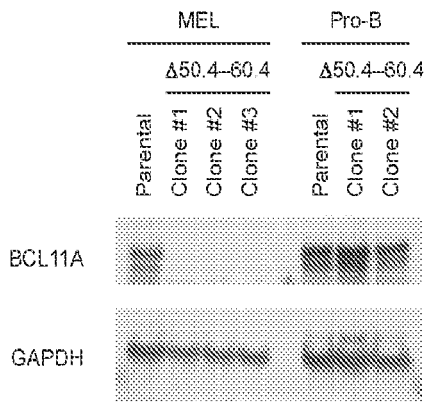
4C



5A


Exon-1/2
Exon-2/3
Exon-4/4 (XL isoform)
Exon-4/5 (L isoform)
BCL11A expression
2
1.5
1
0.5
0
Parental
#1
#2
#3
Δ50.4–60.4 clone
MEL
Parental
#1
#2
Δ50.4–60.4 clone
Pro-B

5B


MEL
Pro-B
Δ50.4–60.4
Δ50.4–60.4
Parental
Clone #1
Clone #2
Clone #3
Parental
Clone #1
Clone #2
BCL11A
GAPDH

5C

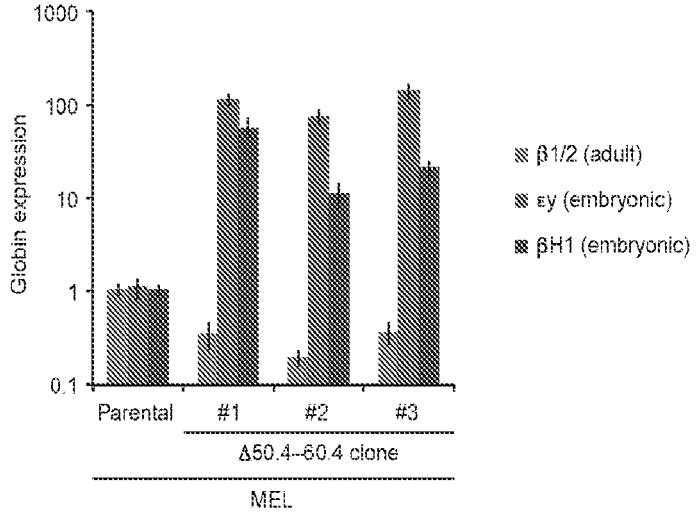
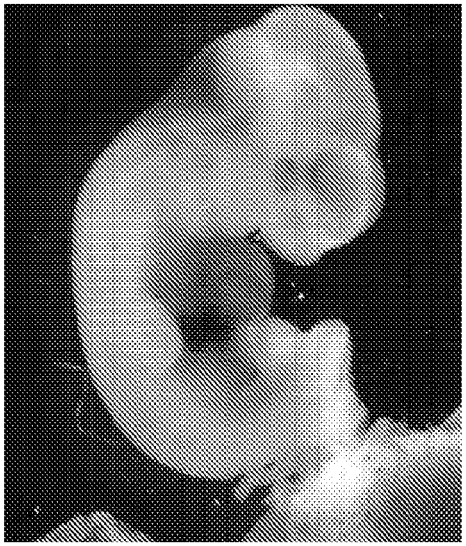

Globin expression
1000
100
10
1
0.1
β1/2 (adult)
εγ (embryonic)
βH1 (embryonic)
Parental
#1
#2
#3
Δ50.4–60.4 clone
MEL

