

# Tumor mutation burden determined by a 645-cancer gene panel and compared with microsatellite instability and mismatch repair genes in colorectal cancer

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**Background:** Tumor mutation burden (TMB) assessed by tumor-related gene panels (CRGP), microsatellite instability (MSI), and mismatch repair (MMR) has been proven to be associated with prognosis, and these factors are prognostic indicators in predicting the benefits of immune checkpoint blockade (ICB) in solid tumors. However, whether the TMB calculated by CRGPs, MSI, and MMR is associated with overall survival (OS) in patients with colorectal cancer (CRC) remains to be explored.

**Methods:** The prognostic threshold of the panel-TMB was explored by a panel of 645 genes (*GP645*) from 41 CRC patients in Jiangsu Cancer Hospital (JCH dataset). The results were further validated using 531 CRC patients from The Cancer Genome Atlas (TCGA) database.

**Results:** Mutations of the *GP645* genes were distributed on 21 chromosomes. Spearman correlation analysis showed that the panel-TMB was positively correlated with TMB measured by whole-exome sequencing (WES) (wTMB) in the TCGA dataset (R=0.75, P<0.001). Kaplan-Meier survival analysis demonstrated that higher panel-TMB in CRC patients was significantly associated with a poor OS (P=0.0062). MSI and MMR status were determined using the *GP645* by next-generation sequencing (NGS). The proportions of MSI-H and dMMR accounted for less than 10% in CRC, the vast majority of MSI-H/dMMR samples also had high TMB [positive predictive value (PPV) =66.6%], and only 13.3% of samples with high TMB were classified as MSI-high/dMMR. In addition, patients with low-TMB were associated with MSS/ pMMR (96.2%), and these results are consistent with earlier studies.

**Conclusions:** GP645 was constructed to evaluate OS in Chinese CRC patients. Panel-TMB and MSI/ MMR might be potential prognostic predictors of CRC patients using the *GP645*.

**Keywords:** Tumor mutation burden (TMB); microsatellite instability (MSI); mismatch repair (MMR); gene panel; colorectal cancer (CRC)

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# Introduction

Colorectal cancer (CRC) is the fourth leading cause of cancer-related death in China (1-3). With the improvement of surgical methods and the combination of chemotherapy drugs and other medical technology, the treatment level of CRC has improved, while the overall prognosis of patients has not significantly improved. Over the past 2 decades, many drugs, including targeted drugs such as antibodies targeting vascular endothelial growth factor (bevacizumab) and the epidermal growth factor receptor (EGFR; cetuximab and panitumumab), and immunotherapy drugs have been approved for the treatment of metastatic CRC (mCRC). The survival period of advanced CRC patients has increased from less than 1 to 3 years, and even 20% of patients can survive for more than 5 years (4-7). However, the optimal combination of these drugs is likely dependent on many factors, including the mutational status of the tumor cells. With the continuous development of genome sequencing, targeted therapy and immunotherapy for CRC have made great progress in recent years. Scientists have found several groups of biomarkers such as gene mutations (KRAS, NRAS, BRAF, HER2, NTRK), tumor mutation burden (TMB), and microsatellite instability/mismatch repair (MSI/MMR) which can be used as prognostic indicators of targeted therapy and immunotherapy (8-14).

MSI are DNA elements composed of repeating motifs that occur as alleles of variable lengths. It was first found in hereditary non-polyposis colorectal cancer (HNPCC) (15), and was then identified in a variety of sporadic tumors (such as gastric cancer, lung cancer, and endometrial cancer) (16). MSI has been associated with improved prognosis and immune checkpoint inhibitors (ICIs). Some evidence has shown that MSI-high (MSI-H) mCRC patients who received nivolumab and nivolumab + ipilimumab had a better response rate and survival time (17,18). MSI increases the probability of somatic mutation. The incidence of somatic mutation was 10-50 times higher than that of MMR proficiency (pMMR) (19). As the increase of mutation frequency would lead to the enhancement of tumor immunogenicity (20), patients with MMR deficiency (dMMR) had higher sensitivity to immunotherapy. Recent studies suggest that dMMR may also be a marker for predicting the efficacy of immunotherapy (21). Solid tumor patients with MSI-H/ dMMR usually develop immunogenicity and extensive T-cell infiltration, which results in a high response to ICI treatment. These findings indicate that MSI/MMR

gene deletion may predict the efficacy of immunotherapy, however, the incidence of dMMR/MSI-H in CRC is only about 10–15% (22). Therefore, more molecular markers are needed to predict the efficacy of immunotherapy.

TMB measured by whole-exome sequencing (WES) is a novel prognostic biomarker for ICI therapy in cancers (12,23). However, TMB is difficult to popularize because of the cost, timeliness, and bioinformatics challenges of WES in the clinical setting (24,25).

Hence, in this study, 645 cancer-related genes and 5 MSI loci (BAT-25, BAT-26, NR-21, NR-24, MONO-27) were obtained for developing a panel for TMB estimation (panel-TMB) and predicting the efficacy of targeted therapy and immunotherapy in CRC. In this study, somatic and genetic mutations of patients were detected in the same experimental species, and TMB, HRR, MMR and MSI of patients were analyzed at the same time, which could provide patients with a better comprehensive treatment plan including targeted drugs, genetic and immunotherapy. The correlation between TMB, MMR and MSI was also analyzed, and multiple tests were combined in one experiment to shorten the detection cycle and cost. In addition, this study clinical samples of the department and TCGA database were comprehensively analyzed to verify the accuracy of the process and shorten the overall smooth testing development cycle. We present the following article in accordance with the REMARK reporting checklist (available at https://dx.doi.org/10.21037/jgo-21-572).

# Methods

# Patient samples

A total of 41 tumor biopsies and whole blood samples were collected from newly diagnosed patients at Jiangsu Cancer Hospital (JCH) between November 29, 2017 and March 18, 2020 for targeted sequencing using the 645 cancer gene panel (GP645). All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Jiangsu Cancer Hospital (No. 2016-062-06). All participants provided written informed consent.

# Library construction

Genomic DNA was extracted from tumor biopsies and whole blood. Libraries were constructed by the KAPA

Hyper DNA Library Prep Kit (KAPA Biosystem). Finally, dual-index libraries were cleaned up with purification beads (AxyPrep Fragment Select-I kit, Corning). The concentration and quality of these libraries were measured using the Qubit 3.0 system (Invitrogen) and Bioanalyzer 2100 (Agilent HS DNA Reagent, Agilent), respectively.

# Hybrid selection and ultra-deep next-generation sequencing (NGS)

5'-biotinylated probes for targeted sequencing covered exons, selected introns, MSI, MMR-related genes, and genetic genes in the 645 cancer-related genes, and were designed and synthesized by the Targetseq Enrichment Kit (Gensmile and iGeneTech, China) (Table S1) in a cohort of 41 patients. These libraries were hybridized to the *GP645* to capture targeted fragments according to the manufacturer's protocol. Then, these fragments were sequenced by the NovaSeq 6000 System (Illumina, USA), and the depth of sequencing was 1,000× for germline mutations and 5,000× for somatic mutations.

### Acquisition of mutation data

The Cancer Genome Atlas (TCGA) database of CRC was obtained from the Genomic Data Commons (GDC) website (https://portal.gdc.cancer.gov/) using the University of California Santa Cruz (UCSC) Xena platform (https:// xenabrowser.net/datapages/) (26), including CRC mutation data and clinical information, such as age, sex, AJCC-TNM stages, pathological stages, tumor stages, and survival outcomes. The statistical results of somatic mutations were visualized with the maftools software.

# Correlation analysis between TMB and overall survival (OS)

First, we screened the TCGA dataset for dbSNP and ExACannotated germline mutations using *GP645*. Meanwhile, we filtered out the germline mutations via blood cell mutations for the JCH dataset using the *GP645*. Then, we calculated the panel-TMB for each sample as the total amount of coding variants/exons length (38 million) based on the number of non-synonymous somatic mutations, including frameshift deletion mutation, in-frame deletion mutation, frameshift insertion mutation, in-frame insertion mutation, missense mutation, nonsense mutation, nonstop mutation, and silent mutation. Using median as the threshold, patients were divided into high TMB group and low TMB group (27).

# MSI status determined by NGS

Five microsatellite loci (BAT40, BAT26, BAT25, NR27, NR21) were used to identify MSI in the *GP645*. The number of microsatellite loci was counted for each of the JCH patients. Only insertions or deletions that increased or decreased the number of repeats were considered. Samples with 2 or more MSIs were identified as MSI-H, samples with one MSI were classified as MSI-low (MSI-L), and samples without MSI were classified as microsatellite stable (MSS). In the outcome analysis, MSI-L samples were grouped with MSS tumors. We further identified MMR status by functional loss mutation of MLH1, MSH2, MSH6, PMS1, PMS2, MSH3, and MLH3.

### Statistical analyses

All statistical analyses were performed using R software (Version 3.5.2). The Benjamini-Hochberg method was used to conduct multiple test adjustments for P values based on false discovery rate (FDR), and P value <0.05 was considered statistically significant. Differential analysis and normalization were mainly carried out using the "limma" package of R software (version 3.5.2). Kaplan-Meier analysis with the log-rank test or Cox regression model was performed using the "survival" package. Student's *t*-test was used for continuous variables, while  $\chi^2$  test was used for categorical variables.

