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Supplementary Table 2: Distribution of tumor characteristics by genetic similarity proportions relative to the 1000 Genomes Project reference populations among CRC tumors from 67 Hispanic/Latino patients.

	1000 Genomes Project Peruvian-in-Lima-like Similarity (n = 67)			1000 Genomes Project European-like Similarity (n = 67)		
	1KG-PEL-like ≤ 0.55 n (%)	1KG-PEL-like > 0.55 n (%)	p-value	1KG-EUR-like ≤ 0.38 n (%)	1KG-EUR-like > 0.38 n (%)	p-value
Tumor Location						
Colon	22 (32.84%)	20 (29.85%)	1	21 (31.34%)	21 (31.34%)	1
Rectum	13 (19.40%)	12 (17.91%)		13 (19.40%)	12 (17.91%)	
Tumor Stage						
Early (Stage I or II)	9 (13.43%)	10 (14.93%)	0.7090	11 (16.42%)	8 (11.94%)	0.9019
Late (Stage III or IV)	16 (23.88%)	13 (19.40%)		14 (20.90%)	15 (22.39%)	
No TNM Applicable/Unknown	10 (14.93%)	9 (13.43%)		9 (13.43%)	10 (14.93%)	
Microsatellite Status						
MSI	6 (8.96%)	7 (10.45%)	0.8571	5 (7.46%)	8 (11.94%)	0.4978
MSS	29 (43.28%)	25 (37.31%)		29 (43.28%)	25 (37.31%)	
Tumor Mutational Burden						
Hypermutated	7 (10.45%)	9 (13.43%)	0.6225	7 (10.45%)	9 (13.43%)	0.7226
Non-Hypermutated	28 (41.79%)	23 (34.33%)		27 (40.30%)	24 (35.82%)	
APC Mutation Status						
Mutated	28 (41.79%)	25 (37.31%)	0.6363	27 (40.30%)	26 (38.81%)	1
Wild type	7 (10.45%)	7 (10.45%)		7 (10.45%)	7 (10.45%)	
TP53 Mutation Status						
Mutated	23 (34.33%)	17 (25.37%)	0.4237	17 (25.37%)	23 (34.33%)	0.1633
Wild type	12 (17.91%)	15 (22.39%)		17 (25.37%)	10 (14.93%)	
KRAS Mutation Status						
Mutated	15 (22.39%)	17 (25.37%)	0.5514	19 (28.36%)	13 (19.40%)	0.2686
Wild type	20 (29.85%)	15 (22.39%)		15 (22.39%)	20 (29.85%)	
SYNE1 Mutation Status						
Mutated	13 (19.40%)	13 (19.40%)	0.7414	10 (14.93%)	16 (23.88%)	0.1767
Wild type	22 (32.84%)	19 (28.36%)		24 (35.82%)	17 (25.37%)	
TCF7L2 Mutation Status						
Mutated	9 (13.43%)	15 (22.39%)	0.1213	13 (19.40%)	11 (16.42%)	0.8701
Wild type	26 (38.81%)	17 (25.37%)		21 (31.34%)	22 (32.84%)	
OBSN Mutation Status						
Mutated	11 (16.42%)	8 (11.94%)	0.7552	7 (10.45%)	12 (17.91%)	0.2456
Wild type	24 (35.82%)	24 (35.82%)		27 (40.30%)	21 (31.34%)	
PIK3CA Mutation Status						
Mutated	11 (16.42%)	8 (11.94%)	0.7552	9 (13.43%)	10 (14.93%)	0.9387
Wild type	24 (35.82%)	24 (35.82%)		25 (37.31%)	23 (34.33%)	
SACS Mutation Status						
Mutated	10 (14.93%)	7 (10.45%)	0.7277	6 (8.96%)	11 (16.42%)	0.2323
Wild type	25 (37.31%)	25 (37.31%)		28 (41.79%)	22 (32.84%)	
AHNAK2 Mutation Status						
Mutated	10 (14.93%)	8 (11.94%)	0.9573	7 (10.45%)	11 (16.42%)	0.3676
Wild type	25 (37.31%)	24 (35.82%)		27 (40.30%)	22 (32.84%)	
FAT3 Mutation Status						
Mutated	10 (14.93%)	7 (10.45%)	0.7277	8 (11.94%)	9 (13.43%)	0.9432
Wild type	25 (37.31%)	25 (37.31%)		26 (38.81%)	24 (35.82%)	
FAT4 Mutation Status						
Mutated	8 (11.94%)	8 (11.94%)	1	8 (11.94%)	8 (11.94%)	1
Wild type	27 (40.30%)	24 (35.82%)		26 (38.81%)	25 (37.31%)	
BRC2 Mutation Status						
Mutated	5 (7.46%)	7 (10.45%)	0.6239	6 (8.96%)	6 (8.96%)	1
Wild type	30 (44.78%)	25 (37.31%)		28 (41.79%)	27 (40.30%)	
MSH3 Mutation Status						
Mutated	5 (7.46%)	5 (7.46%)	1	4 (5.97%)	6 (8.96%)	0.5118
Wild type	30 (44.78%)	27 (40.30%)		30 (44.78%)	27 (40.30%)	
SOX9 Mutation Status						
Mutated	6 (8.96%)	4 (5.97%)	0.7364	4 (5.97%)	6 (8.96%)	0.5118
Wild type	29 (43.28%)	28 (41.79%)		30 (44.78%)	27 (40.30%)	
PTEN Mutation Status						
Mutated	4 (5.97%)	6 (8.96%)	0.501	4 (5.97%)	6 (8.96%)	0.5118
Wild type	31 (46.27%)	26 (38.81%)		30 (44.78%)	27 (40.30%)	
POLE Mutation Status						
Mutated	5 (7.46%)	3 (4.48%)	0.7113	3 (4.48%)	5 (7.46%)	0.4673
Wild type	30 (44.78%)	29 (43.28%)		31 (46.27%)	28 (41.79%)	
FBXW7 Mutation Status						
Mutated	6 (8.96%)	1 (1.49%)	0.1078	2 (2.99%)	5 (7.46%)	0.2585
Wild type	29 (43.28%)	31 (46.27%)		32 (47.76%)	28 (41.79%)	
NF1 Mutation Status						
Mutated	4 (5.97%)	3 (4.48%)	1	3 (4.48%)	4 (5.97%)	0.709
Wild type	31 (46.27%)	29 (43.28%)		31 (46.27%)	29 (43.28%)	
MLH1 Mutation Status						
Mutated	3 (4.48%)	4 (5.97%)	0.7014	3 (4.48%)	4 (5.97%)	0.709
Wild type	32 (47.76%)	28 (41.79%)		31 (46.27%)	29 (43.28%)	
MSH6 Mutation Status						
Mutated	2 (2.99%)	5 (7.46%)	0.2456	5 (7.46%)	2 (2.99%)	0.4275
Wild type	33 (49.25%)	27 (40.30%)		29 (43.28%)	31 (46.27%)	
SMAD4 Mutation Status						
Mutated	1 (1.49%)	6 (8.96%)	0.04807	7 (10.45%)	0 (0.00%)	0.0111
Wild type	34 (50.75%)	26 (38.81%)		27 (40.30%)	33 (49.25%)	
BRAF Mutation Status						
Mutated	2 (2.99%)	4 (5.97%)	0.4145	4 (5.97%)	2 (2.99%)	0.6728
Wild type	33 (49.25%)	28 (41.79%)		30 (44.78%)	31 (46.27%)	
RB1 Mutation Status						
Mutated	3 (4.48%)	2 (2.99%)	1	1 (1.49%)	4 (5.97%)	0.1974
Wild type	32 (47.76%)	30 (44.78%)		33 (49.25%)	29 (43.28%)	
MSH2 Mutation Status						
Mutated	1 (1.49%)	4 (5.97%)	0.1848	3 (4.48%)	2 (2.99%)	1
Wild type	34 (50.75%)	28 (41.79%)		31 (46.27%)	31 (46.27%)	
TET2 Mutation Status						
Mutated	2 (2.99%)	3 (4.48%)	0.6639	2 (2.99%)	3 (4.48%)	0.6728
Wild type	33 (49.25%)	29 (43.28%)		32 (47.76%)	30 (44.78%)	
POLD1 Mutation Status						
Mutated	2 (2.99%)	2 (2.99%)	1	1 (1.49%)	3 (4.48%)	0.3559
Wild type	33 (49.25%)	30 (44.78%)		33 (49.25%)	30 (44.78%)	
MUTYH Mutation Status						
Mutated	1 (1.49%)	1 (1.49%)	1	1 (1.49%)	1 (1.49%)	1
Wild type	34 (50.75%)	31 (46.27%)		33 (49.25%)	32 (47.76%)	

Supplementary Table 3: Association of tumors characteristics with genetic similarity proportions relative to the 1000 Genomes Project reference populations among CRC tumors from 67 Hispanic/Latino patients.

	Odds Ratio (95% CI)
Tumor Location	
1KG-PEL-like ≤ 0.55	1
1KG-PEL-like > 0.55	1.02 (0.37-2.78)
Tumor Stage	
1KG-PEL-like ≤ 0.55	1
1KG-PEL-like > 0.55	0.74 (0.22-2.40)
Microsatellite Status	
1KG-PEL-like ≤ 0.55	1
1KG-PEL-like > 0.55	9.06 (3.68-25.15)
Tumor Mutational Burden	
1KG-PEL-like ≤ 0.55	1
1KG-PEL-like > 0.55	1.55 (0.49-5.05)
APC Mutation Status	
1KG-PEL-like ≤ 0.55	1
1KG-PEL-like > 0.55	0.72 (0.28-1.84)
TP53 Mutation Status	
1KG-PEL-like ≤ 0.55	1
1KG-PEL-like > 0.55	0.60 (0.22-1.61)
KRAS Mutation Status	
1KG-PEL-like ≤ 0.55	1
1KG-PEL-like > 0.55	1.50 (0.57-4.02)
SYNE1 Mutation Status	
1KG-PEL-like ≤ 0.55	1
1KG-PEL-like > 0.55	0.76 (0.29-1.99)
TCF7L2 Mutation Status	
1KG-PEL-like ≤ 0.55	1
1KG-PEL-like > 0.55	2.50 (0.90-0.07)
OBSCN Mutation Status	
1KG-PEL-like ≤ 0.55	1
1KG-PEL-like > 0.55	0.73 (0.24-2.16)
PIK3CA Mutation Status	
1KG-PEL-like ≤ 0.55	1
1KG-PEL-like > 0.55	0.73 (0.24-2.16)
SACS Mutation Status	
1KG-PEL-like ≤ 0.55	1
1KG-PEL-like > 0.55	0.71 (0.22-2.17)
AHNAK2 Mutation Status	
1KG-PEL-like ≤ 0.55	1
1KG-PEL-like > 0.55	0.84 (0.27-2.52)
FAT3 Mutation Status	
1KG-PEL-like ≤ 0.55	1
1KG-PEL-like > 0.55	0.71 (0.22-2.17)
FAT4 Mutation Status	
1KG-PEL-like ≤ 0.55	1
1KG-PEL-like > 0.55	1.12 (0.35-3.57)
BRCA2 Mutation Status	
1KG-PEL-like ≤ 0.55	1
1KG-PEL-like > 0.55	1.65 (0.46-6.40)
MSH3 Mutation Status	
1KG-PEL-like ≤ 0.55	1
1KG-PEL-like > 0.55	1.11 (0.27-4.55)
SOX9 Mutation Status	
1KG-PEL-like ≤ 0.55	1
1KG-PEL-like > 0.55	0.70 (0.16-2.81)
PTEN Mutation Status	
1KG-PEL-like ≤ 0.55	1
1KG-PEL-like > 0.55	1.75 (0.44-7.82)
POLE Mutation Status	
1KG-PEL-like ≤ 0.55	1
1KG-PEL-like > 0.55	0.64 (0.11-2.95)
FBXW7 Mutation Status	
1KG-PEL-like ≤ 0.55	1
1KG-PEL-like > 0.55	0.18 (0.01-1.17)
NF1 Mutation Status	
1KG-PEL-like ≤ 0.55	1
1KG-PEL-like > 0.55	0.81 (0.14-4.21)
MLH1 Mutation Status	
1KG-PEL-like ≤ 0.55	1
1KG-PEL-like > 0.55	11.43 (3.56-53.54)
MSH6 Mutation Status	
1KG-PEL-like ≤ 0.55	1
1KG-PEL-like > 0.55	2.89 (0.55-23.88)
SMAD4 Mutation Status	
1KG-PEL-like ≤ 0.55	1
1KG-PEL-like > 0.55	6.89 (1.04-186.52)
BRAF Mutation Status	
1KG-PEL-like ≤ 0.55	1
1KG-PEL-like > 0.55	2.25 (0.38-19.32)
RB1 Mutation Status	
1KG-PEL-like ≤ 0.55	1
1KG-PEL-like > 0.55	0.73 (0.08-5.11)
MSH2 Mutation Status	
1KG-PEL-like ≤ 0.55	1
1KG-PEL-like > 0.55	4.34 (0.56-123.39)
TET2 Mutation Status	
1KG-PEL-like ≤ 0.55	1
1KG-PEL-like > 0.55	1.66 (0.24-15.08)
POLD1 Mutation Status	
1KG-PEL-like ≤ 0.55	1
1KG-PEL-like > 0.55	0.10 (0.11-11.10)
MUTYH Mutation Status	
1KG-PEL-like ≤ 0.55	1
1KG-PEL-like > 0.55	1.10 (0.03-44.00)