Figure 6

6A



6B

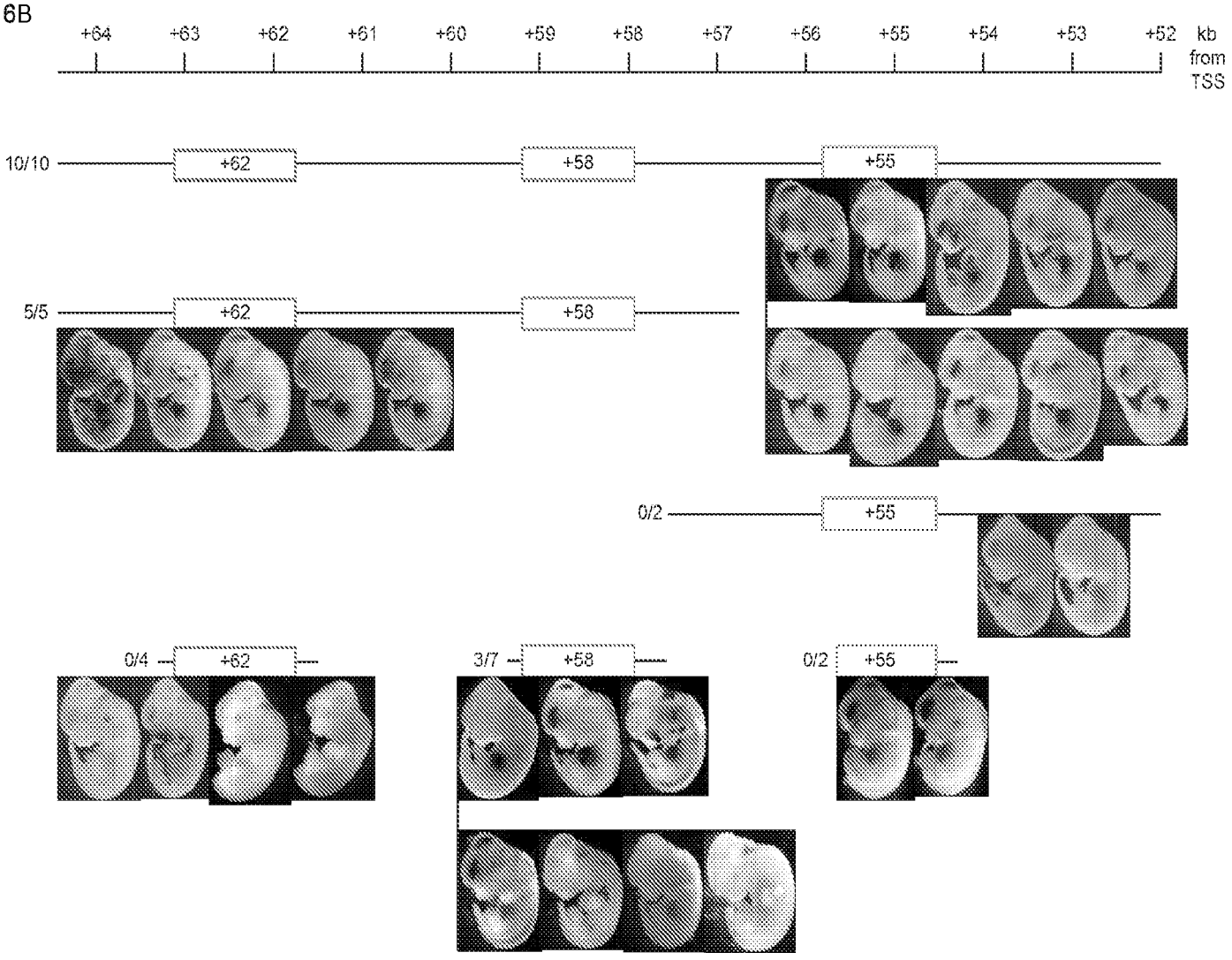


Figure 7

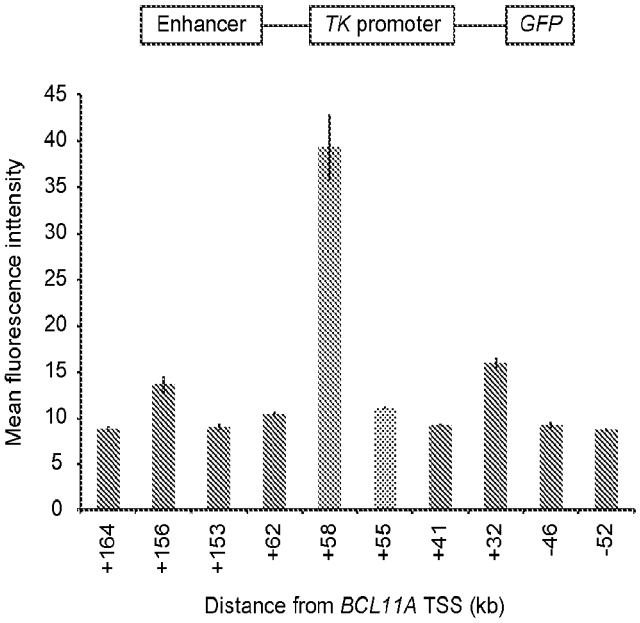