### **Results**

### The mutation profiling of the GP645 in CRC

The somatic and germline mutation data of CRC patients from the JCH and TCGA datasets were processed as shown in *Figure 1* and their clinical information is presented in *Table 1*. The mean age was 58.32 years, and 12 (29.3%) women and 29 (70.7%) men were included. Utilizing maftools software, we classified these mutations into various groups and depicted mutation groups in box plots using various colors (*Figure 1*). We compared the mutation profiling of the JCH and TCGA datasets using the *GP645* developed by us and found that the most common type was missense mutation (*Figure 1*). Single nucleotide polymorphism occurred more frequently than deletion or





Table 1 Clinical data of CRC patients in the JCH (n=41) and TCGA (n=629) datasets in this research

Level	JCH dataset	TCGA dataset
Ν	41	629
Age [median (IQR)]	58.32	61.00
Gender (%)		
Female	12 (29.3)	335 (53.3)
Male	29 (70.7)	294 (46.7)
Status (%)		
Alive	NA	473 (75.2)
Dead	NA	124 (19.7)
Not reported	NA	32 (5.0)
Pathologic_T (%)		
T1	0 (0)	20 (3.2)
T2	3 (7.3)	109 (17.3)
Т3	11 (26.8)	427 (67.9)
Τ4	10 (24.3)	70 (10.6)
ТХ	17 (43.4)	1 (0.2)
Pathologic_N (%)		
NO	9 (21.9)	356 (56.6)
N1	10 (24.3)	151 (24.0)
N2	4 (9.7)	NA
NX	18 (43.9)	118 (18.6)
Pathologic_M (%)		
MO	12 (29.2)	466 (74.1)
M1	15 (36.5)	75 (11.9)
Μ	1 (2.4)	NA
MX	0 (31.7)	64 (10.2)
Pathologic_stage (%)		
Stage I	NA	109 (17.3)
Stage II	NA	229 (36.4)
Stage III	NA	181 (28.8)
Stage IV	NA	90 (14.3)

CRC, colorectal cancer; JCH, Jiangsu Cancer Hospital; TCGA, The Cancer Genome Atlas.

insertion (INS) (*Figure 1*), and C>T transition was the most common form of single nucleotide variants in both the JCH and TCGA datasets (*Figure 1*). The mutation categories

are shown in box plots. We further found that the mutation frequencies of APC, TP53, KRAS, PIK3CA, LRP1B, FAT3, FBXW7, ATM, KMT2D, SMAD4, SOX9, BRAF, SPTA1, AMER1, FAT1, ARID1A, ZFHX3, KMT2B, DYNC2H1, and PTPRT (Figure 1) were greater than 10% in both the JCH and TCGA datasets. Besides, the GP645 genes were distributed on 21 chromosomes (Figure S1). The cooccurrences and exclusive associations between mutated genes of the JCH and TCGA databases are shown in Figure 2A (TCGA dataset) and Figure 2B (JCH dataset).

Next, the pathways of the GP645 genes were investigated in both the JCH and TCGA datasets. As shown Figure 3, the genes in the GP645 were involved in 10 pathways in both the JCH and TCGA databases, including RTK-RAS, PI3K, cell cycle, NOTCH, WNT, Hippo, TGF-Beta, MYC, TP53, and NRF2, and, respectively, the number of genes with mutations in each category was 46, 20, 13, 12, 10, 7, 6, 6, 5, and 3 in TCGA dataset (Figure 3A) and the number of samples with gene mutations in each category was 401, 236, 49, 172, 474, 147, 145, 66, 366, and 23 in JCH dataset (Figure 3C). Meanwhile, the number of genes in each pathway was 45, 18, 12, 11, 10, 5, 6, 5, 4, and 2 in the JCH dataset (Figure 3B), and the number of samples with gene mutations in each category was 40, 36, 26, 40, 35, 33, 16, 35, 29, and 11 in TCGA dataset respectively (Figure 3D). These results suggested that the GP645 genes are primarily involved in important processes in tumor progression.

# The relationship between the panel-TMB database and TMB estimated by TCGA database

To evaluate whether the panel-TMB could reflect TMB estimated by WES (wTMB), we calculated the number of TMB per million bases for 531 CRC patients in TCGA dataset and analyzed the correlation between panel-TMB and wTMB. Non-synonymous mutations (NsMs) derived from WES and the *GP645* were relatively consistent in CRC (*Figure 4A*). Furthermore, panel-TMB and wTMB had a significant positive correlation (R=0.75, P<0.001, 95% CI: 0.75 to 0.82, *Figure 4B*). These results suggested that the panel-TMB of the *GP645* could represent wTMB and might be a potential predictor of prognostic stratification for CRC patients.

# Higher TMB estimated by the panel-TMB is associated with improved OS

We determined the median value as the threshold for panel-

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**Figure 2** The co-occurrences and exclusive associations between mutated genes of the JCH and TCGA databases. (A) The association between mutated genes in TCGA patients. (B) The association between mutated genes in the JCH patients. JCH, Jiangsu Cancer Hospital; TCGA, The Cancer Genome Atlas.



**Figure 3** The pathways of the *GP645* genes in both the JCH and TCGA datasets. (A,C) The numbers of genes with mutations in each category in TCGA and JCH cases. (B,D) The numbers of samples with gene mutations in each category in TCGA and JCH cases. JCH, Jiangsu Cancer Hospital; TCGA, The Cancer Genome Atlas.



**Figure 4** The relationship between panel-TMB and wTMB in TCGA dataset. (A) The distribution of NsMs was obtained by whole-exome sequencing (upper) for 531 CRC patients of TCGA dataset and a 645-gene panel (lower) for 41 CRC patients of the JCH dataset. (B) Panel-TMB and wTMB demonstrated a significant positive correlation in CRC patients. R, Spearman correlation coefficient. TMB, tumor mutation burden; wTMB, TMB by whole-exome sequencing; TCGA, The Cancer Genome Atlas; NsMs, non-synonymous mutations; CRC, colorectal cancer; JCH, Jiangsu Cancer Hospital.

TMB to assess the impact of panel-TMB on the OS of CRC. Kaplan-Meier survival analysis indicated that patients with a higher panel-TMB had improved OS in TCGA dataset (P=0.0062) (*Figure 5A*). Moreover, the low panel-TMB group had a longer 3-year restricted mean survival time (RMST) than the high panel-TMB group in TCGA dataset [2,944.97 (95% CI: 2,574 to 3,315) vs. 2,315.8 (95% CI: 1,926 to 2,705) days] (*Figure 5B*). Unfortunately, there was not enough clinical data to analyze the survival curve of panel-TMB in the JCH dataset.

### Panel-TMB subgroup analysis in the JCH dataset

We calculated the number of TMB per million bases for 41 samples of the JCH dataset and classified them into high-TMB and low-TMB groups (*Table 2, Figure 6*), and also classified MSI status and MMR gene mutations for each of the 41 samples. A total of 15 patients (34.2%) were classified into the high-TMB group, and 26 (65.7%) were classified into the low-TMB group (*Figure 6*). Only 3 patients (7.3%) were identified as having dMMR, and the 3 patients (7.3%)

were also classified as MSI-H (*Figure 6*). The proportion of patients with pMMR was about 92.6% (*Figure 6*). Moreover, we analyzed the MMR and MSI of the high-TMB and low-TMB groups in the JCH dataset. We found that 3 patients were identified as MSI-H and dMMR, and 2 of them had a high TMB value (*Table 2*). Furthermore, dMMR status was identified in 3 cases (7.3%) (*Table 3*), while MSI-H was identified in the same patients (7.3%), and high-TMB was identified in 15 cases (34.2%).

Compared with MMR cases, MSI had a positive predictive value (PPV) of 100.0% and a negative predictive value (NPV) of 100.0%, and TMB had a PPV of 13.6% and an NPV of 96.2%. Compared with TMB, MSI had a PPV of 66.6% and an NPV of 65.8%, and MMR had a PPV of 66.6% and an NPV of 65.8%. Compared with MSI cases, TMB had a PPV of 13.6% and an NPV of 96.2%, and MMR had a PPV of 100.0% and an NPV of 100.0%. These results showed that patients with dMMR were associated with MSI-H, and patients with low-TMB were associated with pMMR and MSS. Meanwhile, patients with high-TMB were not associated with MSI status and MMR status.



**Figure 5** OS analysis of tumor mutation burden as estimated by a 645 cancer-related gene panel (panel-TMB) in TCGA dataset. (A) Panel-TMB was associated with poor OS in TCGA dataset. (B) The RMST was determined by the "survRM2" package in R. OS, overall survival; TMB, tumor mutation burden; TCGA, The Cancer Genome Atlas; RMST, restricted mean survival time.

Table 2 Galculation of panel- 1101b, 10151, and 10101 11 patients in the JC11 Galaset								
Sample	TMB	TMB-group	MSI	MMR				
GS645-171130-01	6.9	L	MSS	pMMR				
GS645-171214-02	2.3	L	MSS	pMMR				
GS645-171226-01	0.26	L	MSS	pMMR				
GS645-180131-01	5.38	L	MSI-H	dMMR				
GS645-180319-04	5.38	L	MSI-L	pMMR				
GS645-180428-01	3.85	L	MSS	pMMR				
GS645-180606-01	4.62	L	MSS	pMMR				
GS645-180621-03	13.85	Н	MSS	pMMR				
GS645-180621-01	8.46	L	MSI-L	pMMR				
GS645-180711-03	11.54	Н	MSS	pMMR				
GS645-180711-03	10	Н	MSS	pMMR				
GS645-180716-02	5.38	L	MSS	pMMR				

Table 2 Calculation of panel-TMB, MSI, and MMR for 41 patients in the JCH dataset

Table 2 (continued)

 Table 2 (continued)

Sample	TMB	TMB-group	MSI	MMR
GS645-180815-01	11.54	Н	MSS	pMMR
GS645-180912-02	8.92	L	MSS	pMMR
GS645-181019-01	4.12	L	MSS	pMMR
GS645-181107-02	25.81	Н	MSS	pMMR
GS645-181112-02	5.62	L	MSS	pMMR
GS645-181128-02	72.76	Н	MSI-H	dMMR
GS645-181229-02	2.75	L	MSS	pMMR
GS645-190107-02	3.43	L	MSS	pMMR
GS645-190107-07	1.42	L	MSS	pMMR
GS645-190117-02	22.65	Н	MSS	pMMR
GS645-190129-04	24.02	Н	MSI-L	pMMR
GS645-190214-01	6.18	L	MSS	pMMR
GS645-190228-03	5.49	L	MSS	pMMR
GS645-190304-03	4.8	L	MSS	pMMR
GS645-190304-04	23.34	Н	MSS	pMMR
GS645-190313-03	10.13	Н	MSI-L	pMMR
GS645-190319-04	12.76	Н	MSS	pMMR
GS645-190322-05	2.06	L	MSS	pMMR
GS645-190329-03	30.2	Н	MSS	pMMR
GS645-190404-05	4.12	L	MSS	pMMR
GS645-190408-03	5.49	L	MSS	pMMR
GS645-190412-05	4.8	L	MSS	pMMR
GS645-190426-03	6.29	L	MSS	pMMR
GS645-190428-02	12.76	Н	MSS	pMMR
GS645-190620-01	5.49	L	MSS	pMMR
GS645-190628-04	4.12	L	MSS	pMMR
GS645-190729-05	85.8	Н	MSI-H	dMMR
GS645-200224-04	10.13	Н	MSS	pMMR
GS645-200318-07	8.81	L	MSS	pMMR

TMB, tumor mutation burden; MSI, microsatellite instability; MMR, mismatch repair; JCH, Jiangsu Cancer Hospital; L, low-TMB group; H, high-TMB group; MSI-H, high-MSI group; MSI-L, low-MSI group; MMS, MSI-stability group; pMMR, mismatch repair proficiency; dMMR, mismatch repair deficiency.