	Odds Ratio (95% CI)
Tumor Location	
1KG-EUR-like ≤ 0.38	1
1KG-EUR-like > 0.38	1.08 (0.40-2.97)
Tumor Stage	
1KG-EUR-like ≤ 0.38	1
1KG-EUR-like > 0.38	1.46 (0.45-4.88)
Microsatellite Status	
1KG-EUR-like ≤ 0.38	1
1KG-EUR-like > 0.38	1.82 (0.53-6.91)
Tumor Mutational Burden	
1KG-EUR-like ≤ 0.38	1
1KG-EUR-like > 0.38	1.43 (0.46-4.67)
APC Mutation Status	
1KG-EUR-like ≤ 0.38	1
1KG-EUR-like > 0.38	0.96 (0.29-3.26)
TP53 Mutation Status	
1KG-EUR-like ≤ 0.38	1
1KG-EUR-like > 0.38	2.26 (0.83-6.40)
KRAS Mutation Status	
1KG-EUR-like ≤ 0.38	1
1KG-EUR-like > 0.38	0.52 (0.19-1.38)
SYNE1 Mutation Status	
1KG-EUR-like ≤ 0.38	1
1KG-EUR-like > 0.38	2.22 (0.81-6.30)
TCF7L2 Mutation Status	
1KG-EUR-like ≤ 0.38	1
1KG-EUR-like > 0.38	0.81 (0.29-2.23)
OBSCN Mutation Status	
1KG-EUR-like ≤ 0.38	1
1KG-EUR-like > 0.38	2.16 (0.73-6.85)
PIK3CA Mutation Status	
1KG-EUR-like ≤ 0.38	1
1KG-EUR-like > 0.38	1.20 (0.41-3.60)
SACS Mutation Status	
1KG-EUR-like ≤ 0.38	1
1KG-EUR-like > 0.38	2.28 (0.74-7.72)
AHNAK2 Mutation Status	
1KG-EUR-like ≤ 0.38	1
1KG-EUR-like > 0.38	1.90 (0.63-6.06)
FAT3 Mutation Status	
1KG-EUR-like ≤ 0.38	1
1KG-EUR-like > 0.38	1.21 (0.39-3.79)
FAT4 Mutation Status	
1KG-EUR-like ≤ 0.38	1
1KG-EUR-like > 0.38	1.04 (0.33-3.30)
BRCA2 Mutation Status	
1KG-EUR-like ≤ 0.38	1
1KG-EUR-like > 0.38	1.04 (0.28-3.80)
MSH3 Mutation Status	
1KG-EUR-like ≤ 0.38	1
1KG-EUR-like > 0.38	1.64 (0.41-7.30)
SOX9 Mutation Status	
1KG-EUR-like ≤ 0.38	1
1KG-EUR-like > 0.38	1.64 (0.41-7.30)
PTEN Mutation Status	
1KG-EUR-like ≤ 0.38	1
1KG-EUR-like > 0.38	1.64 (0.41-7.30)
POLE Mutation Status	
1KG-EUR-like ≤ 0.38	1
1KG-EUR-like > 0.38	1.80 (0.39-10.04)
FBXW7 Mutation Status	
1KG-EUR-like ≤ 0.38	1
1KG-EUR-like > 0.38	2.71 (0.51-22.35)
NF1 Mutation Status	
1KG-EUR-like ≤ 0.38	1
1KG-EUR-like > 0.38	1.40 (0.27-8.18)
MLH1 Mutation Status	
1KG-EUR-like ≤ 0.38	1
1KG-EUR-like > 0.38	1.40 (0.27-8.18)
MSH6 Mutation Status	
1KG-EUR-like ≤ 0.38	1
1KG-EUR-like > 0.38	0.39 (0.05-2.08)
SMAD4 Mutation Status	
1KG-EUR-like ≤ 0.38	NA
1KG-EUR-like > 0.38	NA
BRAF Mutation Status	
1KG-EUR-like ≤ 0.38	1
1KG-EUR-like > 0.38	0.51 (0.06-2.96)
RB1 Mutation Status	
1KG-EUR-like ≤ 0.38	1
1KG-EUR-like > 0.38	4.07 (0.53-115.74)
MSH2 Mutation Status	
1KG-EUR-like ≤ 0.38	1
1KG-EUR-like > 0.38	0.69 (0.08-4.80)
TET2 Mutation Status	
1KG-EUR-like ≤ 0.38	1
1KG-EUR-like > 0.38	1.56 (0.22-14.15)
POLD1 Mutation Status	
1KG-EUR-like ≤ 0.38	1
1KG-EUR-like > 0.38	3.00 (0.33-89.32)
MUTYH Mutation Status	
1KG-EUR-like ≤ 0.38	1
1KG-EUR-like > 0.38	1.03 (0.03-41.38)

Supplementary Table 4: CRC-Related Genes with mutations from Hypermuted and Non-Hypermuted Tumors in 67 Hispanic/Latino Patients. This table details the CRC-related genes with mutations, categorized by hypermutated and non-hypermuted tumors, in a cohort of 67 Hispanic/Latino patients.

		Genes																											
		APC	TP53	KRAS	SYNE1	TCF7L2	OBSCN	PIK3CA	SACS	AHNAK2	FAT3	FAT4	BRCA2	MSH3	SOX9	PTEN	POLE	FBXW7	NF1	MLH1	MSH6	SMAD4	BRAF	RB1	MSH2	TET2	POLD1	MUTYH	
Hypermuted Samples	1																												
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SUM		13	5	9	12	15	12	7	12	12	12	10	10	9	7	8	7	3	6	7	7	2	3	5	5	5	4	1	
Non-hypermuted Samples	1																												
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SUM		40	35	23	14	9	7	12	5	6	5	6	2	1	3	2	1	4	1	0	0	5	3	0	0	0	0	1	

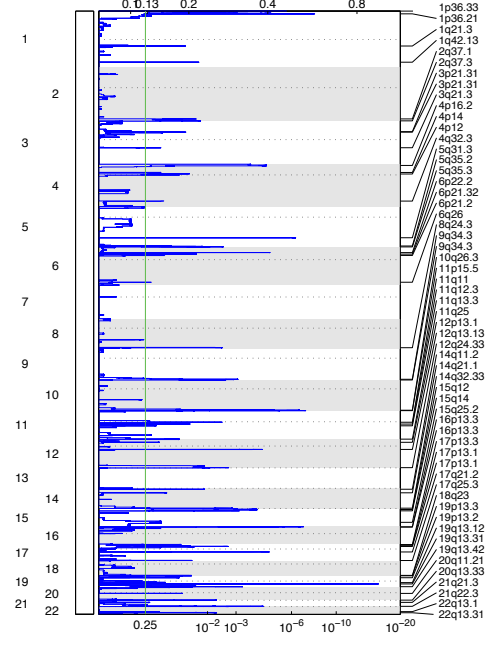
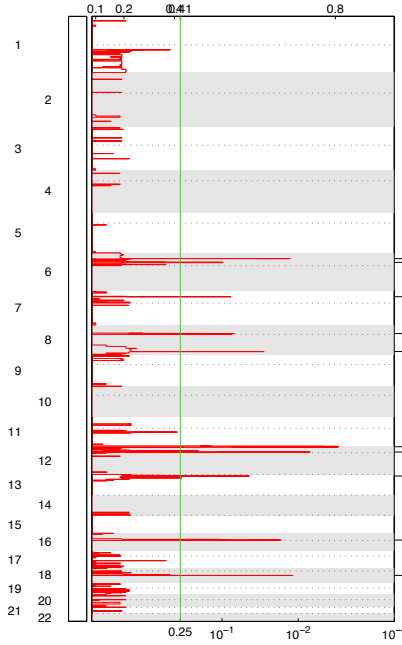
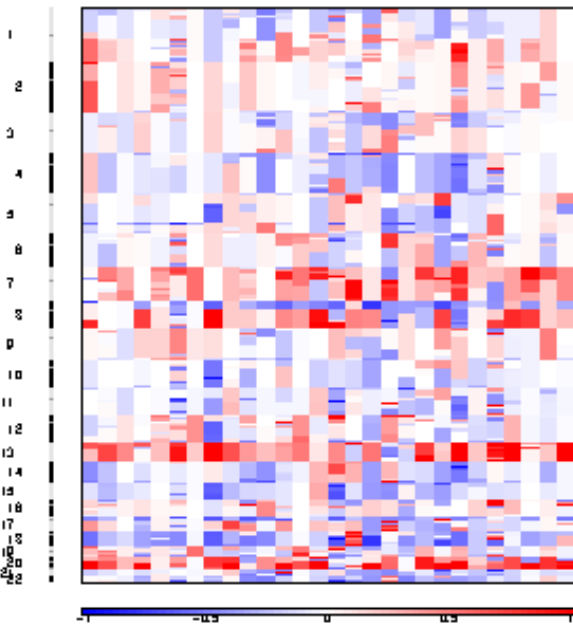
Supplementary Table 5: Number of Tumor Samples with CRC-Related Mutations, Average 1KG-PEL-like Proportion, and Age at Diagnosis in 67 Hispanic/Latino CRC Patients. This table presents the number of tumor samples observed with CRC-related mutations, alongside the average proportion of 1000 Genomes Project Peruvian-in-Lima-like (1KG-PEL-like) and the age at diagnosis.

Mutation Type	Number of Samples	Average 1KG-PEL-like	Average Age at Dx
BRAF V600E	1	0.457	60.1
KRAS G12A	2	0.646	44.55
KRAS G12C	1	0.548	52.6
KRAS G12D	6	0.4875	50.25
KRAS G12V	11	0.6016	57.95
KRAS G13D	7	0.6569	49.39