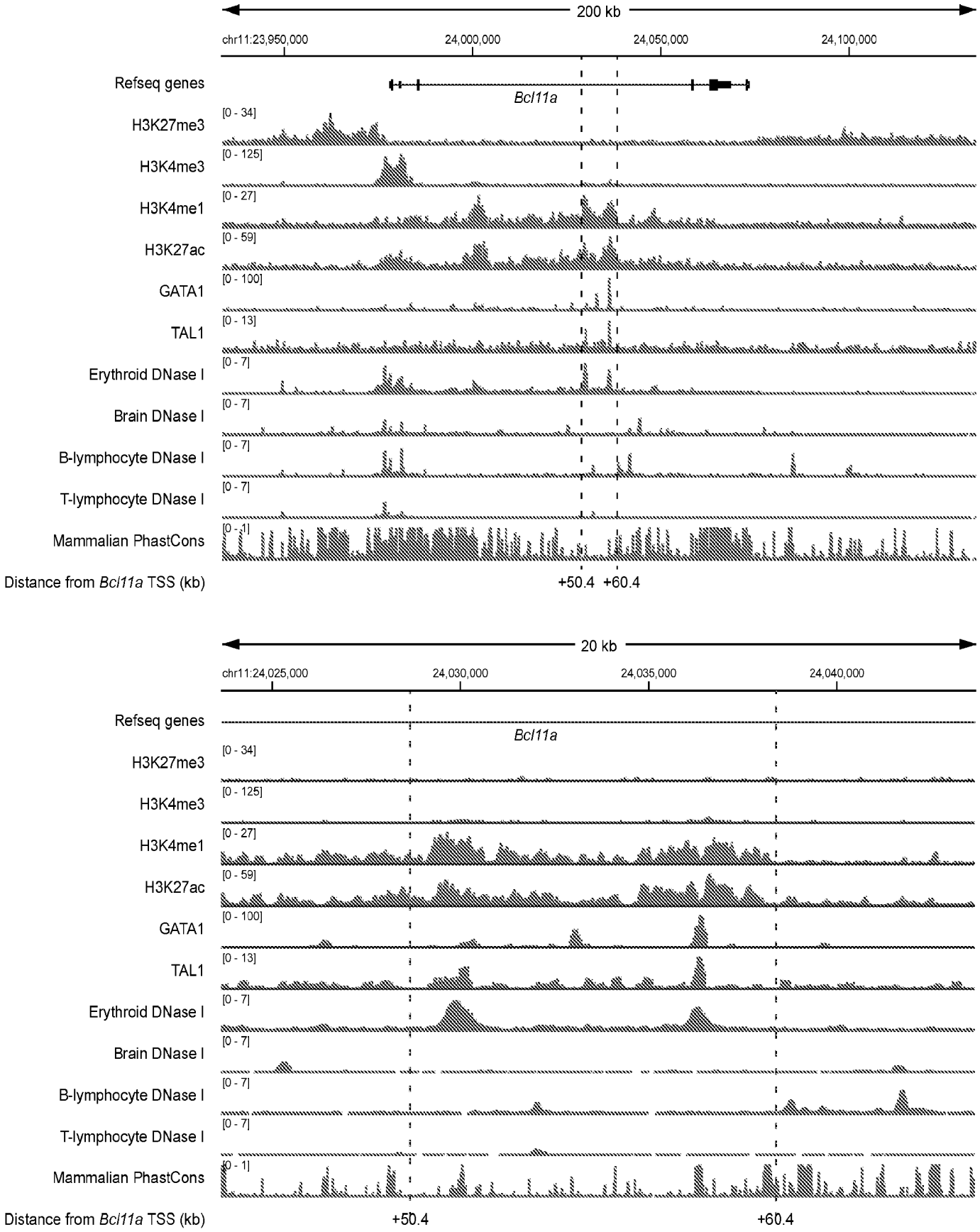
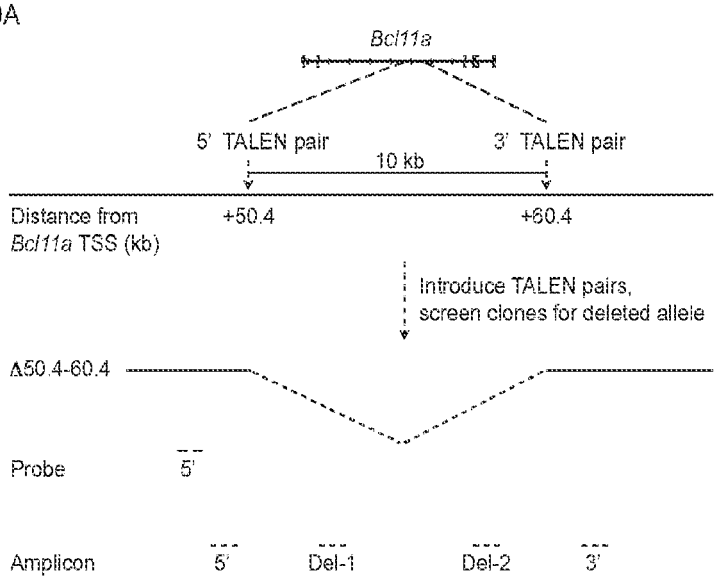