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Group	No. (%)	MSI-H (%)	MSI-L (%)	MSS (%)	PPV (%)	NPV (%)	dMMR (%)	pMMR (%)	PPV (%)	NPV (%)
TMB-H	15 (34.2)	2 (13.3)	2 (13.3)	11 (73.3)	66.6	65.8	2 (13.3)	13 (86.6)	66.6	65.8
TMB-L	26 (65.7)	1 (3.8)	2 (7.6)	23 (88.4)			1 (3.8)	25 (96.1)		
		MSI-H (%)	MSI-L (%)	MSS (%)	PPV (%)	NPV (%)	TMB-H (%)	TMB-L (%)	PPV (%)	NPV (%)
dMMR	3 (7.3)	3 (100.0)	0 (0.0)	0 (0.0)	100.0	100.0	2 (66.6)	1 (33.3)	13.3	96.2
pMMR	38 (92.6)	0 (0.0)	4 (10.5)	34 (89.4)			13 (34.2)	25 (65.7)		
		TMB-H (%)	TMB-L (%)	PPV (%)	NPV (%)	dMMR (%)	pMMR (%)	PPV (%)	NPV (%)	
MSI-H	3 (7.3)	2 (66.6)	1 (33.3)	13.3	96.2	3 (100.0)	0 (0.0)	100.0	100.0	
MSI-L	4 (9.7)	2 (50.0)	2 (50.0)			0 (0.0)	4 (100.0)			
MSS	34 (82.9)	11 (32.3)	23 (67.6)			0 (0.0)	34 (100.0)			

Figure 6 Classification of MSI by next-generation sequencing for 41 patients of the JCH dataset compared with MMR and TMB. TMB, tumor mutation burden; MMR, mismatch repair; JCH, Jiangsu Cancer Hospital; L, low-TMB group; H, high-TMB group; MSI, microsatellite instability; MSI-H, high-MSI group; MSI-L, low-MSI group; MMS, MSI-stability group; pMMR, mismatch repair proficiency; dMMR, mismatch repair deficiency; NPV, negative predictive value; PPV, positive predictive value.

Table 3 Mutations of MMR genes

Sampla	Somatic r	nutation	Germline mutation				
Sample	Gene	Gene Loci Gene		Loci	Frequency (%)		
GS645-180131-01	MSH6	p.y394	MLH3	p.N932Y	18.9		
GS645-181128-02	MSH6	p.R1068*	MSH3	p.K383Rfs*32	27.5		
GS645-190729-05	NA	NA	MSH3	p.K383Rfs*32	11.6		

MMR, mismatch repair.

### Discussion

To established a prognostic system for cancer patients, cancer-related genes have been used to develop cancer panels in lung cancer (28), malignant lymphoma (29), melanoma (30), gastric cancer (31), and other cancers (32). In non-small cell lung cancer (27), TMB quantified by a gene panel was significantly correlated with WES results (P=0.81), and panel/WES TMB could effectively predict the efficacy of immunotherapy in the high-TMB population. Meanwhile, using a cancer panel, the dynamic monitoring of ctDNA could indicate the efficacy of immunotherapy for gastric cancer, and showed potential clinical value in the analysis of drug resistance mechanisms and the prediction of immune-related side effects (31). In this study, to construct a prediction system for Chinese CRC patients, we

also developed a 2.1-Mb *GP645* which includes 5 MSI loci, 7 MMR genes, and 645 cancer-related genes distributed on 21 chromosomes. We found a positive correlation between the panel-TMB and the wTMB. These results suggest that the panel-TMB measured by the *GP645* is an accurate and clinically available tool for measuring TMB and represents the genomic instability in CRC patients, and can replace wTMB in evaluating prognosis. These results are in accordance with those in non-small cell lung cancer (33).

Furthermore, we performed a survival analysis of the panel-TMB measured by the *GP645* using TCGA database and found that high-TMB patients were strongly associated with poor OS in CRC. Previous studies confirmed that TMB measured by a cancer-related gene panel (CRGP) could be used for prognosis and to predict the benefits of immunotherapy (30-32). Thus, these findings indicated that

higher panel-TMB might be an adverse prognostic factor for CRC. However, the present study accounted for less than 40% of cases with high TMB in the JCH dataset.

Understanding genomic instability is also important to carcinogenesis and progression. MSI status has clear guiding significance for CRC patients of different stages. In addition, among CRC patients in China, the incidence of MSI-H/dMMR in right colon cancer is 20.5%, 9.2% in left colon cancer, and 5.1% in rectal cancer. Therefore, MSI/MMR should be tested for left/right colon cancer and rectal cancer (34). Both domestic and international guidelines and consensus recommend that all CRC patients be tested for MMR or MSI. This information is of great significance for patient prognosis, drug efficacy prediction and lynch syndrome screening (35). dMMR/MSI-H is an important molecular marker guiding immunotherapy in advanced patients. For early resectable CRC patients, dMMR/MSI-H patients generally have a good prognosis, but are less likely to benefit from 5-FU-based adjuvant chemotherapy (36). We identified MSI status and MMR genes which are markers of genomic instability to establish a prognostic system in CRC. Solid tumors with MSI-H/ dMMR are usually immunogenic and have extensive T-cell infiltration, and are highly responsive to ICIs. Patients with MSI-H benefited from bevacizumab, while only 5% of mCRC patients with MSI-H benefited from ICIs (8,37). The NICHE clinical trial showed that patients with dMMR benefited from ICIs for early-stage colon cancers, and that neoadjuvant immunotherapy may be a potential defined standard for treating CRC patients (38). In this study, the proportions of MSI-H (7.3%) and dMMR (7.3%) accounted for less than 10% of CRC, and the vast majority of MSI-H/ dMMR samples also had high TMB (PPV =66.6%). However, the converse was not true, as only 13.3% (PPV =13.3%) of samples with high TMB were classified as MSIhigh/dMMR. In addition, patients with low-TMB were associated with MSS/pMMR (96.2%), and these results are consistent with earlier studies (8,32,37).

In summary, we analyzed TMB, MSI/MMR, and gene mutations and found that these biomarkers for clinical detection can provide new classifications for precision medicine in CRC, predict the prognosis of patients with CRC, and improve treatment methods to improve the survival rate of patients with CRC. The panel-TMB measured by the *GP645* targeting ~2.1 Mb of MSI loci, MMR genes, and cancer-related genes could replace wTMB, and higher panel-TMB is associated with poor OS. MSI-H/dMMR and high-TMB was fairly common

but MSI-high was very uncommon in CRC. Panel-TMB and MSI/MMR might be potential prognostic indexes in Chinese CRC patients.

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Jiangsu Cancer Hospital (No. 2016-062-06). All participants provided written informed consent.

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Table S1 645 cancer-related gene list