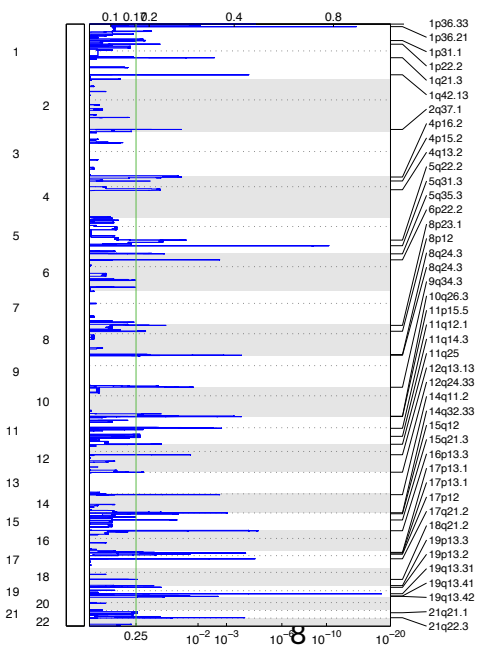
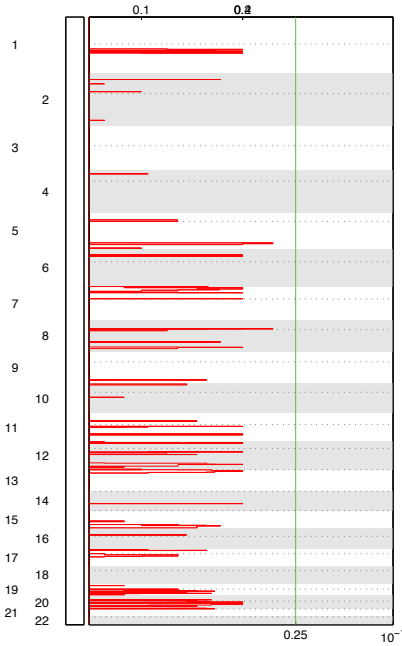
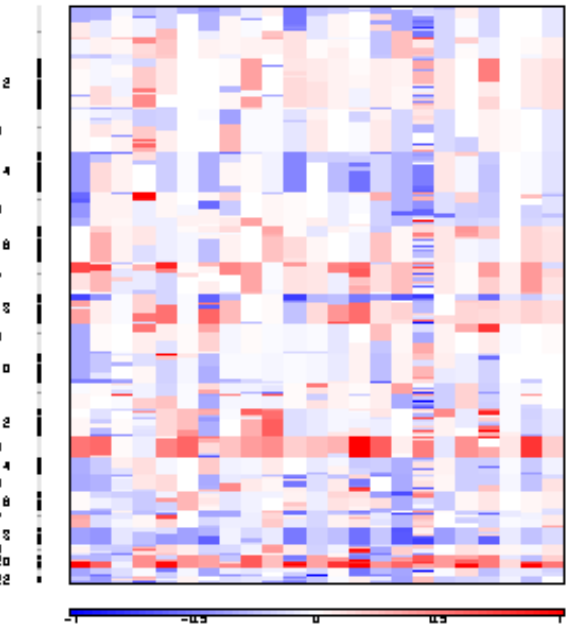
Supplementary Table 6: Number of tumor samples with mutations in tumor suppressor genes and associated demographic data in 67 Hispanic/Latino CRC patients. This table presents the number of tumor samples with mutations in key tumor suppressor genes (APC, TP53, BRCA2, PTEN, FBXW7, NF1, and SMAD4) in a cohort of 67 Hispanic/Latino colorectal cancer (CRC) patients. Alongside the mutation data, the table includes the average proportion of 1000 Genomes Project Peruvian-in-Lima-like (1KG-PEL-like) and the age at diagnosis.

Gene	Number of Samples	Average 1KG-PEL-like	Average Age at Dx
APC	53	0.580	52.8
TP53	40	0.555	51.3
BRCA2	12	0.624	50.2
PTEN	10	0.620	46.5
FBXW7	7	0.570	58.0
NF1	7	0.633	42.6
SMAD4	7	0.653	48.0

Non-Hypermuted Colon Samples



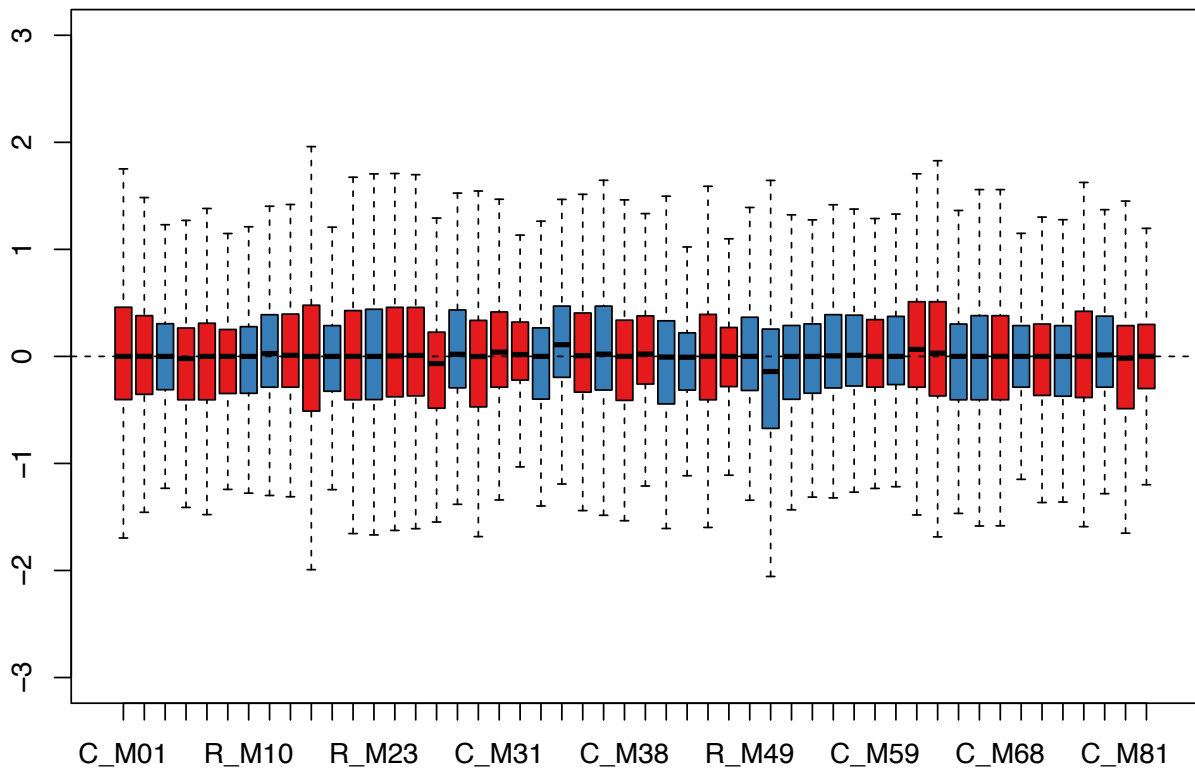
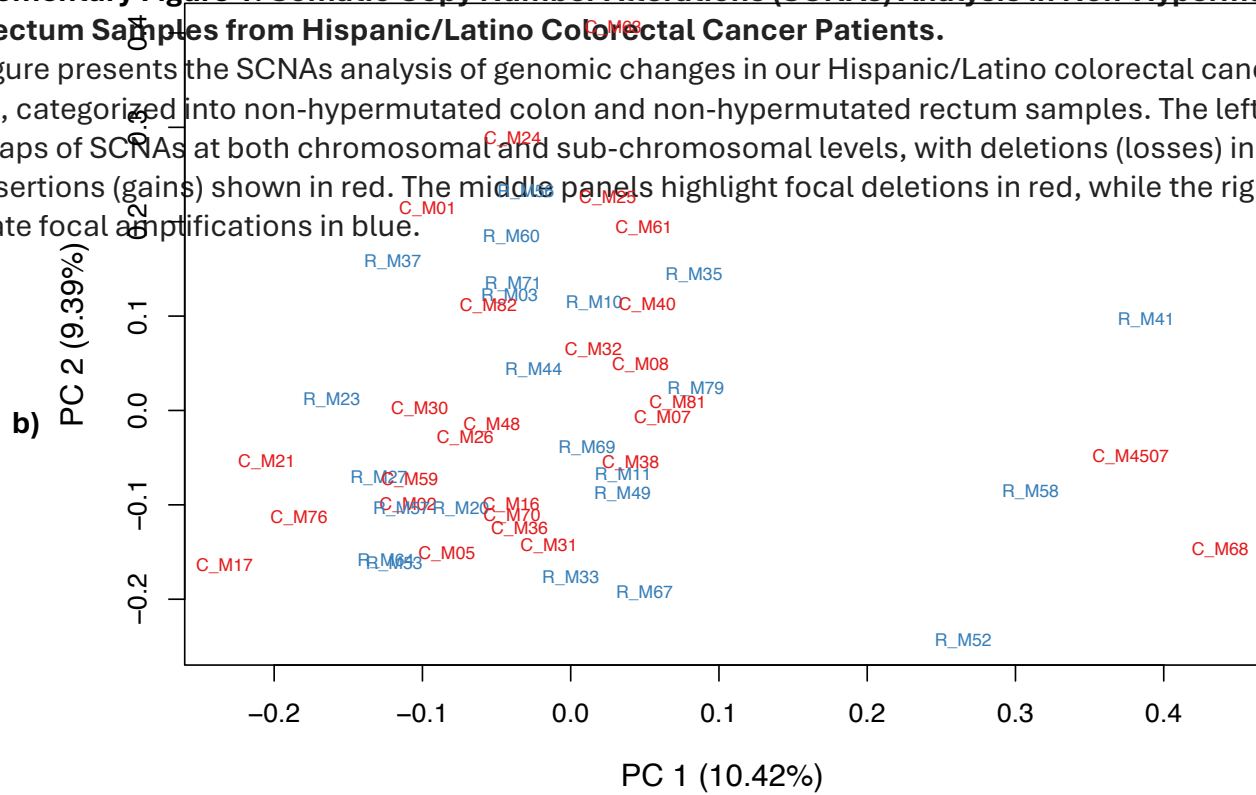
Non-Hypermuted Rectum Samples



a)

Supplementary Figure 1: Somatic Copy Number Alterations (SCNAs) Analysis in Non-Hypermutated Colon and Rectum Samples from Hispanic/Latino Colorectal Cancer Patients.

This figure presents the SCNAs analysis of genomic changes in our Hispanic/Latino colorectal cancer (CRC) cohort, categorized into non-hypermutated colon and non-hypermutated rectum samples. The left panels display heatmaps of SCNAs at both chromosomal and sub-chromosomal levels, with deletions (losses) indicated in blue and insertions (gains) shown in red. The middle panels highlight focal deletions in red, while the right panels illustrate focal amplifications in blue.



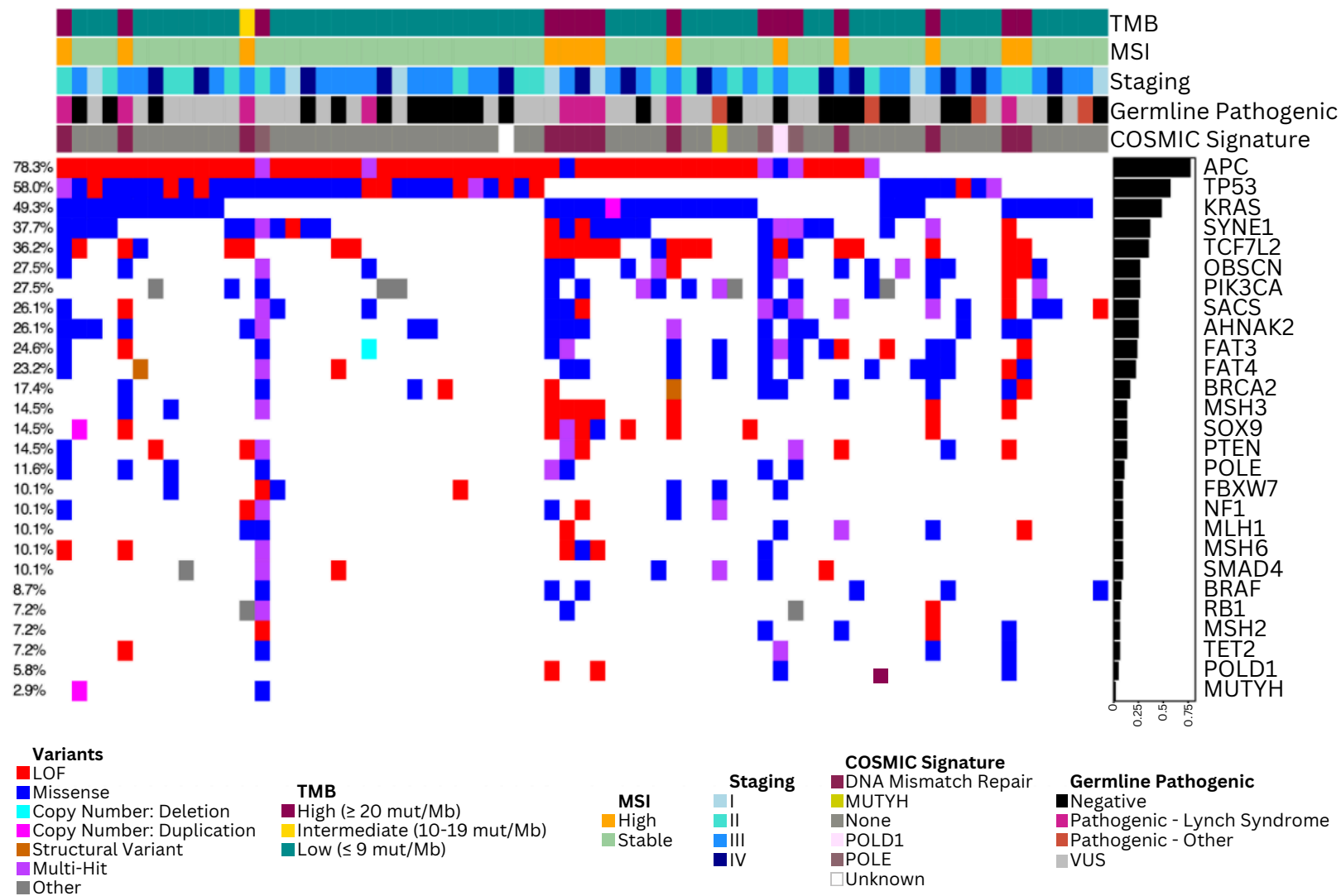
Supplementary Table 7: Differentially Expressed CRC-Related Genes in Non-Hypermuted Colon and Non-Hypermuted Rectum Tumors Among Hispanic/Latino Patients. This table highlights the specific colorectal cancer (CRC)-related genes that show significant differences in expression levels between non-hypermuted colon and rectum tumors in Hispanic/Latino patients.