Enhancer
TK promoter
GFP
Mean fluorescence inttensity
45
40
35
30
25
20
15
10
5
0
+164
+156
+153
+62
+58
+55
+41
+32
-46
-52
Distance from BCL11A TSS (kb)

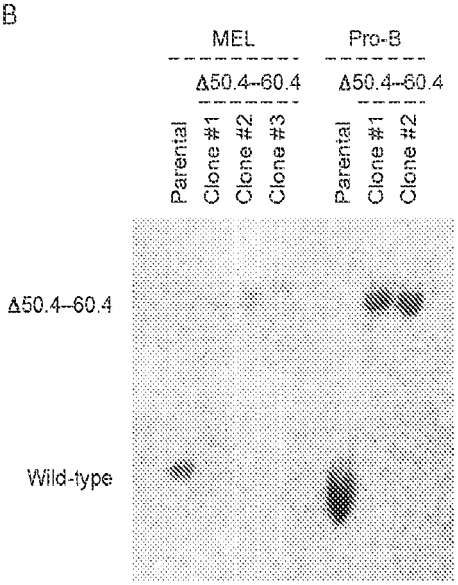
Figure 8


200 kb
chr11:23,950,000
24,000,000
24,050,000
24,100,000
Refseq genes
Bcl11a
H3K27me3
[0 - 34]
H3K4me3
[0 - 125]
H3K4me1
[0 - 27]
H3K27ac
[0 - 59]
GATA1
[0 - 100]
TAL1
[0 - 13]
Erythroid DNase I
[0 - 7]
Brain DNase I
[0 - 7]
B-lymphocyte DNase I
[0 - 7]
T-lymphocyte DNase I
[0 - 7]
Mammalian PhastCons
[0 - 1]
Distance from Bcl11a TSS (kb)
+50.4 +60.4
20 kb
chr11:24,025,000
24,030,000
24,035,000
24,040,000
Refseq genes
Bcl11a
H3K27me3
[0 - 34]
H3K4me3
[0 - 125]
H3K4me1
[0 - 27]
H3K27ac
[0 - 59]
GATA1
[0 - 100]
TAL1
[0 - 13]
Erythroid DNase I
[0 - 7]
Brain DNase I
[0 - 7]
B-lymphocyte DNase I
[0 - 7]
T-lymphocyte DNase I
[0 - 7]
Mammalian PhastCons
[0 - 1]
Distance from Bcl11a TSS (kb)
+50.4
+60.4