		ARFRP1	C11orf30	CYP2D6	FANCD2	GSTM1	JUN	MSH6	PDGFRA	RAD52	SMARCD1	TSC1
ABCCCMACPNBPAMNBPAMNBPAMNBPAMNBPAMNBPAMNBAM <td></td> <td>ABCB1</td> <td>C8orf34</td> <td>CYP4B1</td> <td>FANCE</td> <td>GSTP1</td> <td>KAT6A</td> <td>MSI1</td> <td>PDGFRB</td> <td>RAD54B</td> <td>SMO</td> <td>TSC2</td>		ABCB1	C8orf34	CYP4B1	FANCE	GSTP1	KAT6A	MSI1	PDGFRB	RAD54B	SMO	TSC2
ABACCARLONCARLONHANCO <t< td=""><td></td><td>ABCC3</td><td>CALR</td><td>CYSLTR2</td><td>FANCF</td><td>H3F3A</td><td>KDM3B</td><td>MSI2</td><td>PDK1</td><td>RAD54L</td><td>SMYD3</td><td>TSHR</td></t<>		ABCC3	CALR	CYSLTR2	FANCF	H3F3A	KDM3B	MSI2	PDK1	RAD54L	SMYD3	TSHR
ALDCAURDCAURDFAUNCHANCLHANCLHANCLKAUMAK		ABL1	CARD11	DAXX	FANCG	H3F3B	KDM5A	MST1	PDPK1	RAF1	SNCAIP	TSHZ2
ACMCPCNSPDOMEAMACSMAC		ABL2	CARM1	DCUN1D1	FANCI	H3F3C	KDM5C	MST1R	PGR	RANBP2	SOCS1	TSHZ3
ACM02CARSCARCEFARCERANCE		ACVR1	CASP7	DDR1	FANCL	HAS3	KDM6A	MTAP	PHB	RARA	SOD2	TTF1
ACTCBLCHARCHARMACHMACHMACHMITAMMINGCOMEMSOUTOSOUTOSOUTOANTACBLDESMATMATMATMATMITAMMINGCORECOLSOUTOTOTALANTACCMUDUMJFRAMMISTIMEMATMIRAMRURAMRURAMRURAMSOUTO </td <td></td> <td>ACVR1B</td> <td>CASP8</td> <td>DDR2</td> <td>FANCM</td> <td>HDAC1</td> <td>KDR</td> <td>MTHFR</td> <td>PHOX2B</td> <td>RASA1</td> <td>SOS1</td> <td>TXN</td>		ACVR1B	CASP8	DDR2	FANCM	HDAC1	KDR	MTHFR	PHOX2B	RASA1	SOS1	TXN
M71CRUECRUEM73M32M33 <th< td=""><td></td><td>AGO2</td><td>CBFB</td><td>DDX43</td><td>FAS</td><td>HDAC6</td><td>KEAP1</td><td>MTOR</td><td>PIK3C2B</td><td>RB1</td><td>SOX10</td><td>TXNRD2</td></th<>		AGO2	CBFB	DDX43	FAS	HDAC6	KEAP1	MTOR	PIK3C2B	RB1	SOX10	TXNRD2
ANT2CENBDRAWFARSHIST1HEDKUTMUTMPKNCDPKNCDRECULSO/L2PVNCDANT3CCM00DMMTAFCBNANIST1HSBKLALMNC0PKNCDRECSO/L2UT1AALX12CCM00DMMTAFCGRANIST1HSBKLALMYCDPKNCDRELSO/L2UT1AALX12CCM00DMMTAFCGRANIST1HSBKLALMYCDPKNCBRFM20SPRCDULF1AAMRE1CCM0DMMTAFCGRANIST1HSBKLATMYCDPKNCBRFM20SPRCDULF1AAMRE1CCM0DMTAFCF1PNIST1HSBKLATSMYCDPKNCBRHADSFLATVEGRAAPCCD24DV54HFGF1PNIST1HSBKLATSMYCDPKNCBRHADSFLATVEGRAAPRA1CD26ADU54HFGF1PNIST1HSBLKASMCOBPKATRTTTSTLATVEGRAAPRA1CD26ADU54HFGF3NIST1HSBLKASMCOBPKATRTTTSTLATVEGRAAPRA1CD26AFGF4RHSTHSBLKASNODAPLATRTTTSTLATVEGRAAPRA1CD26AFGF3RHSTHSBLKASNODAPLATRTTTSTLATVEGRAAPRA1CD26AFGF4RHSTHSBLKASNODAPLATRTTTSTLATVEGRAAPRA1CD26AFGF4RHSTHSBLKASNODAPLATRTTTSTLATV		AKT1	CBL	DICER1	FAT1	HGF	KEL	MTRR	PIK3C2G	RBM10	SOX17	TYMS
ALXCOMUMARCHFEXILYHISTINGNKIATMARCMIRCOMRECOLLSUMAUZAF1ALX718COMEDMITANFCGRAHISTINGNKIATMIRCOMPICGORETSPAPULTAF1AMRDICOZ2DMITANFCGRAHISTINGNKIAT2MIRCOPICGORETSPAPULTAF1AMRDICOZ2DMITANFAF10HISTINGNKIAT20MIRCOPICBARESTPICBA <td></td> <td>AKT2</td> <td>CBR3</td> <td>DIS3</td> <td>FAT3</td> <td>HIST1H1C</td> <td>KIT</td> <td>MUTYH</td> <td>PIK3C3</td> <td>RECQL</td> <td>SOX2</td> <td>TYRO3</td>		AKT2	CBR3	DIS3	FAT3	HIST1H1C	KIT	MUTYH	PIK3C3	RECQL	SOX2	TYRO3
ALKCORREDMATTFOGREAMISTIMEKUTLEAMYCLPICKCDRELS0/39UCT/MIALCX122CCR03DMITTAFOGREAMISTIMEKUTLEAMYCLPICKCDRETSPENDUGT/MIAMRD11CC22DOTLFOF10MISTIMEKUTLEAMYCLPICKCDPIRADESPENDUFF1APRC1CC227DOTLFOF10MISTIMEKUTLEAMYCDPICKSD<		AKT3	CCND1	DNAJB1	FBXW7	HIST1H2BD	KLF4	MXI1	PIK3CA	RECQL4	SOX4	U2AF1
ALMERIECOUNCICOUNCIACOUNCIACOUNCIAHISTINGEKNTCAKNTCAMYACMYACOREVACSPENUSETINGANNEREICOZZEDOTILFOFI2HISTINGEKNTCAKNTCAKNTCARNBDESPETAIVEGASAPCKICOZZEDORADFOFI2HISTINGEKNTCAKNTCANENSERIBETASPETAIVEGASAPCKICOZZEDORADDOSANFOFI2HISTINGEKNTCANENSARICTASPETAIVEGASAPRICACOZZEDOSANFOFI2HISTINGEKNTSNNCOAPLATRITASTATAVIESCIAPRICACOZANEEDFOFI2HISTINGELUKINEGAPPLATRITASTATAVIESCIAPRICACOZANEEDFOFI2HISTINGELUKINEGAPPLATRITASTATAVIESCIAPRICACOZANEEDFOFI2HISTINGLUKINEGAPPLATRITANITAVIESCIAPRICACOZANEEDFOFI2HISTINGLUKINEGAPPLATRITANITAVIESCIAPRICACOZANEECFOFI2HISTINGLUKINEGAPPLATRITANITANITANITAAPRICACOZANEECFOFI2HISTINGLUKINITANITARITANITANITANITANITANITANITANITANITANITANITANITANITANITANITANITANITANITA </td <td></td> <td>ALK</td> <td>CCND2</td> <td>DNMT1</td> <td>FCGR2A</td> <td>HIST1H3A</td> <td>KLHL6</td> <td>MYC</td> <td>PIK3CB</td> <td>REL</td> <td>SOX9</td> <td>UGT1A1</td>		ALK	CCND2	DNMT1	FCGR2A	HIST1H3A	KLHL6	MYC	PIK3CB	REL	SOX9	UGT1A1
MRERICONETCONETCHATTFORTOMESTIMEDMATCAMYCMPRACOPRACOSPREDLMPTANREDICOLTILFGF14INSTIMEMATCAMYCBBPRACESPREDLPPTAPCCOLZICPQDCPQDRF14MESTIMEKMTCAMYCBBPRACESPREDCPPTAPECCOLZICPQDCPG14MESTIMEKMTSTMYCBIPRACESPREDCPTAVECALAPRCDDECPG14CPTTMESTIMEKMTSTNEOAPLUCRHTASTACEWESCILTARIDIACDD2CPG75FGF4MESTIMELATS2NCCATPLUCRHTASTATAWESCILTARIDIACDD2CPG76FGF7MESTIMELATS2NCCATPLUCRHTASTATAWESCILTARIDIACDD2CPG77FGF7MESTIMELATS2NCCATPLUCRHTASTATAWITTARIDIACDD2CPG77FGF7MESTIMELATS1NCCATPLUCRHTASTATAWITTARIDIACDD1FGF7MESTIMELATS1NCCATPLUCRHTASTATAWITTARIDIACDD1FGF7MESTIMELATS1NCCATPLUCRHTASTATAWITTARIDIACDD1FGF7MESTIMELATS1NCCATPLUCRHTASTATAWITTARIDIACDD1FGF7MESTIMELATS1NCCATPLUCRHTASTATANCTA <t< td=""><td></td><td>ALOX12B</td><td>CCND3</td><td>DNMT3A</td><td>FCGR3A</td><td>HIST1H3B</td><td>KMT2A</td><td>MYCL</td><td>PIK3CD</td><td>RET</td><td>SPEN</td><td>UGT1A4</td></t<>		ALOX12B	CCND3	DNMT3A	FCGR3A	HIST1H3B	KMT2A	MYCL	PIK3CD	RET	SPEN	UGT1A4
ANRIDITCO22DUT1LFGF12MISTIMADMMT2CMVD3BPRISITPMIRIDPMIRIDITPMIRIDITAPCCO224DPG70RGF4MISTIMATMVT2DPMICR2BRHEDSPTALVPCAAPRCO2EAPDUSA4FGF23MISTIMATKMT2DMVC3DPMICR3HACDSFR2VTCN1APALACO2EAPDUSA4FGF3MISTIMATLMT3MC0A0PLL2RUT0STA74WFSC1APALDACD270AEEDFGF8MISTIMATLMT3MC0A1PLL2ROS1STA74WFSC1APALDACD770AEEDFGF8MISTIMATLMT3MC0A1PLL2ROS1STA74WFSC1APALDACD770AEGF17FGF8MISTMALMT3MC01PLC2ROS1STA74WFSC1APALDACD770EGF17FGF8MISTMALMT3MC01PLC2ROS1STA74WFSC1ASNSCDC42EGF17FGF8MISTMALMT0NFE1PLC2ROS1STA74WFSC1ASNSCDC42EGF17FGF8MISTMALMT0NFE1PLC2ROS1STA74WFSC1ASNSCDC42EGF17FGF8MISTMALMT0NFE1PLC2ROS1STA74WFSC1ASNSCDC42EGF17FGF8MISTMALMT0NFE1PLC2ROS1STA74WFSC1ASNSCDC42EGF17FGF8MISTMALMT0NFE1PLC2 </td <td></td> <td>AMER1</td> <td>CCNE1</td> <td>DNMT3B</td> <td>FGF10</td> <td>HIST1H3C</td> <td>KMT2B</td> <td>MYCN</td> <td>PIK3CG</td> <td>RFWD2</td> <td>SPOP</td> <td>UMPS</td>		AMER1	CCNE1	DNMT3B	FGF10	HIST1H3C	KMT2B	MYCN	PIK3CG	RFWD2	SPOP	UMPS
APCCO274DPVDFGF14HISTHAGEMAT2DMYO3BEPRAREPRARESPA14VEGAAPACCO276DOSAMRGF29HISTHAGENASTENNYO3BEPRARESPACVTCNAPACCO4MDYNC2H1FGF29HISTHAGENASTENNUCOAPLATATTTSTAG2VHASCHAPADECO5MEEGAGRHISTHAGELIATS1NCOA3PLATATTTSTAG2VHASCHAPADD8CO778EEGFGR4HISTHAGELIAK1NEGB1PAAIP1PSSKA4STAT34VHT1APADD8CO778EGR7RGR78HIST2H3CLIAK1NEGB1PAAIP1PSSKA4STAT34VHT1APADD2CO738EGR7RGR78HIST2H3CLIAK1NEGB1PAAIC1RAGC2STAT34VHT1APAD2CO738EGR7RGR78HIST2H3CLIAK8NEL1PABC1RAGC3STAT41VKT1APAD2CO738EGR7RGR78HIST2H3CLIAK8NEL1PABC1RAGC3STAT41VKT1APAD3CO738EGR7RGR78HIST3H3LIA<1		ANKRD11	CD22	DOT1L	FGF12	HIST1H3D	KMT2C	MYD88	PIK3R1	RHBDF2	SPRED1	UPF1