Gene	logFC	logCPM	LR	p-value
SMAD4	-0.27	6.43	3.40	0.065367
POLE	0.30	6.74	3.23	0.072237
KRAS	-0.32	6.18	2.33	0.127193
BRAF	-0.20	6.89	2.31	0.128846
PIK3CA	-0.19	5.62	1.98	0.159811
MLH1	0.13	4.92	1.74	0.187624
MSH6	0.16	6.03	1.59	0.207689
SOX9	-0.24	7.65	1.59	0.207998
RB1	-0.17	6.04	1.21	0.271250
MUTYH	-0.15	4.06	1.21	0.271699

Supplementary Figure 2: Differential Gene Expression (DGE) Analysis in Non-Hypermuted Colon and Non-Hypermuted Rectum Tumors Among Hispanic/Latino Patients. This figure presents a comprehensive differential gene expression analysis of colorectal cancer (CRC) tumors from Hispanic/Latino patients, categorized into non-hypermuted colon and rectum groups. **a) Principal Component Analysis (PCA) Plot:** This plot displays the distribution of samples along two principal components, PC1 and PC2, capturing the majority of the variance in the genetic data. Colon samples are represented in red, while rectum samples are shown in blue. **b) Relative Log Expression (RLE) Plot:** This diagnostic plot assesses the quality and normalization of gene expression data, ensuring consistent expression levels across non-hypermuted colon (red) and non-hypermuted rectum (blue) tumor samples.

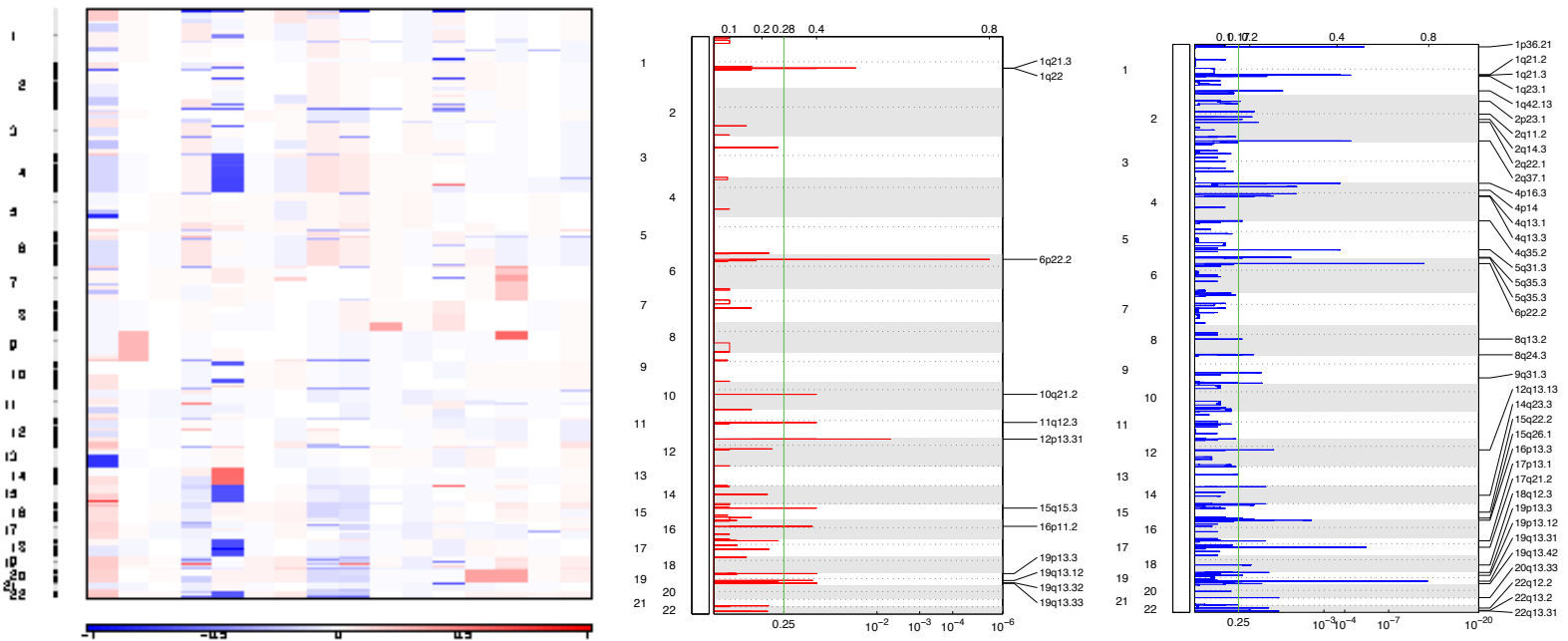
Supplementary Table 8. Mutation frequencies across CRC projects. This table includes gene names, mutation frequencies from the current Moonshot study (N=67), and frequencies from external studies: Innocenti et al. 2023-JCO (N= 540), Innocenti et al. 2023-JCO NHW (N= 463), Nunes et al. 2024-Nature (N= 1063). The included p-values demonstrate the significance levels when comparing frequencies with our study.

Gene	Moonshot Study (N = 67)	Innocenti et al. 2023-JCO (N = 540)		Innocenti et al. 2023-JCO (N = 463), NHW		Nunes et al. 2024-Nature (N =1063)	
	Mutated <i>n</i> (%)	Mutated <i>n</i> (%)	p-value	Mutated <i>n</i> (%)	p-value	Mutated <i>n</i> (%)	p-value
APC	54 (80.60%)	355 (65.70%)	0.0142	300 (64.58%)	0.0103	785 (73.85%)	0.2204
TP53	40 (59.70%)	368 (68.10%)	0.1673	312 (67.39%)	0.2132	639 (60.11%)	0.9468
KRAS	34 (50.75%)	159 (29.40%)	0.0004	125 (27.00%)	7.347E-05	469 (44.12%)	0.2899
SYNE1	26 (38.81%)	0 (NA)	1	0 (NA)	1	0 (NA)	1
TCF7L2	25 (37.31%)	0 (NA)	1	0 (NA)	1	158 (14.86%)	1.312E-06
OBSCN	19 (28.36%)	0 (NA)	1	0 (NA)	1	0 (NA)	1
PIK3CA	19 (28.36%)	91 (16.90%)	0.0217	83 (17.93%)	0.0429	250 (23.52%)	0.3670
SACS	18 (26.87%)	0 (NA)	1	0 (NA)	1	0 (NA)	1
AHNAK2	18 (26.87%)	0 (NA)	1	0 (NA)	1	0 (NA)	1
FAT3	17 (25.37%)	37 (6.90%)	5.793E-07	33 (7.13%)	1.792E-06	0 (NA)	1
FAT4	16 (23.88%)	0 (NA)	1	0 (NA)	1	0 (NA)	1
BRCA2	12 (17.91%)	14 (2.60%)	5.436E-09	11 (2.38%)	5.441E-09	0 (NA)	1
MSH3	10 (14.93%)	0 (NA)	1	0 (NA)	1	0 (NA)	1
SOX9	10 (14.93%)	39 (7.20%)	0.0283	31(6.70%)	0.0184	160 (15.05%)	0.9776
PTEN	10 (14.93%)	20 (3.70%)	0.0001	18 (3.89%)	0.0002	93 (8.75%)	0.0884
POLE	8 (11.94%)	15 (2.80%)	0.0002	12 (2.59%)	0.0002	0 (NA)	1
FBXW7	7 (10.45%)	54 (10.00%)	0.908	52 (11.23%)	0.8489	191 (17.97%)	0.1163
NF1	7 (10.45%)	11 (2.00%)	0.0001	9 (1.94%)	0.0001	0 (NA)	1
MLH1	7 (10.45%)	4 (0.70%)	1.203E-08	4 (0.86%)	2.702E-07	0 (NA)	1
MSH6	7 (10.45%)	11 (2.00%)	0.0001	10 (2.16%)	0.0003	0 (NA)	1
SMAD4	7 (10.45%)	70 (13.00%)	0.5546	17 (12.31%)	0.0127	131 (12.32%)	0.6492
BRAF	6 (8.96%)	84 (15.60%)	0.1496	74 (15.98%)	0.1331	245 (23.05%)	0.0071
RB1	5 (7.46%)	7 (1.30%)	0.0006	7 (1.51%)	0.0022	0 (NA)	1
MSH2	5 (7.46%)	1 (0.20%)	1.816E-08	1 (0.22%)	1.602E-07	0 (NA)	1
TET2	5 (7.46%)	12 (2.20%)	0.0135	10 (2.16%)	0.0144	0 (NA)	1
POLD1	4 (5.97%)	6 (1.10%)	0.0031	6 (1.13%)	0.0086	0 (NA)	1
MUTYH	2 (2.99%)	2 (0.40%)	0.0154	2 (0.043%)	0.0240	0 (NA)	1

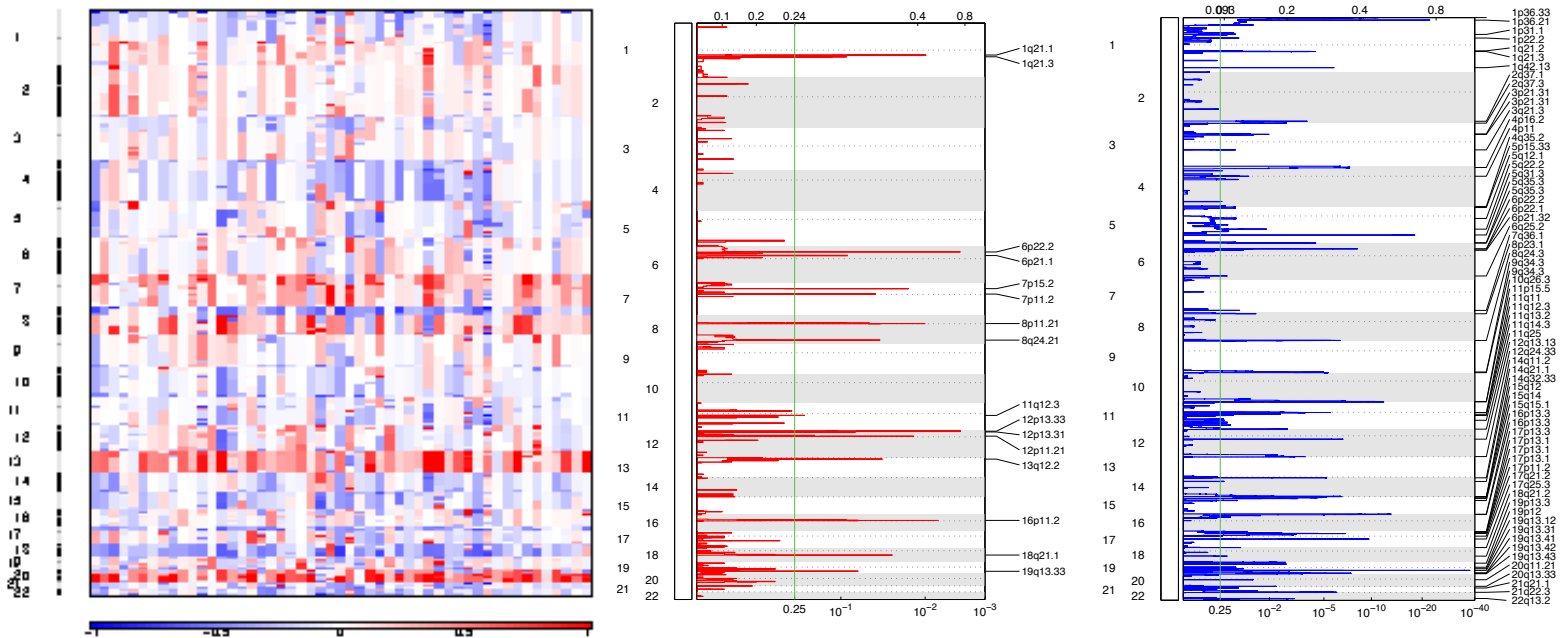


Supplementary Figure 3: Oncoplot of Our 67 CRC H/L Patient Cohort. This oncoplot identifies CRC-related genes and somatic mutations within our cohort of 67 Hispanic/Latino colorectal cancer (CRC) patients. The top panel displays the total mutational burden (TMB), microsatellite stability (MSI), cancer staging, germline pathogenic mutations, and COSMIC signatures calculated for each sample. The middle panel highlights CRC-related genes, categorized by the type of mutation observed. The bottom panel provides legends for the middle and upper panels, detailing the color codes used.