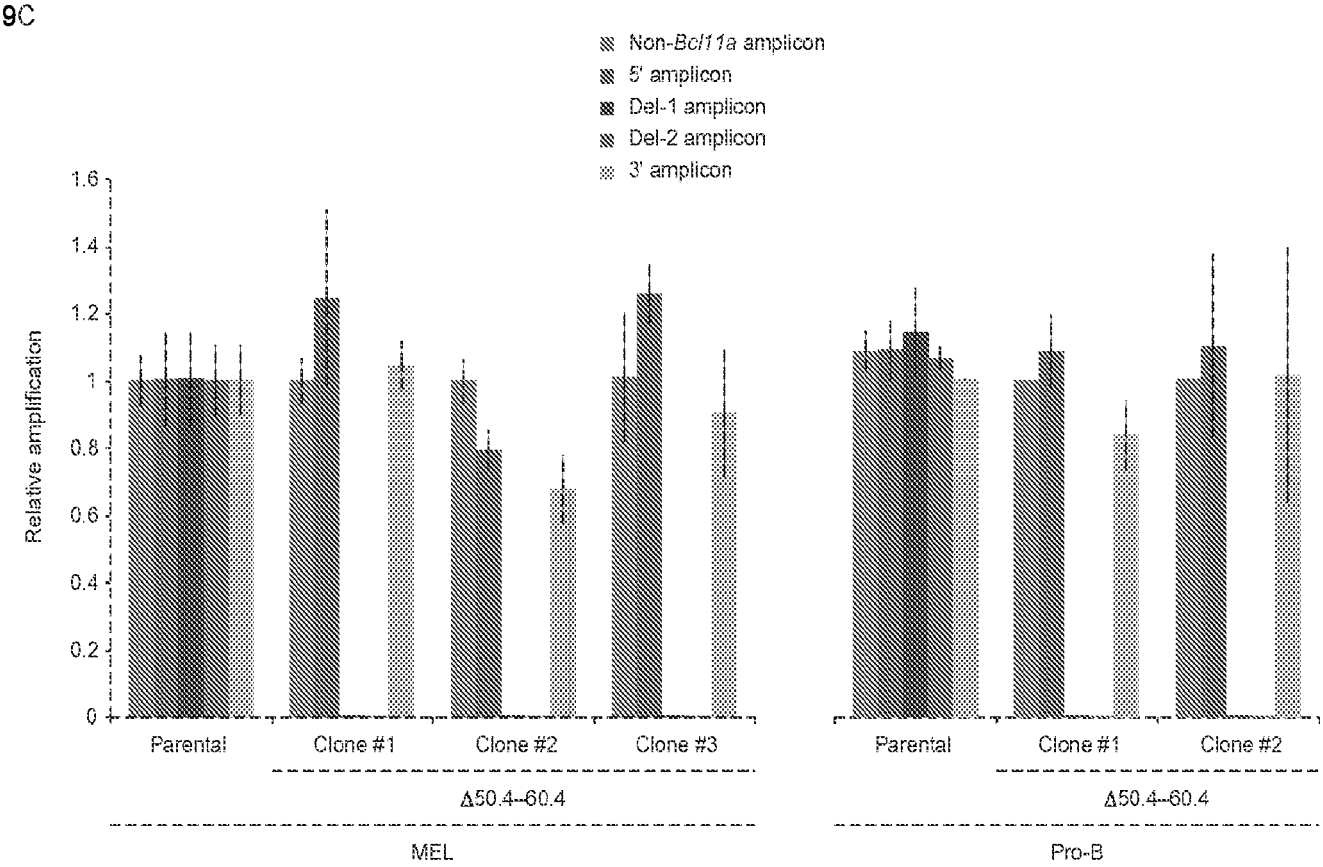
9A


Bcl11a
5' TALEN pair
3' TALEN pair
10 kb
Distance from Bcl11a TSS (kb)
+50.4
+60.4
Introduce TALEN pairs, screen clones for deleted allele
Δ50.4-60.4
Probe
5'
Amplicon
5'
Del-1
Del-2
3'

9B


MEL
Pro-B
Δ50.4--60.4
Δ50.4--60.4
Parental
Clone #1
Clone #2
Clone #3
Parental
Clone #1
Clone #2
Δ50.4--60.4