PENI         CO278         DROSHA         FRIP         HISTINGF         KNSTIN         MYODI         PRIAB         RHA         SPAC         VHL           AR         COBEAP         DUS-4         RF33         MISTINGF         KRAS         NBN         PRIAT         RTIC         STAG2         WISCI           ARIDIA         COTO         E2P3         RGF4         HISTINSI         LATS2         NCCAI         PLCQ2         RWF4         STAT3         WHSCILT           ARIDIA         COTO         E2P3         RGF4         HISTINSI         LATS2         NCCAI         PLCQ2         RWF4         STAT3         WTTN           ARIDIA         COA         EGFR         RGFR1         HISTINSI         LATS         NPL1         PMS1         RPS0         STAT4         WTTN           ASM2         COCA         EGFR         RGFR1         HISTINSI         LATS         NPL2         PADD         RRAS         STAT4         WTTN           ASM1         COCA         EGFR         RGFR1         HIAA         LATS         NADD         RPL2         RADD         STAT4         XPL0           ASM1         COCA         EPAS         RLT         HIAAB         LALD         NEDD		APC	CD274	DPYD	FGF14	HIST1H3E	KMT2D	МҮОЗВ	PIK3R2	RHEB	SPTA1	VEGFA
AR         COBEAP         DUSPL         PGF23         HISTHAG         KRAS         NBN         PIMT         RICTOR         SRF2         VTCN1           ARIDA         COTO         EZ7         FGF4         HISTHAD         LATS         RCCA2         RIFL         STATA         WHSCLL           ARIDA         COT79         EEGL         FGF4         HISTHAD         LUA         NDRG1         PLC22         RUFL         STATA         WHSCLL           ARIDA         COT79         EEGL7         FGFR1         HISTHAD         LUA         NDRG1         PLA2         RDS1         STATA         WTT           ARIDA         COC73         EEGL7         FGFR3         HATA         LIPL8         NEL1         PMS2         RPG70         STATA         VTT           ASIL2         COC13         EFL4P         PGFR3         HATA         LIPL8         NFE12         POL1         RRAC         STAT3         XAPC1           ASIL2         COC14         EFL4P         PLA         HATA         LIPL4         NFE12         POL1         RRAC         STAT3         XAPC1           ASIL4         COC14         EFL4P         PLA         HATA         LIPL4         NRAC         NRAC		APEX1	CD276	DROSHA	FGF19	HIST1H3F	KNSTRN	MYOD1	PIK3R3	RHOA	SRC	VHL
ARAF         CD44         DYNC2H1         PGF3         HISTIH3H         LATS1         NCOA3         PLAT         RIT         STAG2         WHSC1           ARIDIA         CO70         EE73         FGF4         HISTIH3J         LATS2         NCOR1         PLC2         RIF43         STAT4         WHSC1           ARID2         CO73B         EGF1         FGFR         HIST1H3J         LAG         NRG1         PMAP1         RPS6K4         STAT3B         WUT1           ARID3         CO730         EGFA         FGFR1         HIST3H3         LMO1         NF1         PMS2         RPFGR         STAT3B         WUT1           ASNL1         COC42         EFTAX         FGFR3         HIST3H3         LMO1         NF1         PMS2         RFTG         RFAG         STAT3B         WUT1           ASNL1         COC42         EFTA         HCHA         LZT11         NK24         PMR0         RRAS         STAG         XPC1           ATT         CAK8         EPA31         FLT1         HK14         LZT11         NK24         POA1         RMR1         SUT2         XRC2           ATR         COK8         EPA31         FLT1         HK14         NK24         NK44		AR	CD3EAP	DUSP4	FGF23	HIST1H3G	KRAS	NBN	PIM1	RICTOR	SRSF2	VTCN1
ARIDIA         CD70         E2F3         FGF4         HISTIHAJ         LATS2         NCORI         PLC2         RNF43         STAT3         WHSCH.T           ARID2         CD79A         EED         FGFR         HISTIHAJ         LIG4         NDR01         PLX2         ROS1         STAT4         WISP3           ARID50         CD74         EED         FGFR1         HIST2H3C         LINKI         NERB1         PMAIP         RPS6K42         STAT4         WISP3           ARID53         CDA12         EIF1AX         FGFR2         HIST2H3D         LINRI         NE22         PNRC1         RPASK22         STAT3         WIT1           ASNL1         CDC12         EIF4A2         FGFR4         HLA-A         LRN         NFR2         PNRC1         RRAS2         STAT9         XPC1           ASNL2         CDK12         EIF3         FLCN         HAMAR         LTN         NFEBA         POL1         RRAS2         STAT9         XPC21           ATR         CDK4         EP300         FLT4         HRF1A         LZT1         NCO21         PPAR0         RRF1         STAT9         XPC21           AURK6         CDK13         FLT4         HRAS1         MAD21         NOT101		ARAF	CD44	DYNC2H1	FGF3	HIST1H3H	LATS1	NCOA3	PLAT	RIT1	STAG2	WHSC1
ARID18         CD734         EED         FGF8         HIST1HSJ         LIG4         NDRG1         PLX2         ROS1         STAT4         WISP3           ARID2         CD738         EGFL7         FGFR1         HIST3HC         LIMK1         NEGR1         PMAP1         RPS6KJ8         STATA         WTT1           ARID62         CD738         EGFR1         FGFR3         HIST3H0         LIN28         NEL1         PMS2         RPTC0         STK11         XAP           ASNS         CDC73         EIF4A2         FGFR3         HLA-A         LRP18         NF2         PNRC1         RRAGC         STK19         XAP           ASXL1         CDC73         EIF4A2         FGFR3         HLA-A         LRP18         NF2         PNRC1         RRAGC         STK19         XAPC           ASXL1         CDK13         EF442         FGFR3         FLC9         HNF1A         LTR1         NK02-1         PON1         RM11         SUZ12         XRC21           ATR         CDK8         EFAS1         FLT3         HK281         MAT         NK02-1         PPR21A         RUK11         TAP2         ZBTS2           AURA         CDK182         EFAS1         FC13         HK281		ARID1A	CD70	E2F3	FGF4	HIST1H3I	LATS2	NCOR1	PLCG2	RNF43	STAT3	WHSC1L1
ARID2         CD73B         EGFL7         FGFR1         HIST2H3C         LIMK1         NEGR1         PMAIP1         RPSKA4         STAT3A         WTT1           ABNS         CDCA         EGFR         FGFR4         HIST3H3         LMO1         NF1         PMS2         RPT0R         STAT3B         WWTR1           ASNL         CDC73         EIFAX         FGFR4         HIST3H3         LMO1         NF1         PMS2         RPT0R         STAT3B         WWTR1           ASNL         CDC13         EIFAX         FGFR4         HIA-A         LRT         NFE2L2         POLD1         RRAGC         STK49         XPC02           ATT         CDK12         ELF3         FLON         HMMR         LYN         NFRB4         POLE         RRAGC         STK49         XPC02           ATT         CDK3         EFA31         FL13         HOK13         LTN         NAF1         NOTCH1         PPA10         RRAT         STAT3         XRC02           ATTR         CDK3         EFA43         FOX1         HSD313         MAF1         NOTCH1         PPA27A         RUX1T         TAP2         ZST22           AURRA         CDK14         EPHA3         FOX1         HSD34         MA		ARID1B	CD79A	EED	FGF6	HIST1H3J	LIG4	NDRG1	PLK2	ROS1	STAT4	WISP3