Hypermuted Samples

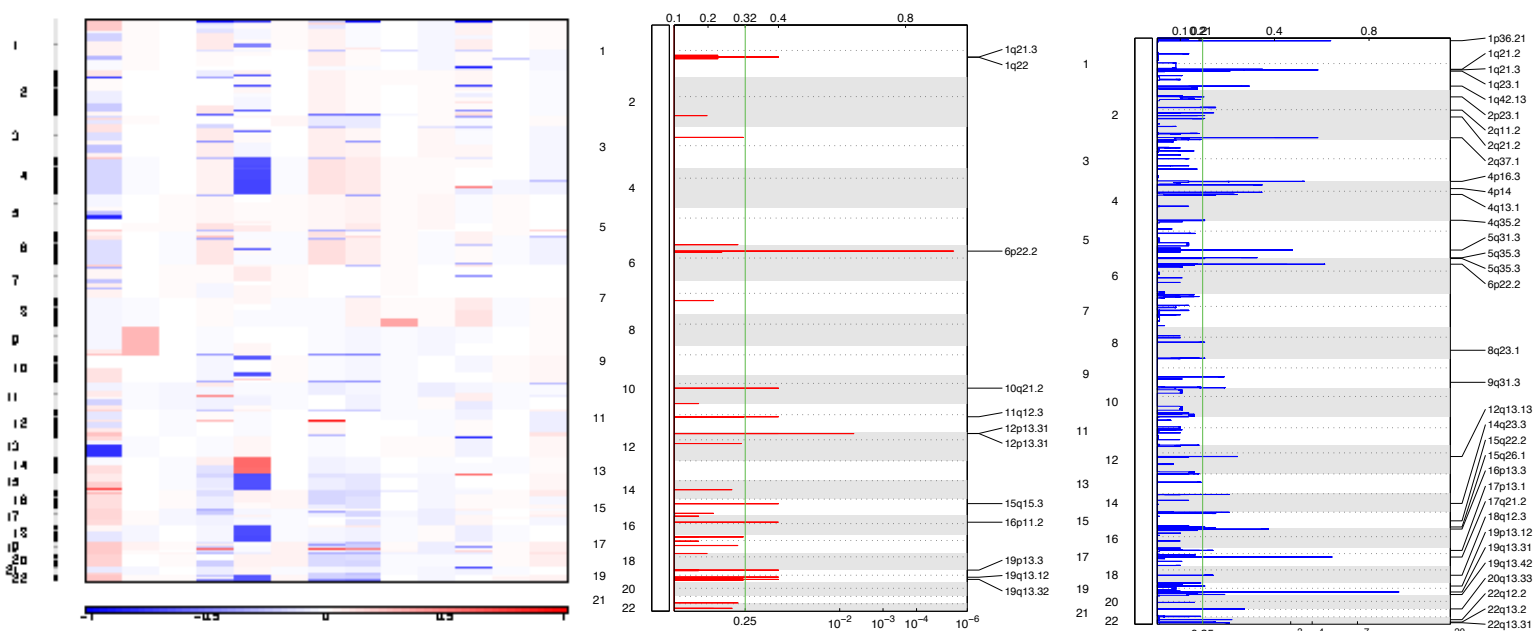


Non-Hypermuted Samples

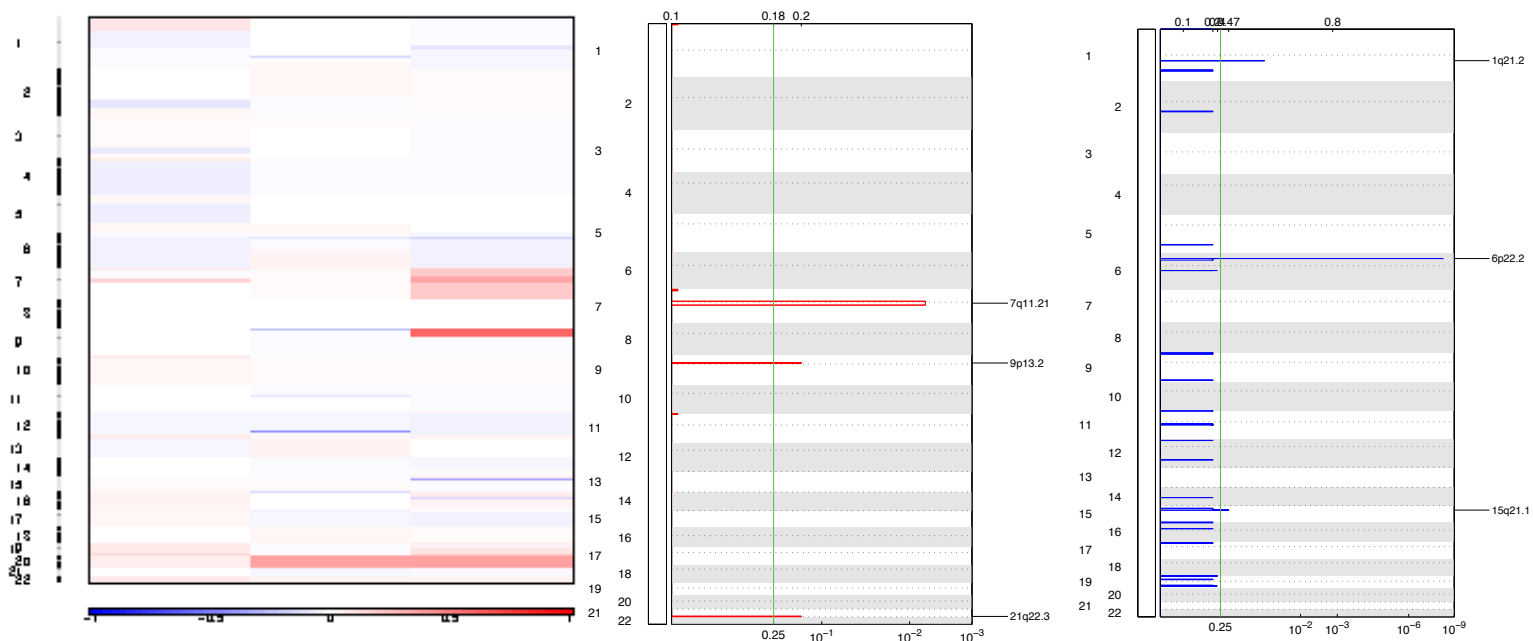


Supplementary Figure 4: Somatic Copy Number Alterations (SCNAs) Analysis of the hypermutated and non-hypermuted samples from the 67 Hispanic/Latino Colorectal Cancer Patients. This figure presents the SCNAs analysis of genomic changes in 67 Hispanic/Latino colorectal cancer (CRC) patients, categorized into hypermutated and non-hypermuted samples. The left panels display heatmaps of SCNAs at both chromosomal and sub-chromosomal levels, with deletions (losses) indicated in blue and insertions (gains) shown in red. The middle panels show focal deletions in red, while the right panels display focal amplifications in blue. 13