Wild-type

9C


Non-Bcl11a amplicon
5' amplicon
Del-1 amplicon
Del-2 amplicon
3' amplicon
Relative amplification
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
Parental
Clone #1
Clone #2
Clone #3
Δ50.4--60.4
MEL
Parental
Clone #1
Clone #2
Δ50.4--60.4
Pro-B

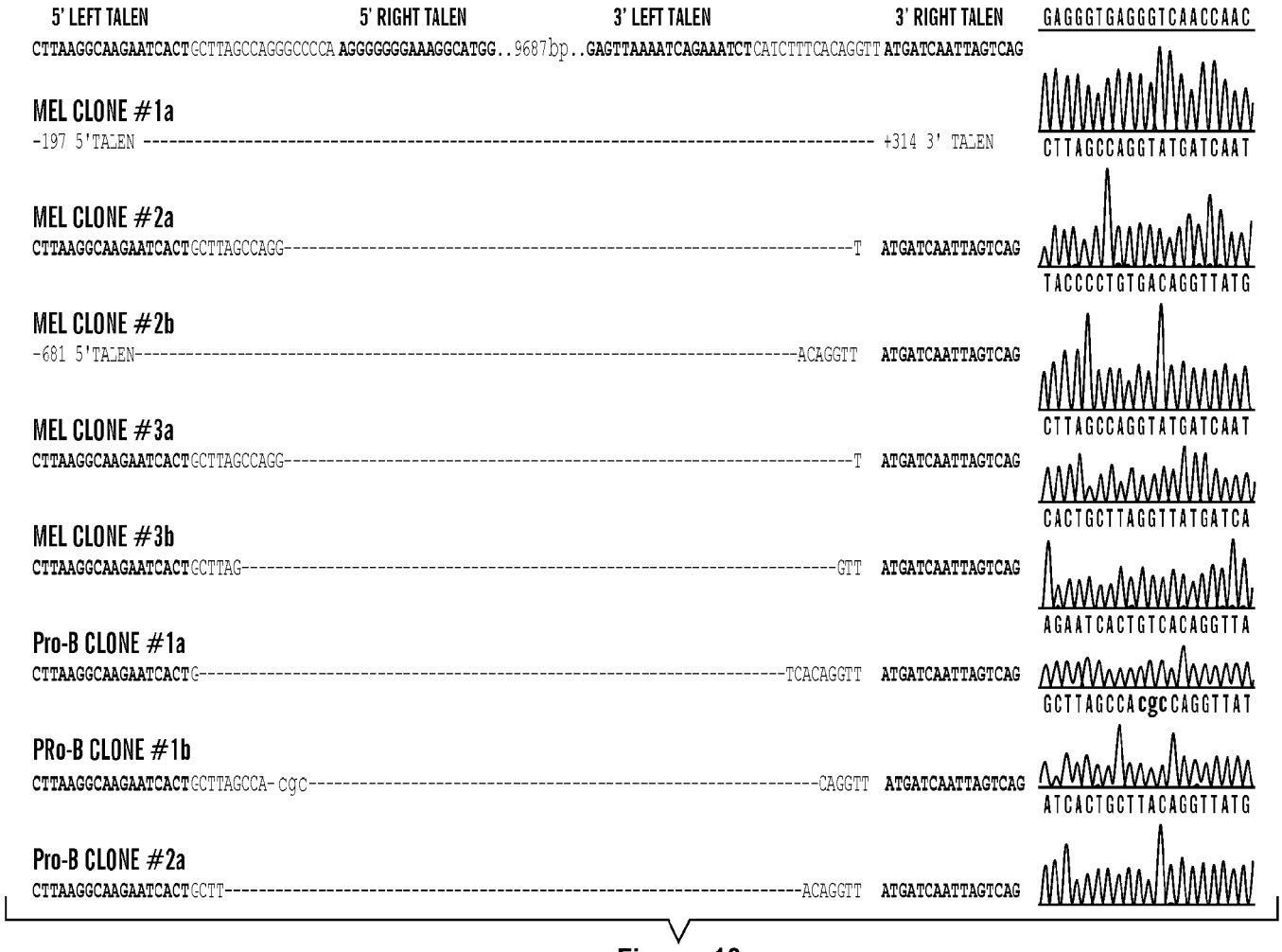
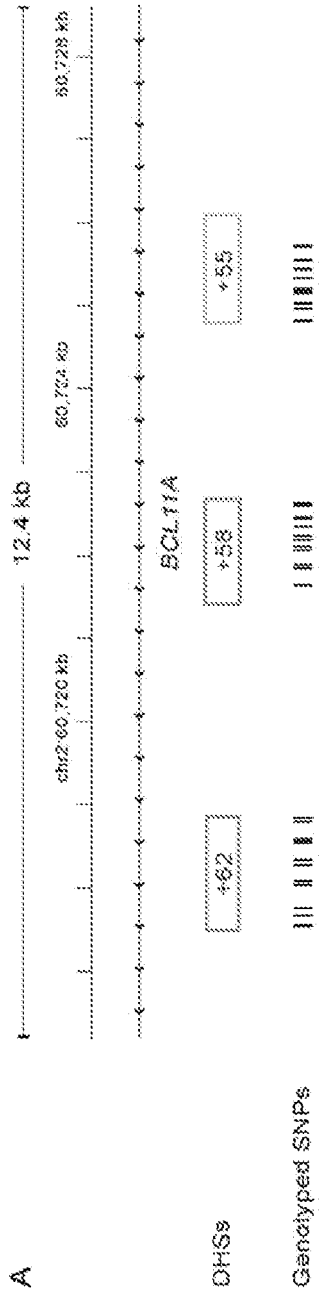