ARIDEB         CDA         EGFR         FGFR2         HIST2H3D         LIN28B         NEL1         PMS1         RPSCR2         STAT3B         WUTT1           ASNL1         CDC42         EIFLAX         FGFR3         HIST2H3D         LNO1         NF1         PMS2         PFTOR         STK10         XPC           ASNL1         CDC473         EIFLAX         FGFR4         HLA-A         LIN         NF2         PINC1         RFASS         STK10         XPC1           ASNL1         CDK1         EIFLA         FL         HH         HLA-A         LIN         NFKBIA         POLE         RFASS         STK40         XPC1           ATR         CDK4         EPAS1         FLT1         HMF1A         LZTR1         NCX2-1         PON1         RFM1         SVX         XPC2           ATR         CDK6         EPAM1         FLT1         HMF3         MAGI2         NCS3-1         PDN1         RFL1         TAF1         YZ           AURKA         CDKN1B         EPHA3         FOX1         HSP3A1         MAP2K1         NOT0+2         PPP2R2         RUWX1T1         TAP2         ZBT2           AXNN         CDKN2A         EPHA3         FOX1         HSP3A1         MAP2K1 </td <td></td> <td>ARID2</td> <td>CD79B</td> <td>EGFL7</td> <td>FGFR1</td> <td>HIST2H3C</td> <td>LIMK1</td> <td>NEGR1</td> <td>PMAIP1</td> <td>RPS6KA4</td> <td>STAT5A</td> <td>WT1</td>		ARID2	CD79B	EGFL7	FGFR1	HIST2H3C	LIMK1	NEGR1	PMAIP1	RPS6KA4	STAT5A	WT1
SNNS         CDC42         EIF IAX         FGFR9         HIST3H2         LMO1         NF1         PMS2         RPTOR         STK11         XAP           ASXL1         CDC73         EIF4A2         FGFR4         HLA-A         LRP1B         NF2         PNRC1         RRAGC         STK19         XPC           ASXL2         CDH1         EIF4         FL         HLA-A         LRN         NF22L         POLE         RRAS         STK40         XPC1           ATTC         CDK4         EF430         FL1         HNF1A         LZTR1         NK22-1         PONT         RRM1         SUZ1         XRCC1           ATTR         CDK6         EPAS1         FL13         HOXB13         MAF         NK23-1         PPARG         RSF1         SYK         XRCC2           ATTR         CDK6         EPAS1         FL13         HAB3         MAF         NK23-1         PPARG         RSF1         SYK         XRC23           AURK8         CDKR1A         EPHA2         FOX1         HSB3B1         MAP2K1         NOTC14         PPAR2         RKRA         TBK2         ZBT2           AURK4         CDKR1A         EPHA3         FOX1         HSD3B1         MAP2K1         NOTC14		ARID5B	CDA	EGFR	FGFR2	HIST2H3D	LIN28B	NEIL1	PMS1	RPS6KB2	STAT5B	WWTR1
SXL1         CDC73         EIFA42         FGFR4         HLA-A         LIPIB         NF2         PNRC1         RRAGC         STN:49         XPC1           ASXL2         CDH1         EF4E         FH         HLA-B         LTK         NFE2L2         POLD1         RRAS         STN:40         XPC1           ATC         CDK12         ELT3         FLCN         HMRTA         LYN         NFKBIA         POLE         RRAS         SUL2         XRCC1           ATR         CDK6         EP4S1         FLT3         HNC813         MAF         NKX3-1         PPARG         RSF1         SYK         XCC23           ATR         CDK8         EP4S1         FLT3         HNC813         MAE         NKX3-1         PPARG         RDX1         TAP1         YAP1           AURK8         CDKN18         EP4A3         FOX1         HSD81         MALT         NOTCH3         PP4R2         RUNX111         TAP2         ZETS1           AURK         CDKN2A         EP4A5         FOX1         HSD81         MAP2K1         NOTCH3         PP4R2         RUNX111         TAP2         ZETS1           AUR         CDKN2A         EP4A5         FOX1         HSD81         MAP3K1         ND71		ASNS	CDC42	EIF1AX	FGFR3	HIST3H3	LMO1	NF1	PMS2	RPTOR	STK11	XIAP
ASXL2         CDH1         EF4E         FH         HLA-8         LTK         NFE2L2         POLD         RRAS         STM40         XPC1           ATIC         CDK12         ELF3         FLCN         HMMR         LYN         NFE2L2         POLD         RRAS2         SUFU         XRCC1           ATM         CDK4         EP30         FLT1         HNFLA         LZTR1         NKX2-1         PON1         RRM1         SUZ12         XRCC2           ATR         CDK8         EPCAM         FLT3         HOXB13         MAF         NKX3-1         PPARG         RFL1         TAP1         YAP1           AURKA         CDKN14         EPHA2         FOXA1         HSD3B1         MAL1         NOTCH2         PP2R2R         RUNX1         TAP1         YEP1           AURKA         CDKN18         EPHA3         FOX1         HSD3B1         MAP2K1         NOTCH2         PP2R2R         RUNX1         TAP2<		ASXL1	CDC73	FIF4A2	FGFR4	HI A-A	I RP1R	NF2	PNRC1	RRAGC	STK19	XPC
ATC         CDM1         ELGN         HIMMR         LVN         INREIA         POLE         RPASE         SUUU         XRCC1           ATM         CDM4         EP300         FLT1         HIMMR         LZTR1         NKX2-1         PON1         RRAS         SUUU         XRCC2           ATR         CDK8         EPAS1         FLT3         HKB13         MAF         NKX2-1         PPARG         RSF1         SYK         XRC23           ATR         CDK8         EPAS1         FLT4         HRAS         MAGI2         NOS2         PPARG         RSF1         SYK         XRC3           AURK8         CDKN18         EPH43         FOX11         HSD381         MAF1         NOTCH1         PPP2R1A         RUNX11T1         TAP1         YES1           AURK8         CDKN18         EPH43         FOX11         HSD381         MAF1         NOTCH3         PP4R2         RXRA         TBX3         ZHF3           AXIN2         CDKN28         EPH43         FOX11         HSD381         MAF2K1         NOTCH3         PP4R2         RXRA         TBX3         ZHF3           AXIN2         CDKN28         EPH44         FSH7         ICN14         MAP3K1         NOT14         PDF41<		ASXL2	CDH1	FIF4F	FH	HLA-B	ITK	NFF2L2	POLD1	RRAS	STK40	XPO1
ATM         CDK4         EP300         FLT         INDUX         INDUX </td <td></td> <td>ATIC</td> <td>CDK12</td> <td>ELE3</td> <td>FLCN</td> <td>HMMR</td> <td></td> <td>NEKRIA</td> <td>POLE</td> <td>RRAS2</td> <td>SUEL</td> <td>XBCC1</td>		ATIC	CDK12	ELE3	FLCN	HMMR		NEKRIA	POLE	RRAS2	SUEL	XBCC1
ATR         CDK6         EP35         FLT         IM         Left         IM         Im <td></td> <td>ΔΤΜ</td> <td></td> <td>EP300</td> <td>FIT1</td> <td>HNIF1A</td> <td>1 7TR1</td> <td>NKX2-1</td> <td>PON1</td> <td>RRM1</td> <td>SU712</td> <td>XBCC2</td>		ΔΤΜ		EP300	FIT1	HNIF1A	1 7TR1	NKX2-1	PON1	RRM1	SU712	XBCC2
ATTR         CLORAB         EVECAM         FLIG         HRAD         MAGI2         NOS2         PPINID         RTEL1         TAFF         YAP1           AURKA         CDKN1A         EPHA2         FOXA1         HSD3B1         MAGI2         NOS2         PPINID         RTEL1         TAFF         YAP1           AURKB         CDKN1A         EPHA3         FOXL2         HSP90AA1         MAGI2         NOTCH2         PPP2R2A         RUNX1T         TAP1         YES1           AURKB         CDKN2B         EPHA3         FOXL2         HSP90A1         MAP2K1         NOTCH2         PPP2R2         RUNA         TAS3         ZHF33           AXIN         CDKN2B         EPHA5         FOXD1         HSP81         MAP2K1         NOTCH3         PPPAR2         RVRA         TAS3         ZHF33           AXIN         CDKN2B         EPHB1         FRS2         ID3         MAP2K1         NOTCH4         PPP6R2         RVRA         TEX3         ZHF73           AXIN         CDKN2B         EPHB4         FSHR         IDH1         MAP3K1         NDO1         PRIX4         SDH0         TEX         ZMF73           BABM1         CENPA         ERBB3         FVN         INGR1         MAPX4		ATR	CDK6	EPAS1	FLT3	HOXB13	ΜΔΕ	NKX3-1	PPARG	RSF1	SVK	XRCC3