Hypermuted MSI Samples

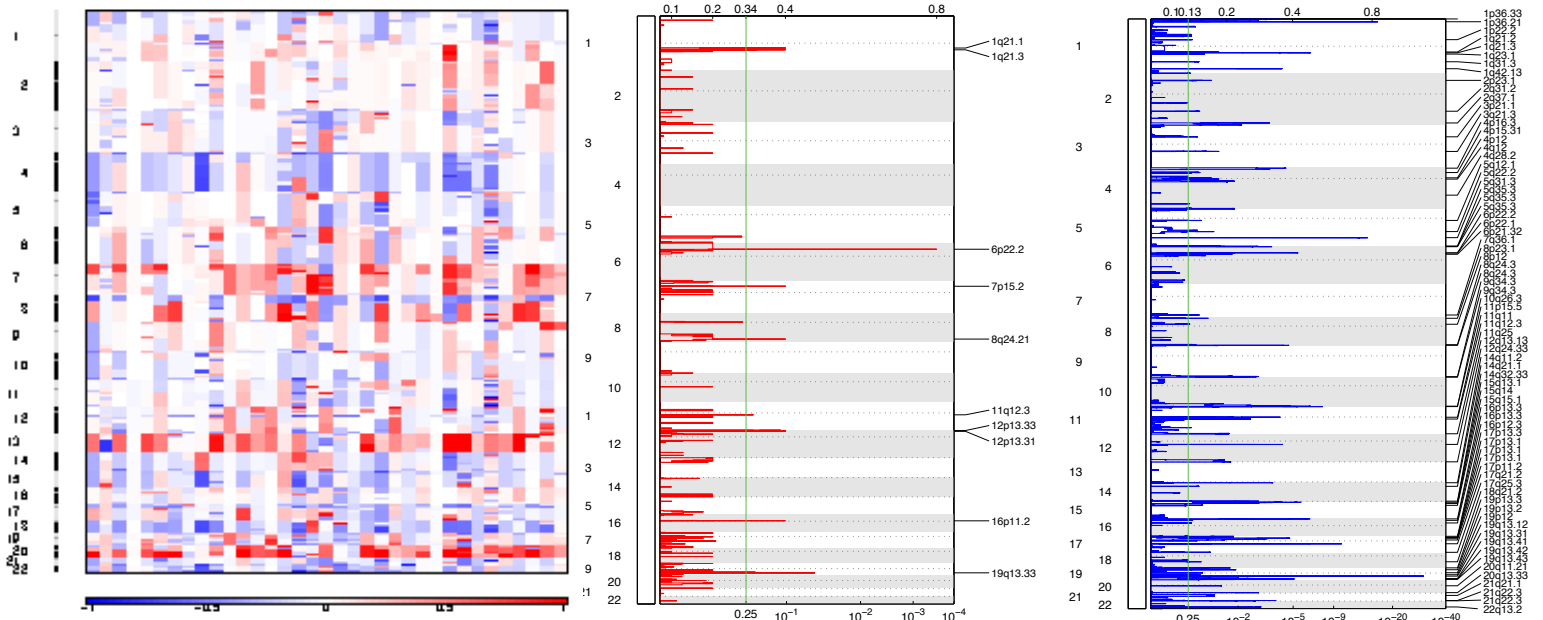


Hypermuted MSS Samples

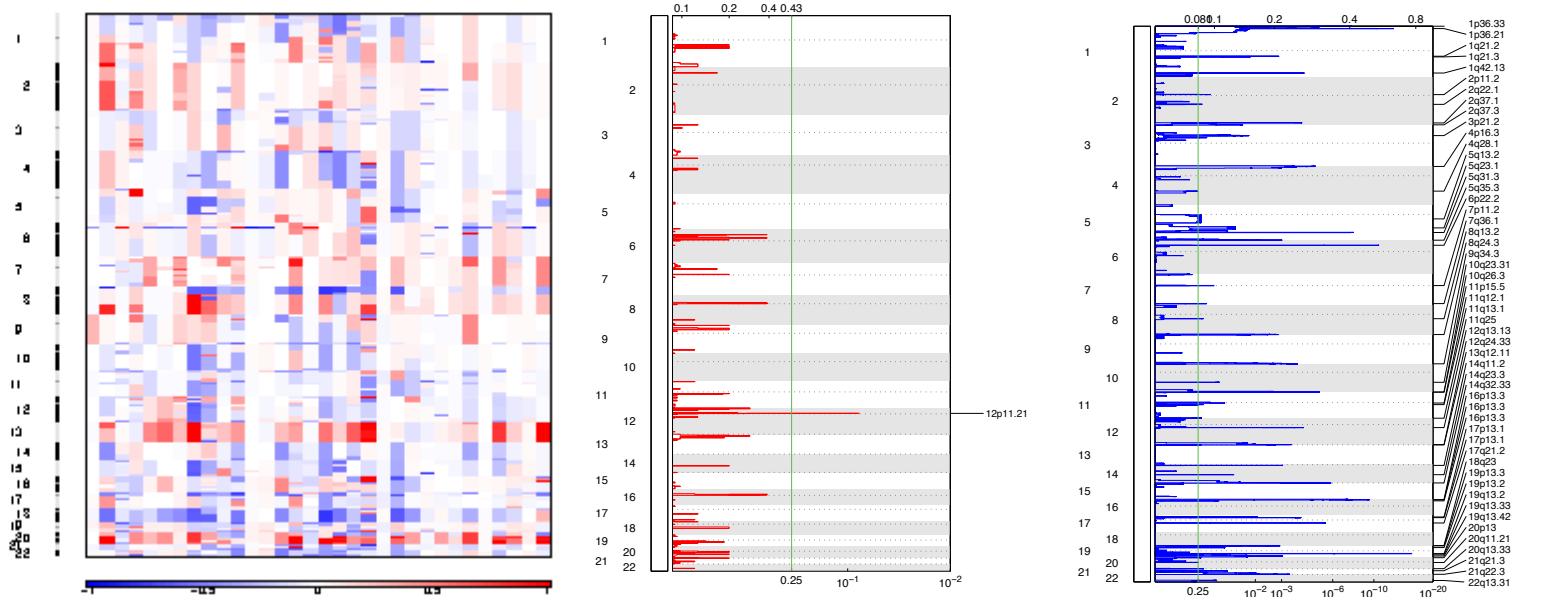


Supplementary Figure 5: Somatic Copy Number Alterations (SCNAs) Analysis in Hypermuted MSI and Hypermuted MSS Samples from Hispanic/Latino Colorectal Cancer Patients. This figure presents the SCNAs analysis of genomic changes in our Hispanic/Latino colorectal cancer (CRC) cohort, categorized into hypermutated MSI (microsatellite instability) and hypermutated MSS (microsatellite stable) samples. The left panels display heatmaps of SCNAs at both chromosomal and sub-chromosomal levels, with deletions (losses) indicated in blue and insertions (gains) shown in red. The middle panels highlight focal deletions in red, while the right panels illustrate focal amplifications in blue.

≤55% 1KG-PEL-like Samples

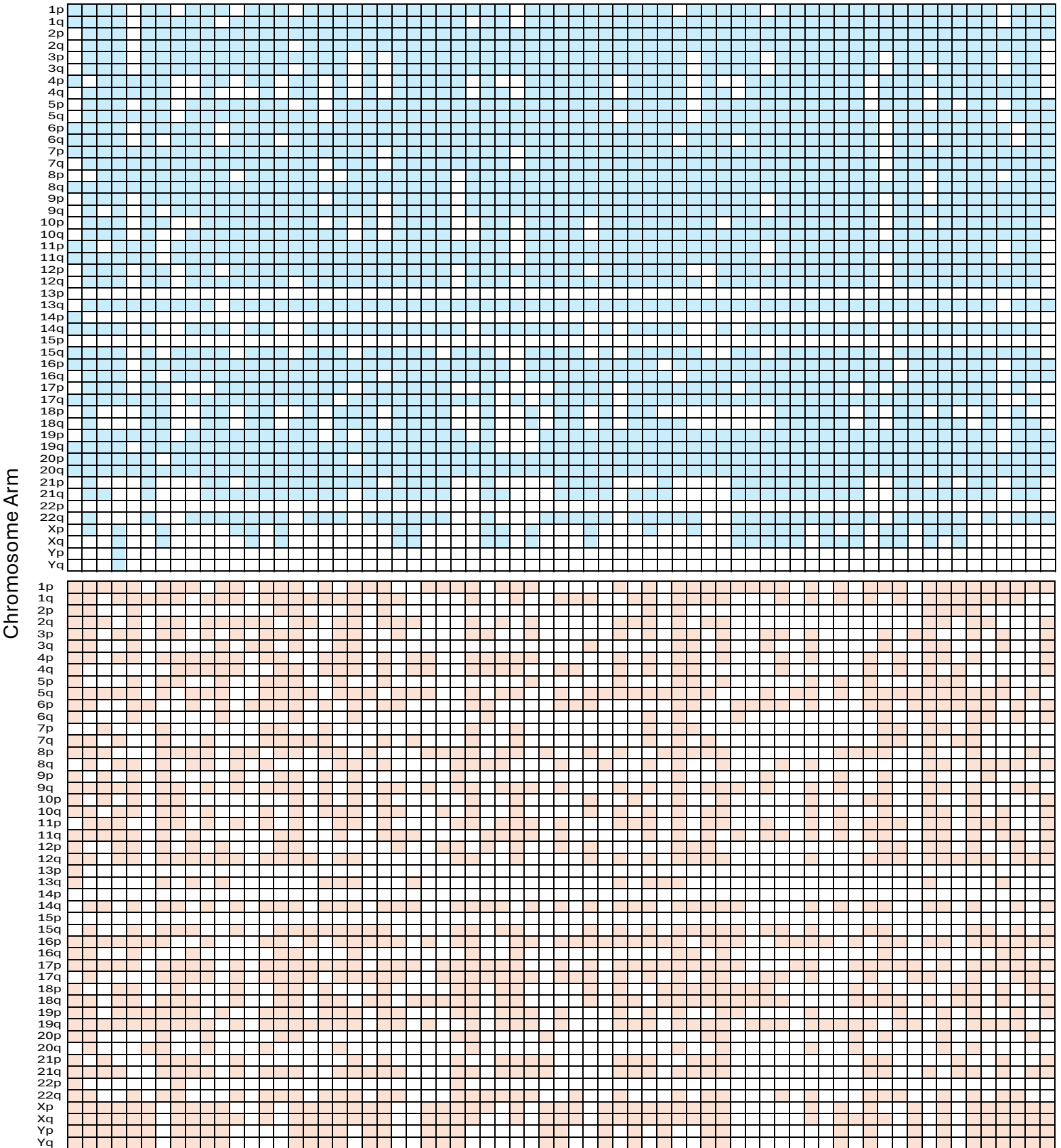


>55% 1KG-PEL-like Samples

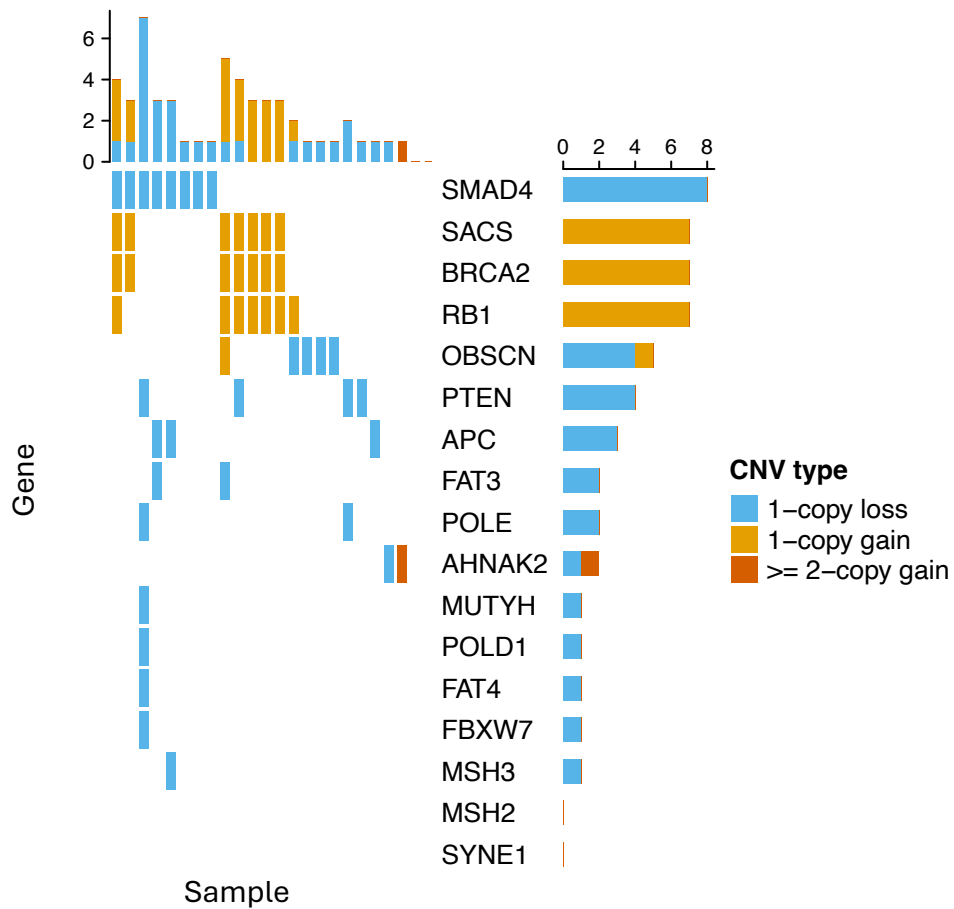


Supplementary Figure 6: Somatic Copy Number Alterations (SCNAs) Analysis Based on 1KG-PEL-like Proportion in Hispanic/Latino Colorectal Cancer Patients. This figure presents the SCNAs analysis of genomic changes in our Hispanic/Latino colorectal cancer (CRC) cohort, categorized into samples with ≤ 55% 1000 Genomes Project Peruvian-in-Lima-like (1KG-PEL-like) proportion and samples with >55% 1KG-PEL-like proportion. The left panels display heatmaps of SCNAs at both chromosomal and sub-chromosomal levels, with deletions (losses) indicated in blue and insertions (gains) shown in red. The middle panels highlight focal deletions in red, while the right panels illustrate focal amplifications in blue.