5' LEFT TALEN
5' RIGHT TALEN
3' LEFT TALEN
3' RIGHT TALEN
GAGGGTGAGGGTCAACCAAC
CTTAAGGCAAGAATCACTGCTTAGCCAGGGCCCCAAGGGGGGGAAAGGCATGG..9687bp..GAGTTAAAATCAGAAATCTCATCTTTCACAGGTTATGATCAATTAGTCAG
MEL CLONE #1a
-197 5'TALEN ---------- +314 3' TALEN
CTTAGCCAGGTATGATCAAT
MEL CLONE #2a
CTTAAGGCAAGAATCACTGCTTAGCCAGG----------T ATGATCAATTAGTCAG
TACCCCTGTGACAGGTTATG
MEL CLONE #2b
-681 5'TALEN----------ACAGGTT ATGATCAATTAGTCAG
CTTAGCCAGGTATGATCAAT
MEL CLONE #3a
CTTAAGGCAAGAATCACTGCTTAGCCAGG----------T ATGATCAATTAGTCAG
CACTGCTTAGGTTATGATCA
MEL CLONE #3b
CTTAAGGCAAGAATCACTGCTTAG----------GTT ATGATCAATTAGTCAG
AGAATCACTGTCACAGGTTA
Pro-B CLONE #1a
CTTAAGGCAAGAATCACTG----------TCACAGGTT ATGATCAATTAGTCAG
GCTTAGCCAcgcCAGGTTAT
PRo-B CLONE #1b
CTTAAGGCAAGAATCACTGCTTAGCCA-cgc----------CAGGTT ATGATCAATTAGTCAG
ATCACTGCTTACAGGTTATG
Pro-B CLONE #2a
CTTAAGGCAAGAATCACTGCTT----------ACAGGTT ATGATCAATTAGTCAG