AURKA         COURT         EP-MAP         FLA*         INAC         MAURA         COURT         FINITE         INAC			CDK8	EPCAM	FLTA	HEAS	MAGI2				TAE1	
NUMA         CLANITA         FLOATA         INDUCT         INDUCT <thinduct< th=""> <thinduct< th=""> <thinduct< th=""></thinduct<></thinduct<></thinduct<>		ΔΠΡΚΔ			FOXA1	HSD3B1	ΜΑΔΙΤ1	NOTCH1				VES1
AXIM1         CORNAZ         EFNAS         FOXEL         Hols OSM         INTEXT         HOLGLE         HOLGLE </td <td></td> <td>AUIRKB</td> <td></td> <td>EDHA3</td> <td></td> <td>HSPONAAI</td> <td></td> <td>NOTCH2</td> <td>DDD2R2A</td> <td>RUNX1T1</td> <td></td> <td>ZBTB2</td>		AUIRKB		EDHA3		HSPONAAI		NOTCH2	DDD2R2A	RUNX1T1		ZBTB2
AXINU         CUMULA         FUNJ			CDKNDA	EPHAS	FOXL2	HORDI	MAP2KI	NOTCH2			TAF2	75472
AXL         CUNN2C         EPHRA         FUSSE         INSPERS         INSPERS <thinspers< th=""> <thinspers< <="" td=""><td></td><td></td><td></td><td>EPHAJ</td><td>FOXO1</td><td></td><td></td><td>NOTCHA</td><td></td><td></td><td></td><td>ZFNA3</td></thinspers<></thinspers<>				EPHAJ	FOXO1			NOTCHA				ZFNA3
ALL         CLANCE         EPHBJ         FR32         IDS         IMAPSA         INMINIT         FPMINIT         SUMA         TOPS         2XM73           B2M         CEBPA         EPHB4         FSHR         IDH1         MAPSATIS         NQO1         PRDM14         SDHAFZ         TCF7L2           BABAMI         CENPA         ERBB2         FUBP1         IDH2         MAPSATIS         NQO1         PREX2         SDHB         TDG           BARAMI         CHD2         ERBB3         FVN         IFNGR1         MAPKA         NRASS         PRKA1         SDHC         TEK           BARD1         CHD4         ERBB4         GAB2         IGF1         MAPKA1         NRAS         PRKA1         SDHA         TER           BCL10         CHEK2         ERCC2         GALNT12         IGF2         MAX         NTHL1         PRKD1         SEM3C         TERT           BCL211         CREBP         ERCC4         GATA1         IKBKE         MC1         NTRK3         PTCH1         SETD3         TGFB1           BCL211         CRL         ERCC5         GATA4         IL1A         MDM4         NUP2         PTN         SETD8         TIPAP           BCD8         CSF1R<			CDKN2D			100320					TOER	ZNF217
DEM         CEDPA         EPRB4         FORM         DR11         IMAPSA'S         NGU1         PREX2         SDMB         TOG           BABAM1         CENPA         ERBB2         FUBP1         IDH2         MAPSA'S1         NOO1         PREX2         SDHB         TDG           BAR1         CHD2         ERBB3         FYN         IFNGF1         MAPK3         NSD1         PRKA11         SDHA         TCF           BAR1         CHD4         ERBB4         GAB2         IGF1         MAPK3         NSD1         PRKA11         SDHA         TERC           BC10         CHEK2         ERCC2         GALNT12         IGF2         MAX         NTH1         PRK0         SEM32         TERT           BC11         CHEK2         ERCC3         GATA1         IKBKE         MCL1         NTRK1         PRK0         SEN3         TGFB1           BC1211         CRKL         ERCC4         GATA         ILA         MDC1         NTRK2         PRS8         SEN3         TGFB1           BC1211         CRKL         ERC5         GATA         ILA         MDC1         NTR3         PTCH1         SETD2         TGFB1           BC2211         CRKL         ERG5         GA		ROM	CDRN2C		FROZ		MAPSKI			SDHAED		ZNF703
BADMINCEUVAENB22FUBP1IDR2IMAPSILIANGU2FIREZSUTBTUSBAP1CHD2ERBB3FYNIFNGR1MAPK1NRASPRKAA1SDHCTEKBARD1CHD4ERBB4GAB2IGF1MAPK3NSD1PRKAA11SDHDTERCBBC3CHEK1ERCC1GABRA6IGF1MAPK3NSD1PRKA11ASDHDTERCBC10CHEK2ERCC2GALNT12IGF2MAXNTHL1PRKDCSESN1TET1BC12CICERCC3GATA1IKBKEMCL1NTRK1PRKDCSESN2TET2BC1211CRKLERCC4GATA2IKZF1MDC1NTRK3PTCH1SETD2TGFB1BC122CRLF2ERFGATA4IL1AMDM4NUF2PTENSETD8TGFBR2BC16CSDE1ERGGATA6IL4MECOMNUP33PTP4A1SF3B1TIPARPBC0RCSF1RERRF11GEHIL8MEF2BP2RV8PTPDSH2B3TMEM127BCR1CTLA4ETV1GL1INHAMEN1PAK1PTPOSH2D3TMFM127BCR3CTLFESR2GID4INHAMETPAK3PTPRSH0C2TNFABCR4CTLNETV1GL1INHAMETPAK7PTPRSH01TMFA93BIRC3CTLA4ETV1GL1INHAMETPAK7PTPRSH02TMFA193BIRC4 <td></td> <td></td> <td></td> <td></td> <td></td> <td>ו חעו</td> <td>MAPSK 13</td> <td>NQOT</td> <td></td> <td>SDHAF2</td> <td></td> <td></td>						ו חעו	MAPSK 13	NQOT		SDHAF2		
BAPTCHU2EHBS3FTNIPNGH1MAPK1NPASPHKA11SDHCTEKBARD1CHD4ERBB4GAB2IGF1MAPK3NSD1PRKAR14SDHDTERCBBC3CHEK1ERCC1GABRA6IGF1RMAPKAP1NTSC2PRKC1SEM3CTERTBCL10CHEK2ERCC2GALNT12IGF2MAXNTHL1PRKD1SESN1TET1BCL2CICERCC3GATA1IKBKEMCL1NTRK1PRKDCSESN2TET2BCL211CREBPERCC4GATA2IKZF1MDC1NTRK2PRS8SESN3TGFB1BCL211CRKLERCSGATA3I.10MDM2NTRK3PTCH1SETD2TGFBR1BCL212CRLF2ERFGATA4I.1AMDM4NUF2PTENSETD8TGFBR2BCL6CSDE1ERGGATA6I.L4MECOMNUP33PTPA1SF3B1TIPARPBCORCTCFESR1GGHI.L7MED12OPRM1PTPN11SGK1TLR2BCR3CTLA4ETV1GIL1INHAMEN1PAK1PTPR0SH2B3TMEM127BCR4CTLA4ETV1GIL1INPA4METPAK3PTPR5SH0C2TNFBIRC7CTLA4ETV1GIL1INPA4METPAK7PTPR5SH0C1TNFSF14BIRC7CTNA1ETV5GNA13INPP4BMGAPALB2QK1SLO1B1TNFSF14<		BABAMI	CENPA	ERBB2	FUBPT		MAP3K14	NQU2	PREX2	SDHB	TDG	
BARDICHD4EHBB4GAB2ICF1MAPK3NSD1PHRAH1ASDHDTERCBBC3CHEK1ERCC1GABRA6IGF1RMAPKAP1NT5C2PRKCISEMA3CTERTBCL10CHEK2ERCC2GALNT12IGF2MAXNTHL1PRKD1SESN1TET1BCL2CICERCC3GATA1IKBKEMCL1NTRK1PRKDCSESN2TET2BCL2L1CREBBPERCC4GATA2IKZF1MDC1NTRK2PRS8SESN3TGFB1BCL2L2CRLF2ERFGATA4IL10MDM2NTRK3PTCH1SETD2TGFBR1BCL2L2CRLF2ERFGATA4IL1AMDM4NUF2PTENSETD8TGFBR2BCCACSDE1ERGGATA6IL4MECOMNUP33PTPA1SF3B1TIPARPBCCRCSF1RERRF11GEN1IL7RMED12OPRM1PTPN1SGK1TLR2BCRACTCFESR2GID4INHAMEN1PAK1PTPR0SH2B3TMEM127BCR3CTLA4ETV1GL1INPA4METPAK3PTPR5SH0C2TNFBIRC7CTNA1ETV6GNA11INP4AMETPAK7PTPRSH01TNFRSF14BIRC7CTNA1ETV6GNA13INP4BMGAPALB2QK1SLO1B3TNFSF11BIRC4CUL3EZ/11GNA2INSRMITFPAR12RA25SLO21B3TNFSF11		BAP I	CHD2	ERBB3	FYN			NRAS	PRKAAT	SDHC	TER	
BBC3         CHEK1         EHCC1         GABRAB         IGF1H         MAPAPT         NI5C2         PHKC1         SEMM3C         TEH1           BCL10         CHEK2         ERCC2         GALNT12         IGF2         MAX         NTHL1         PRKD1         SESN1         TET1           BCL2         CIC         ERCC3         GATA1         IKBKE         MCL1         NTRK1         PRKDC         SESN2         TET2           BCL211         CREBBP         ERCC4         GATA2         IKZF1         MDC1         NTRK3         PTCH1         SETD2         TGFB1           BCL211         CRKL         ERCC5         GATA3         IL10         MDM2         NTRK3         PTCH1         SETD3         TGFB1           BCL212         CRL72         ERF         GATA4         IL1A         MDM4         NUP2         PTEN         SETD3         TGFBR2           BCCR         CSP1R         ERRF11         GEN1         IL7R         MED12         OPRM1         PTPA1         SF3B1         TIMPAP           BCOR         CSF1R         ERRF1         GAH         IL8         MEP2B         P2RY8         PTRD         SH2B3         TMEM127           BCR         CTCF         ESR2		BARDI	CHD4	ERBB4	GAB2	IGFI		NSDI	PRKARTA	SDHD	TERC	