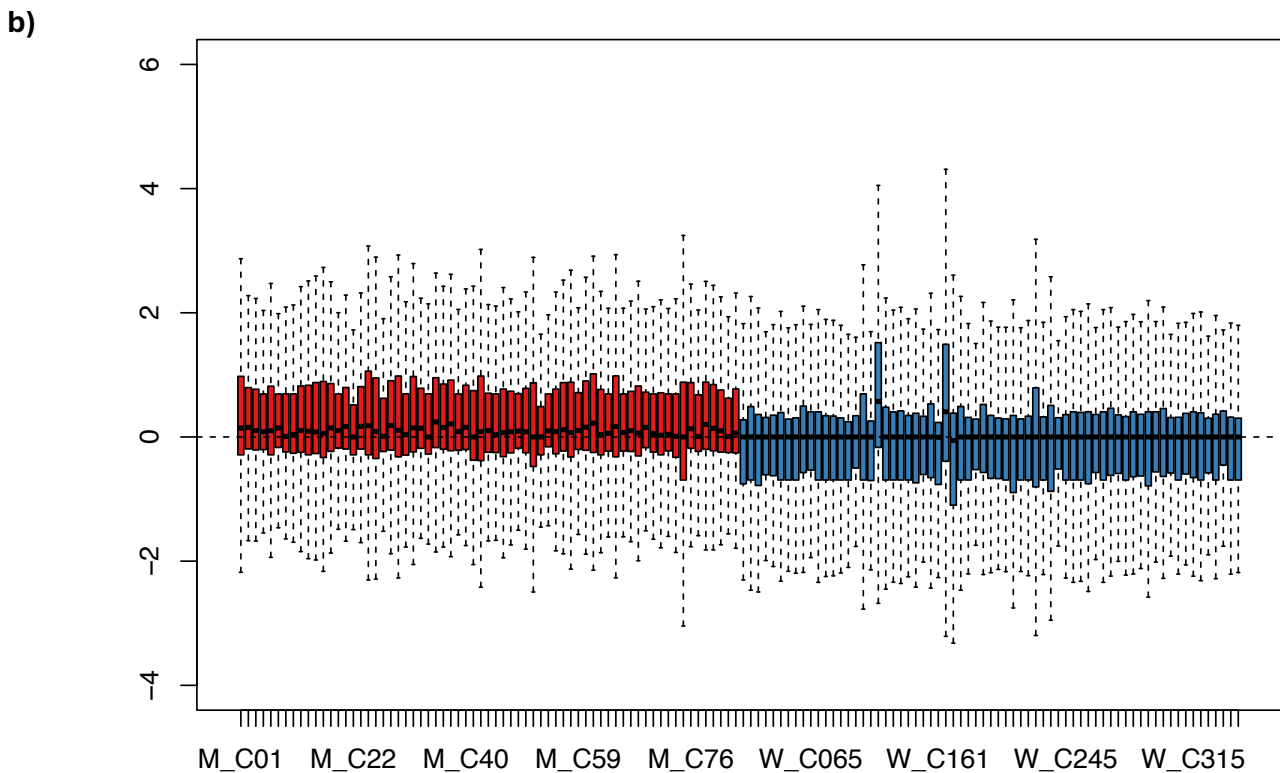
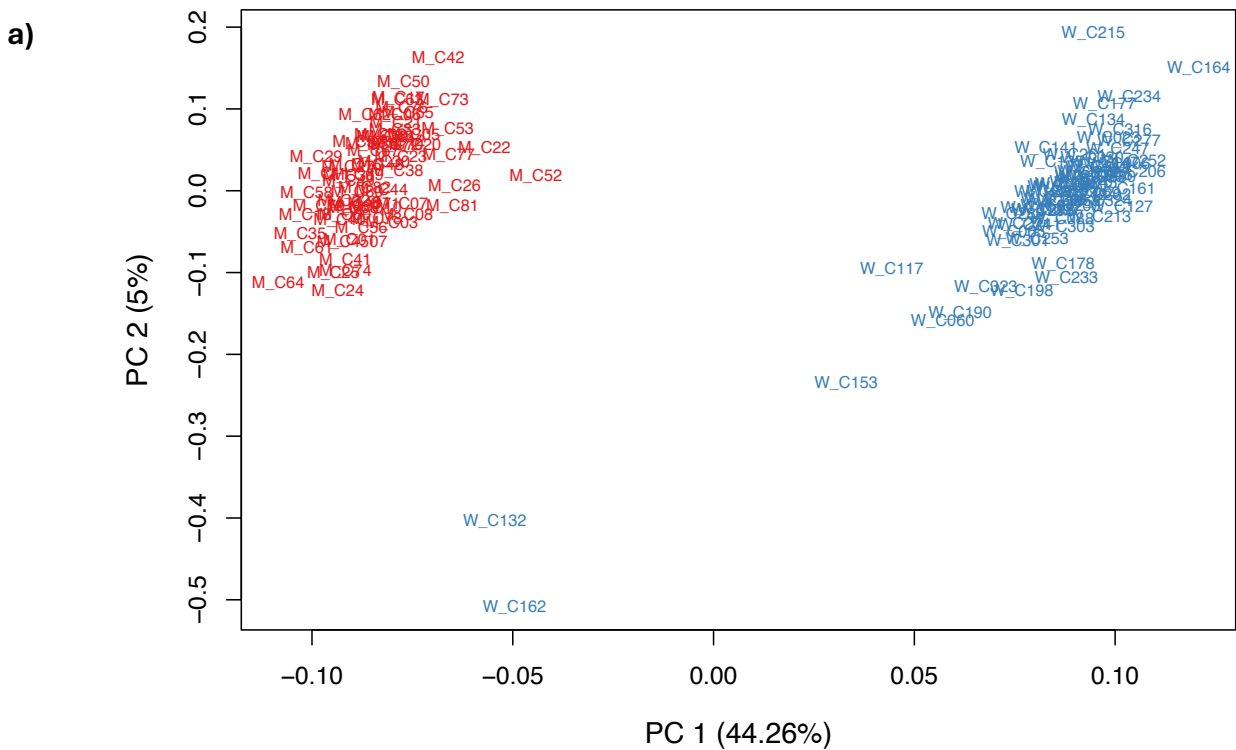
Supplementary Table 9: Chromosomal and sub-chromosomal aberrations in 67 Hispanic/Latino CRC Patients. This table presents the results of a visual inspection of chromosomal and sub-chromosomal aberrations in our H/L CRC cohort. Amplifications are indicated in blue, while deletions are shown in orange.



Samples



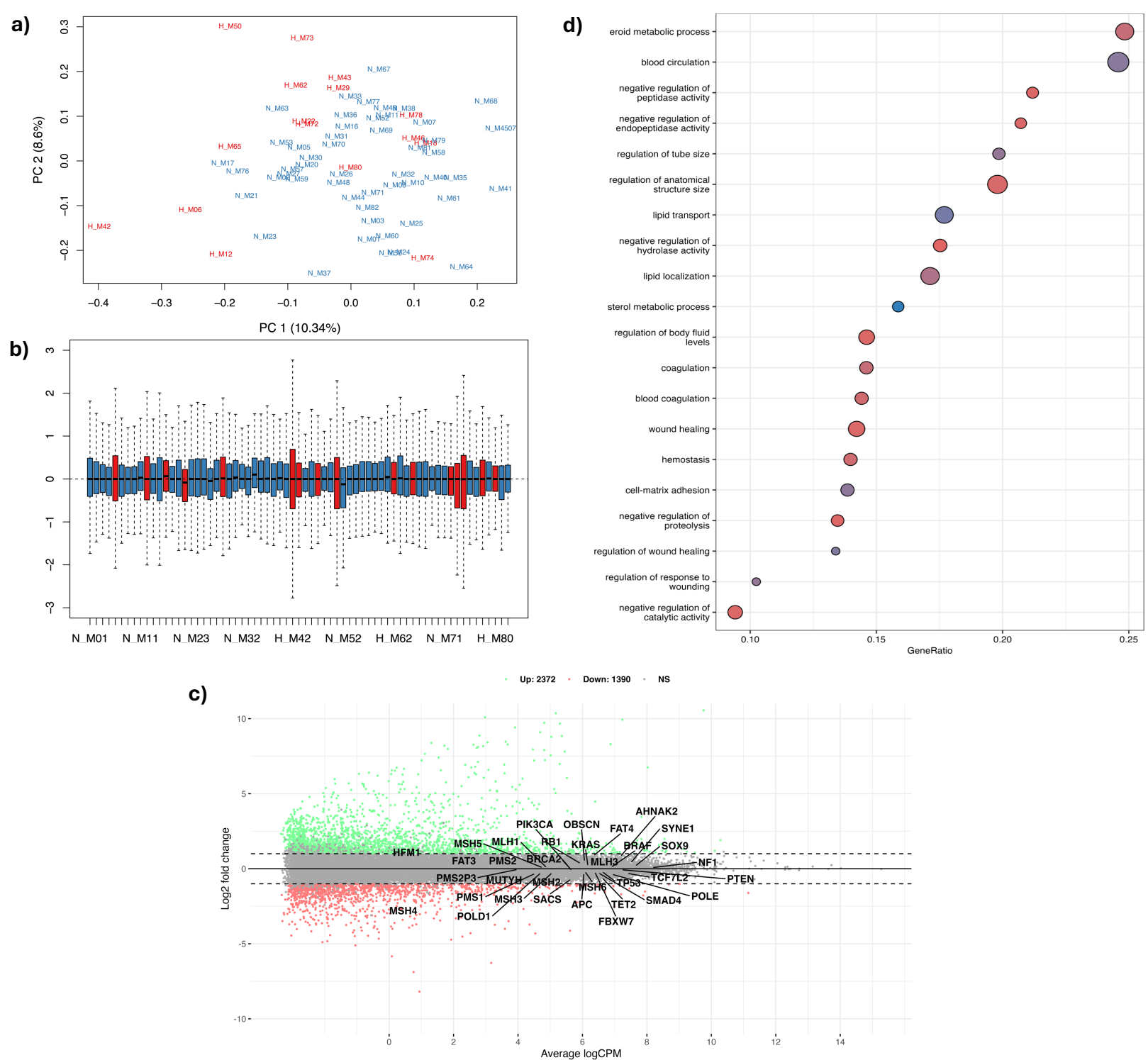
Supplementary Figure 7: SCNAs in Selected CRC-Related Genes in 67 Hispanic/Latino CRC Patients. This figure illustrates somatic copy number alterations (SCNAs) in selected colorectal cancer (CRC)-related genes in 67 Hispanic/Latino CRC patients. The right panel features a bar graph showing the genes and the number of samples affected.



Supplementary Figure 8: Differential gene expression (DGE) analysis among CRC tumors from 67 Hispanic/Latino patients and 67 Non-Hispanic White patients. DGE analysis identified unique gene expression patterns in our Hispanic/Latino (H/L) CRC cohort compared to Non-Hispanic White (NHW) CRC cases from two publicly available databases: TCGA-COAD and TCGA-READ. **a) Principal component analysis (PCA) plot.** The plot displays the distribution of these samples along two principal components, PC1 and PC2, which capture the majority of the variance in the genetic data between Hispanic Latino (red) and non-Hispanic white (blue). **b) Relative Log Expression (RLE) plot.** This diagnostic plot was to assess the quality and normalization of gene expression data. It was particularly useful for ensuring the consistency of expression levels across Hispanic/Latino patients (red) and Non-Hispanic White samples (blue).

Supplementary Table 11: Patient Demographics and Clinical Characteristics of 67 Non-Hispanic Whites (NHW) records. This table provides information on patient demographics and clinical characteristics, including age at diagnosis, gender, tumor location, and pathological stage. The data is compiled from individual records obtained from public databases projects TCGA-COAD and TCGA-READ.

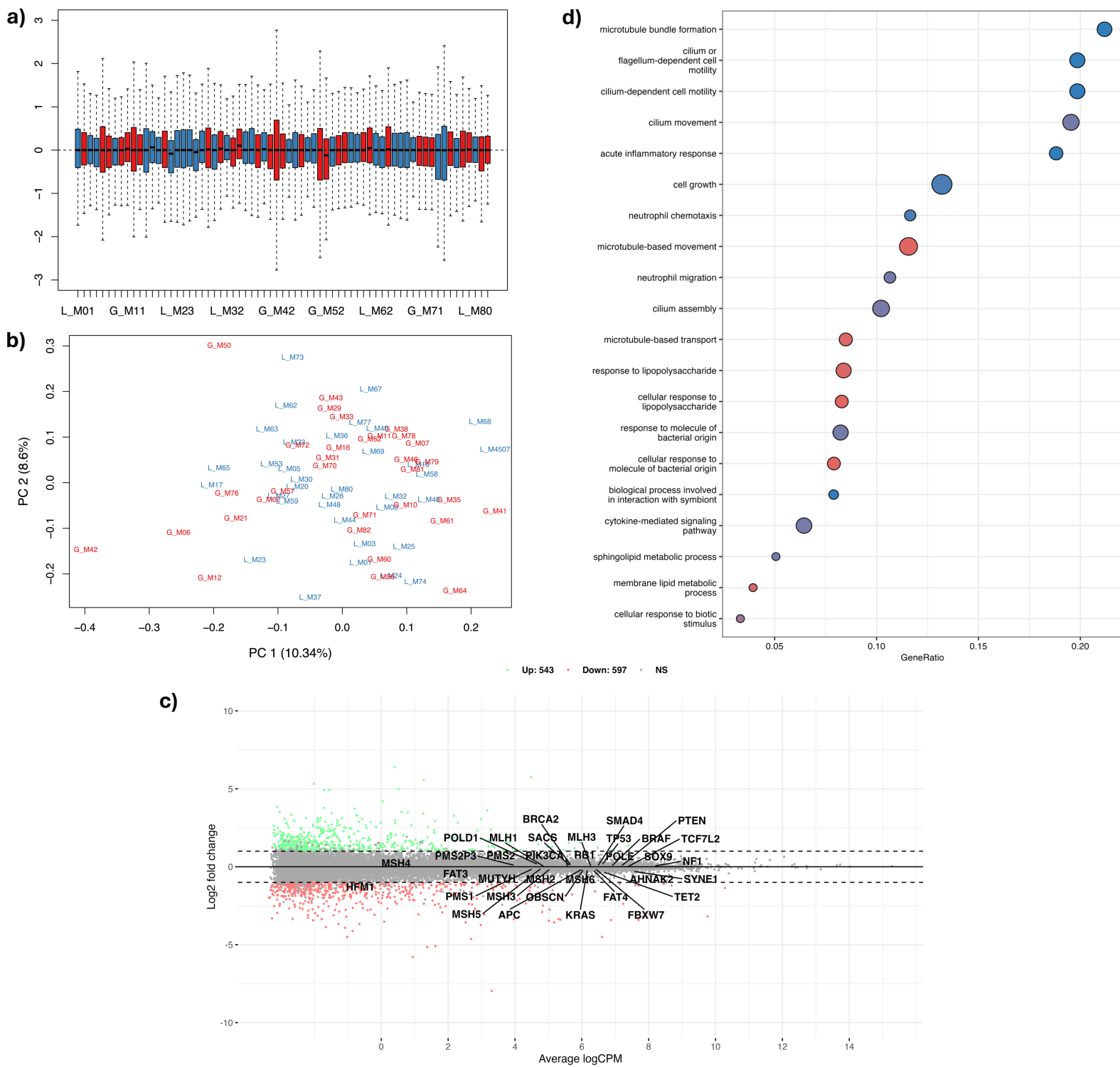
Characteristic	TCGA NHW Samples (n = 67) <i>n (%)</i>
Age at Diagnosis	
< 50 years	30 (44.8%)
>50 years	37 (55.2%)
Gender	
Male	36 (53.7%)
Female	31 (46.3%)
Tumor Location	
Colon	43 (64.2%)
Rectum	24 (35.8%)
Pathological Stage	
Early (Stage I or II)	25 (37.3%)
Late (Stage III or IV)	38 (5.97%)
No TNM Applicable/Unknown	4 (28.4%)