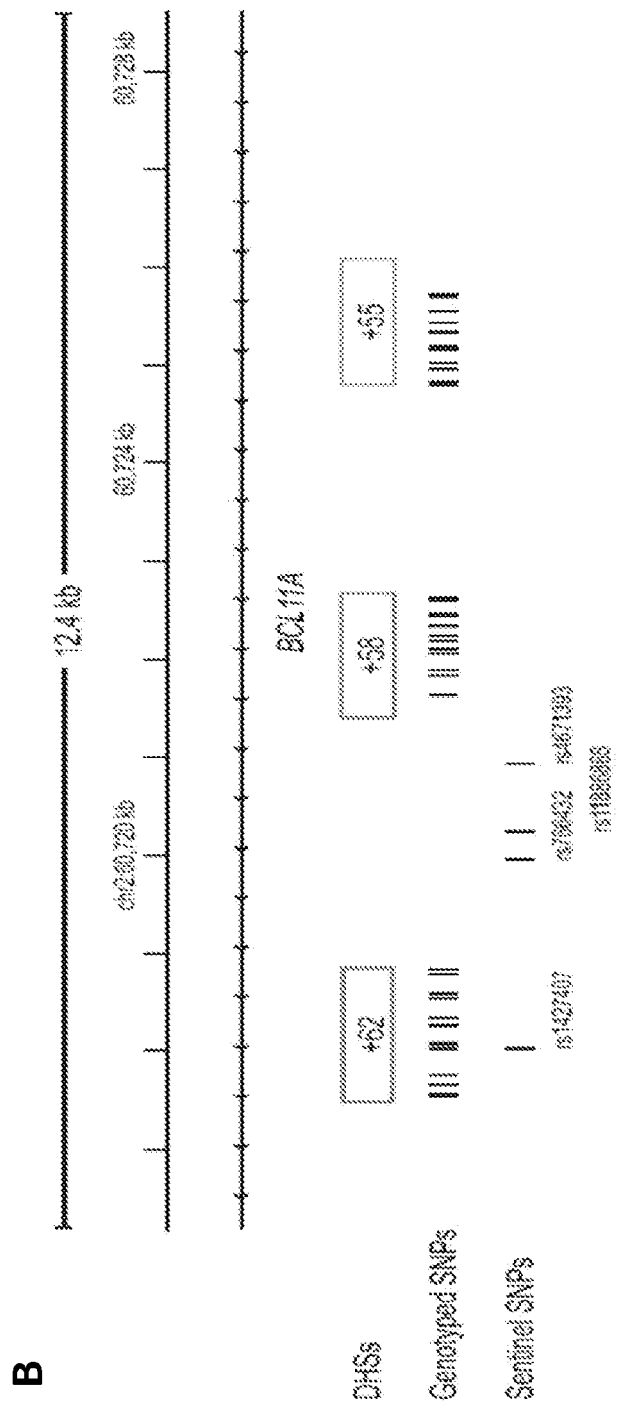
Figure 10

Figure 11



DHS	SNP	coordinate	MAF	β	P	Conditional on rs1427407 β	Conditional on rs1427407 P
+62	rs1427407	60,718,043	0.2460	0.6634	7.23×10^{-62}	-	-
+55	rs7606173	60,725,451	0.4238	-0.4691	2.86×10^{-34}	-0.2632	9.66×10^{-11}

Figure 11


B
12.4 kb
chr2:60,720 kb
60,724 kb
60,728 kb
BCL11A
DHSs
+62
+58
+55
Genotyped SNPs
Sentinel SNPs
rs1427407
rs766432
rs4671393
rs1896909