Supplementary Figure 9: Differential Gene Expression (DGE) Analysis Among CRC Hypermuted and Non-Hypermuted Tumors in Hispanic/Latino Patients. This figure presents a detailed differential gene expression (DGE) analysis between hypermutated and non-hypermutated colorectal cancer (CRC) tumors in our cohort of Hispanic/Latino (H/L) patients, highlighting unique gene expression patterns in these two groups. **a)** Principal Component Analysis (PCA) Plot: This plot shows the distribution of samples along two principal components, PC1 and PC2, capturing the majority of variance in the genetic data. Hypermutated samples are represented in red, while non-hypermutated samples are in blue. **b)** Relative Log Expression (RLE) Plot: This diagnostic plot assesses the quality and normalization of gene expression data, ensuring consistency of expression levels across hypermutated (red) and non-hypermutated (blue) samples. **c)** Mean-Average (MA) Plot: This scatter plot depicts the upregulated and downregulated CRC-related genes based on log2 fold change, illustrating the differential expression between the two groups. **d)** Pathway Analysis: This graph presents distinct cellular pathways identified through pathway analysis by comparing hypermutated and non-hypermutated CRC tumors in Hispanic/Latino patients. It displays the names of the pathways, adjusted p-values, and the number of genes altered in each pathway. 21

Supplementary Table 12: Differentially Expressed CRC-Related Genes in Hypermutedated and Non-Hypermutedated Tumors from Hispanic/Latino Patients. It highlights the specific genes that exhibit significant differences in expression levels between these two groups.

Gene	logFC	logCPM	LR	p-value
MSH4	-2.16	1.03	84.72	3.4314E-20
TET2	-0.57	6.60	25.02	5.6636E-07
SACS	-0.65	5.67	15.05	1.0466E-04
FAT4	0.83	6.32	13.79	2.0458E-04
PMS1	-0.28	4.57	5.74	0.016590
AHNAK2	0.79	7.17	5.56	0.018360
RB1	0.31	5.97	5.06	0.024463
MSH2	-0.38	5.32	4.79	0.028548
OBSCN	0.45	6.07	4.74	0.029478
APC	-0.27	6.05	4.67	0.030707
POLE	-0.34	6.87	4.64	0.031235
FAT3	0.64	2.90	4.36	0.036876
TCF7L2	-0.29	7.33	4.33	0.037424



Supplementary Figure 10: Differential Gene Expression (DGE) Analysis Among CRC Tumors with Varying 1KG-PEL-like Proportions in Hispanic/Latino Patients. This figure presents a comprehensive differential gene expression analysis among colorectal cancer (CRC) tumors from Hispanic/Latino patients, categorized by 1000 Genomes Project Peruvian-in-Lima-like (1KG-PEL-like) proportions. The analysis compares samples with 1KG-PEL-like proportions >55% and those with 1KG-PEL-like proportions ≤55%. **a)** Principal Component Analysis (PCA) Plot: This plot displays the distribution of samples along two principal components, PC1 and PC2, which capture the majority of the variance in the genetic data. Samples with 1KG-PEL-like >55% are shown in red, while samples with 1KG-PEL-like ≤55% are shown in blue. **b)** Relative Log Expression (RLE) Plot: This diagnostic plot assesses the quality and normalization of gene expression data, ensuring consistency of expression levels across samples with 1KG-PEL-like >55% (red) and 1KG-PEL-like ≤55% (blue). **c)** Mean-Average (MA) Plot: This scatter plot visualizes the upregulated and downregulated CRC-related genes based on log₂ fold change. **d)** Pathway Analysis: This graph presents the distinct cellular pathways identified through pathway analysis by comparing CRC tumors with 1KG-PEL-like proportions >55% and 1KG-PEL-like proportions ≤55%. The graph displays the names of the pathways, adjusted

Supplementary Table 13: Differentially Expressed CRC-Related Genes among CRC Tumors with Varying 1KG-PEL-like Proportions in Hispanic/Latino Patients. It highlights the specific genes that exhibit significant differences in expression levels between samples with 1KG-PEL-like proportions >55% and those with 1KG-PEL-like proportions ≤55%.

Gene	logFC	logCPM	LR	p-value
TET2	-0.29	6.60	6.09	0.013612
HFM1	-0.66	-0.04	5.77	0.016315
AHNAK2	-0.43	7.17	2.38	0.123152
MSH6	-0.17	6.07	2.11	0.146291
SYNE1	-0.27	7.48	1.90	0.168190
MSH4	-0.40	1.03	1.82	0.177668
MSH2	-0.19	5.32	1.50	0.220839
RB1	0.13	5.97	1.14	0.285359
MUTYH	-0.12	4.12	1.12	0.290929
APC	-0.11	6.05	0.81	0.368395

Supplementary Table 14: Gene Fusions. This table presents the gene fusions identified in 67 Hispanic/Latino colorectal cancer (CRC) patients. The data includes the locations of gene fusions and recurrent deletion peaks identified from somatic copy number alterations (SCNAs) in selected CRC-related genes. Specific details provided are the upstream gene, Ensembl ID for the upstream gene, upstream breakpoint, downstream gene, Ensembl ID for the downstream gene, and downstream breakpoint.

Gene Upstream	Ensembl Upstream	Breakpoint Upstream	Gene Downstream	Ensembl Downstream	Breakpoint Downstream
EML4	ENSG00000143924	42295516	ALK	ENSG00000171094	2923528
ERLIN2	ENSG00000147475	37741818	FGFR1	ENSG00000077782	38457534
PTPRK	ENSG00000152894	128520259	RSPO3	ENSG00000146374	127148648
RAF1	ENSG00000132155	12590798	TMEM40	ENSG00000088726	12749840
PMS2P9	ENSG00000233448	77043778	AC105052.5	ENSG00000286830	102703481
AC108865.1	ENSG00000250829	186891368	AC110772.2	ENSG00000250971	187019821
GNAS	ENSG00000087460	58895684	BCAS1	ENSG00000064787	54058723
PMS2P11	ENSG00000241350	77015855	CCDC146	ENSG00000135205	77167658
PMS2P9	ENSG00000233448	77043778	CCDC146	ENSG00000135205	77167658
PPP1R13B	ENSG00000088808	103753000	EML1	ENSG00000066629	99850853
PFKFB3	ENSG00000170525	6226365	LINC02649	ENSG00000215244	6326546
CLPB	ENSG00000162129	72380281	MYEOV	ENSG00000172927	69341510
CDH17	ENSG00000079112	94145928	RUNX1T1	ENSG00000079102	92017363
FBXO25	ENSG00000147364	435707	SEPTIN14	ENSG00000154997	55796092
OR51S1	ENSG00000176922	4848669	TP53I11	ENSG00000175274	44933050
DST	ENSG00000151914	56603564	ABHD16A	ENSG00000204427	31701028
ELL	ENSG00000105656	18521921	AC011447.3	ENSG00000267383	20240637
PSD3	ENSG00000156011	18936034	AC100849.1	ENSG00000253557	19085078
AC127502.3	ENSG00000283345	30513698	AC127502.1	ENSG00000215302	30474356
AL611929.1	ENSG00000234768	168194688	AFDN	ENSG00000130396	167943129
WARS2	ENSG00000116874	119076350	AGBL4	ENSG00000186094	49045800
UHRF1BP1L	ENSG00000111647	100088915	ANKS1B	ENSG00000185046	99779972
SMAD4	ENSG00000141646	51030623	ANO4	ENSG00000151572	100901646
EHBP1	ENSG00000115504	62942896	ANXA4	ENSG00000196975	69652998
VSTM5	ENSG00000214376	93850412	AP003066.1	ENSG00000254587	96975663
ASH1L	ENSG00000116539	155395459	ARID4B	ENSG00000054267	235182793
IGH@-ext	IGH-	105588395	ARL4D	ENSG00000175906	43400325
ERC1	ENSG00000082805	1028572	CACNA1C	ENSG00000151067	2448976
SAP30BP	ENSG00000161526	75671863	CAVIN1	ENSG00000177469	42405388
PMS2P6	ENSG00000174384	73097567	CCDC146	ENSG00000135205	77167658
POGZ	ENSG00000143442	151459152	CDC42SE1	ENSG00000197622	151059773
TANC1	ENSG00000115183	159065971	DAPL1	ENSG00000163331	158804282
GALK2	ENSG00000156958	49235941	DENND2A	ENSG00000146966	140602542
TMED5	ENSG00000117500	93180054	DHCR24	ENSG00000116133	54854234
SEC61A2	ENSG00000065665	12129794	DHTKD1	ENSG00000181192	12117673
MAP2K2	ENSG00000126934	4117419	EBI3	ENSG00000105246	4236936
VPS41	ENSG00000006715	38817817	ELMO1	ENSG00000155849	37342763
MSI2	ENSG00000153944	57529724	GDPD1	ENSG00000153982	59234492
VAV3	ENSG00000134215	107683488	HMCN1	ENSG00000143341	185965802
MAN2B1	ENSG00000104774	12658063	HNRNPM	ENSG00000099783	8483158
VGLL4	ENSG00000144560	11720394	HRH1	ENSG00000196639	11259003
PPFIA1	ENSG00000131626	70272436	IGH@-ext	IGH	106373964
GINS1	ENSG00000101003	25413854	ILDR2	ENSG00000143195	166958101
MARK2	ENSG00000072518	63839560	LNCAROD	ENSG00000231131	52561115
DUSP16	ENSG00000111266	12519862	MANSC1	ENSG00000111261	12330958
AUTS2	ENSG00000158321	70698620	MDGA2	ENSG00000139915	46882221
NPEPPS	ENSG00000141279	47531555	MED1	ENSG00000125686	39451290
STARD13	ENSG00000133121	33285470	MTMR6	ENSG00000139505	25274187
CAPRIN1	ENSG00000135387	34086413	PAMR1	ENSG00000149090	35474744
MCM3AP	ENSG00000160294	46236829	PCBP3	ENSG00000183570	45744231
DHX9	ENSG00000135829	182856578	PDC-AS1	ENSG00000229739	186519776
CTIF	ENSG00000134030	48539312	RAB31	ENSG00000168461	9775278
WWC1	ENSG00000113645	168431444	REEP5	ENSG00000129625	112887183
PAK1	ENSG00000149269	77473552	RIMKLA	ENSG00000177181	42409984
AL669831.4	ENSG00000230092	805799	SEPTIN14	ENSG00000154997	55796092
AL391840.3	ENSG00000287811	79538843	SH3BGR12	ENSG00000198478	79673614
TRIM37	ENSG00000108395	59106441	SKA2	ENSG00000182628	591313667
SPATA13	ENSG00000182957	24160932	SLC46A3	ENSG00000139508	28718022
MDGA2	ENSG00000139915	46877489	SNX13	ENSG00000071189	17875790
RAB11FIP3	ENSG00000090565	510800	SPN	ENSG00000197471	29670734
REEP5	ENSG00000129625	112921163	SSBP2	ENSG00000145687	81461103
C2CD5	ENSG00000111731	22453896	ST8SIA1	ENSG00000111728	22070625
CTTN	ENSG00000085733	70425401	STARD10	ENSG00000214530	72759381
LDLR	ENSG00000130164	11089615	TMPRSS9	ENSG00000178297	2389761
USP32	ENSG00000170832	60219670	USH2A	ENSG00000042781	216097213
DNAJC1	ENSG00000136770	22003213	VKORC1	ENSG00000167397	31091342
CLTC	ENSG00000141367	59660588	VMP1	ENSG00000062716	59808796