BCL10CHER2EHCC2GALN 172IGF2MAXNIHL1PHRD1SESN1IEH1BCL2CICERCC3GATA1IKBKEMCL1NTRK1PRKDCSESN2TET2BCL2L1CREBBPERCC4GATA2IKZF1MDC1NTRK2PRSS8SESN3TGFB1BCL2L11CRKLERCC5GATA3IL10MDM2NTRK3PTCH1SETD2TGFBR1BCL2L2CRLF2ERFGATA4IL1AMDM4NUF2PTENSETD8TGFBR2BCL6CSDE1ERGGATA6IL4MECOMNUP93PTP411SF3B1TIPARPBCORCSF1RERRF11GEN1IL7RMED12OPRM1PTPN11SGK1TLR2BCORL1CSF3RESR1GGHIL8MEF2BP2RY8PTPDSH2B3TMEM127BCRCTCFESR2GID4INHAMEN1PAK1PTPOSH2D1ATMPRS22BIRC3CTLA4ETV1GL11INHBAMERTKPAK3PTPRSH0C2TNFBIRC7CTNNA1ETV6GNA11INPP4AMETPAK7PTPRSH01TNFAIP3BLMCTNNB1EWS11GNA2INSRMITFPAR12QKISLC01B1TNFSF14BMPR1ACTINEXT1GNA3INSRMITFPAR14RAC1SLT1TOP1BRC41CUL4AEZH2GPR124IRF2MKNK1PAR52RAC2SLT1TOP2A<		BBC3	CHEKI	ERCC1	GABRAG	IGF1R	MAPKAPI	NT5C2	PRKCI	SEMA3C	TERI	
BCL2CICERCC3GATA1IKBKEMCL1NTHK1PHKDCSESN2TET2BCL2L1CREBBPERCC4GATA2IKZF1MDC1NTRK2PRS8SESN3TGFB1BCL2L11CRKLERCC5GATA3IL10MDM2NTRK3PTCH1SETD2TGFBR1BCL2L2CRLF2ERFGATA4IL1AMDM4NUF2PTENSETD8TGFBR2BCL6CSDE1ERGGATA6IL4MECOMNUP93PTP4A1SF3B1TIPARPBCORCSF1RERRF11GEN1IL7RMED12OPRM1PTPN1SGK1TLR2BCORCSF1RERRF11GEN1IL7RMED12OPRM1PTPN0SH2B3TMEM127BCRCTCFESR2GID4INHAMEN1PAK1PTPR0SH2D1ATMPRSS2BIRC3CTLA4ETV1GL11INHBAMERTKPAK3PTPR5SHOC2TNFBIRC7CTNNA1ETV6GNA111INPP4BMGAPALB2QKISLC01B1TNFRSF14BMR14CTTNEXT1GNA2INSRMITFPARP1RAC1SLT1TOP1BRC41CUL3EZH1GNA3INSRMITFPARP2RAC2SLC1B3TNFSF11BRA4CUL3EZH1GNA3INSRMITFPARP1RAC1SLT1TOP1BRC41CUL4AEZH2GPR124IRF2MKNK1PARP2RAC2SLX4TP53 <td></td> <td>BCL10</td> <td>CHEK2</td> <td>ERCC2</td> <td>GALN112</td> <td>IGF2</td> <td>MAX</td> <td>NIHL1</td> <td>PRKD1</td> <td>SESN1</td> <td>1E11</td> <td></td>		BCL10	CHEK2	ERCC2	GALN112	IGF2	MAX	NIHL1	PRKD1	SESN1	1E11	
BCL2L1CHEBBPERCC4GATA2IKZF-1MDC1NTHK2PHSS8SESN3TGFB1BCL2L11CRKLERCC5GATA3IL10MDM2NTRK3PTCH1SETD2TGFBR1BCL2L2CRLF2ERFGATA4IL1AMDM4NUF2PTENSETD8TGFBR2BCL6CSDE1ERGGATA6IL4MECOMNUP93PTP4A1SF3B1TIPARPBCORCSF1RERRF11GEN1IL7RMED12OPRM1PTPN11SGK1TLR2BCORL1CSF3RESR1GGHIL8MEF2BP2RY8PTPDSH2B3TMEM127BCRCTCFESR2GID4INHAMEN1PAK1PTPR0SH2D1ATMPRSS2BIRC3CTLA4ETV1GL11INHBAMERTKPAK3PTPR5SHOC2TNFBIRC7CTINNA1ETV6GNA111INPP4AMETPAK7PTPRTSHQ1TNFAF14BMR14CTTNEXT1GNAQINPP11MGMTPARK2RAB35SLC01B1TNFRSF14BRAFCUL3EZH1GNASINSRMITFPARP1RAC1SLT1TOP1BRC41CUL4AEZH2GPR124IRF2MKNK1PARP2RAC2SLX4TP53BRD4CYLDFAM175AGRM1IRS1MLH3PAX5RAD50SMAD2TP53BP1BRIP1CYP17A1FAM66CGRIN2AIRS2MPLPBRM1RAD51SMAD3 <td< td=""><td></td><td>BCL2</td><td></td><td>ERCC3</td><td>GAIA1</td><td>IKBKE</td><td>MCL1</td><td>NIRK1</td><td>PRKDC</td><td>SESN2</td><td>1E12</td><td></td></td<>		BCL2		ERCC3	GAIA1	IKBKE	MCL1	NIRK1	PRKDC	SESN2	1E12	
BCL2L11CHRLEHCCSGATA3IL10MDM2NTHR3PTCH1SETD2TGHBH1BCL2L2CRLF2ERFGATA4IL1AMDM4NUF2PTENSETD8TGFBR2BCL6CSDE1ERGGATA6IL4MECOMNUP93PTP4A1SF3B1TIPARPBCORCSF1RERRFI1GEN1IL7RMED12OPRM1PTPN11SGK1TLR2BCORL1CSF3RESR1GGHIL8MEF2BP2RY8PTPR0SH2B3TMEM127BCRCTCFESR2GID4INHAMEN1PAK1PTPR0SH2D1ATMPRSS2BIRC3CTLA4ETV1GL11INHBAMERTKPAK3PTPR0SH0C2TNFBIRC7CTNNA1ETV6GNA11INPP4AMETPAK7PTPR1SH01TNFAIP3BLMCTNNB1EWSR1GNA13INPP4BMGAPALB2QK1SLC01B1TNFSF14BMPR1ACTTNEXT1GNAQINPP11MGMTPARK2RAB35SLC01B3TNFSF11BRAFCUL3EZH1GNASINSRMITFPARP1RAC1SL11TOP1BRCA2CXCR4FADDGPS2IRF4MLH1PARP2RAC2SL12TOP2ABRD4CYLDFAM175AGREM1IRS1MLH3PAX5RAD50SMAD2TP53BP1BRD4CYLDFAM46CGRIN3AJAK1MRE11APCAPRAD51BSMAD4TRAF		BCL2L1	CREBBP	ERCC4	GATA2	IKZF1	MDC1	NTRK2	PRSS8	SESN3	TGFB1	
BCL2L2CHLP2EHFGATA4IL1AMDM4NUF2PTENSETD8TGFBR2BCL6CSDE1ERGGATA6IL4MECOMNUP93PTP411SF3B1TIPARPBCORCSF1RERRFI1GEN1IL7RMED12OPRM1PTPN11SGK1TLR2BCORL1CSF3RESR1GGHIL8MEF2BP2RY8PTPDSH2B3TMEM127BCRCTCFESR2GID4INHAMEN1PAK1PTPROSH2D1ATMPRSS2BIRC3CTLA4ETV1GL11INHBAMETKPAK3PTPRSH0C2TNFBIRC7CTNNA1ETV6GNA11INPP4AMETPAK7PTPRTSHQ1TNFAIP3BLMCTNNB1EWSR1GNA2INPP4BMGAPALB2QKISLC01B1TNFRSF14BMPR1ACTTNEXT1GNAQINPP11MGMTPARK2RAB35SLC01B3TNFSF11BRAFCUL3EZH1GNASINSRMITFPARP1RAC1SLIT1TOP1BRCA2CXCR4FADDGPS2IRF4MLH1PARP3RAD21SLX4TP53BRD4CYLDFAM175AGREM1IRS1MLH3PAX5RAD50SMAD2TP53BP1BRG1CYP17A1FAM46CGRIM3JAK1MRE11APCAPRAD51BSMAD4TRAF2BTG2CYP1B1FANCAGSK3BJAK2MSH2PDCD1RAD51DSMAD4TRAF7		BCL2L11	CRKL	ERCC5	GATA3	IL10	MDM2	NTRK3	PICH1	SEID2	IGFBR1	
BCL6CSDE1ERGGATA6IL4MECOMNUP33PTP4A1SF3B1TIPARPBCORCSF1RERRFI1GEN1IL7RMED12OPRM1PTPN11SGK1TLR2BCORL1CSF3RESR1GGHIL8MEF2BP2RY8PTPRDSH2B3TMEM127BCRCTCFESR2GID4INHAMEN1PAK1PTPROSH2D3ATMFMPSS2BIRC3CTLA4ETV1GLI1INHBAMERTKPAK3PTPRSSHOC2TNFBIRC7CTNNA1ETV6GNA11INPP4MMETPAK7PTPRTSHQ1TNFAIP3BLMCTNNB1EWSR1GNA3INPP4BMGAPALB2QKISLC01B1TNFRSF14BMPR1ACTTNEXT1GNAQINPP11MGMTPAR2RAB35SLC01B3TNFSF11BRAFCUL3EZH1GNASINSRMITFPARP1RAC1SLT1TOP1BRCA1CUL4AEZH2GPR124IRF2MKNK1PARP3RAD21SLX4TP53BRD4CYLDFAM175AGREM1IRS1MLH3PAX5RAD50SMAD2TP53BP1BRI91CYP17A1FAM6CGRIN2AIRS2MPLPBRM1RAD51SMAD3TP63BTG2CYP1B1FANCAGSK3BJAK2MSH2PDCD1RAD51DSMARCA4TRAF7BTG2CYP1C8FANCCGST1JAK3MSH3PDCD1LG2RAD51DSMARCA4 <td></td> <td>BCL2L2</td> <td>CRLF2</td> <td>ERF</td> <td>GATA4</td> <td>IL1A</td> <td>MDM4</td> <td>NUF2</td> <td>PTEN</td> <td>SETD8</td> <td>TGFBR2</td> <td></td>		BCL2L2	CRLF2	ERF	GATA4	IL1A	MDM4	NUF2	PTEN	SETD8	TGFBR2	
BCOHCSF1REHRFI1GEN1IL7RMED12OPRM1PTPN11SGK1TLR2BCORL1CSF3RESR1GGHIL8MEF2BP2RY8PTPRDSH2B3TMEM127BCRCTCFESR2GID4INHAMEN1PAK1PTPROSH2D1ATMPRSS2BIRC3CTLA4ETV1GLI1INHBAMERTKPAK3PTPRSSHOC2TNFBIRC7CTNNA1ETV6GNA11INPP4AMETPAK7PTPRTSHQ1TNFAIP3BLMCTNNB1EWSR1GNA13INPP4BMGAPALB2QKISLC01B1TNFRSF14BMPR1ACTTNEXT1GNAQINPP1MGMTPARK2RAB35SLC01B3TNFSF11BRAFCUL3EZH1GNASINSRMITFPARP1RAC1SLT1TOP1BRCA1CUL4AEZH2GPR124IRF2MKNK1PARP2RAC2SLT2TOP2ABRCA2CXCR4FADDGPS2IRF4MLH1PARP3RAD21SLX4TP53BRD4CYLDFAM175AGREM1IRS2MPLPBRM1RAD51SMAD3TP63BRG1CYP17A1FAM6CGRIN3JAK1MRE11APCAPRAD51BSMAD4TRAF2BTG2CYP1B1FANCAGSK3BJAK2MSH2PDCD1RAD51CSMARCA4TRAF7BTKCYP2C8FANCCGSTA1JAK3MSH3PDCD1LG2RAD51DSMARCB1 <t< td=""><td></td><td>BCL6</td><td>CSDE1</td><td>ERG</td><td>GATA6</td><td>IL4</td><td>MECOM</td><td>NUP93</td><td>PTP4A1</td><td>SF3B1</td><td>IIPARP</td><td></td></t<>		BCL6	CSDE1	ERG	GATA6	IL4	MECOM	NUP93	PTP4A1	SF3B1	IIPARP	
BCORL1CSF3RESR1GGHIL8MEF2BP2RY8PTPRDSH2B3TMEM127BCRCTCFESR2GID4INHAMEN1PAK1PTPROSH2D1ATMPRSS2BIRC3CTLA4ETV1GL11INHBAMERTKPAK3PTPRSSHOC2TNFBIRC7CTNNA1ETV6GNA11INPP4AMETPAK7PTPRTSHQ1TNFAIP3BLMCTNNB1EWSR1GNA13INPP4BMGAPALB2QKISLCO1B1TNFRSF14BMPR1ACTTNEXT1GNAQINPP11MGMTPARK2RAB35SLCO1B3TNFSF11BRAFCUL3EZH1GNASINSRMITFPARP1RAC1SLIT1TOP1BRCA1CUL4AEZH2GPR124IRF2MKNK1PARP2RAC2SLIT2TOP2ABRCA2CXCR4FADDGPS2IRF4MLH1PARP3RAD21SLX4TP53BRD4CYP17A1FAM46CGRIN2AIRS2MPLPBRM1RAD51SMAD3TP63BTG1CYP19A1FAM58AGRM3JAK1MRE11APCAPRAD51BSMAD4TRAF2BTG2CYP1B1FANCAGSK3BJAK2MSH3PDCD1LG2RAD51DSMARCB1TRAP		BCOR	CSF1R	ERRFI1	GEN1	IL7R	MED12	OPRM1	PTPN11	SGK1	TLR2	
BCRCTCFESR2GID4INHAMEN1PAK1PTPROSH2D1ATMPRSS2BIRC3CTLA4ETV1GLI1INHBAMERTKPAK3PTPRSSH0C2TNFBIRC7CTNNA1ETV6GNA11INPP4AMETPAK7PTPRTSHQ1TNFAIP3BLMCTNNB1EWSR1GNA13INPP4BMGAPALB2QKISLC01B1TNFRSF14BMPR1ACTTNEXT1GNAQINPP11MGMTPARK2RAB35SLC01B3TNFSF11BRAFCUL3EZH1GNASINSRMITFPARP1RAC1SLIT1TOP1BRCA1CUL4AEZH2GPR124IRF2MKNK1PARP2RAC2SLIT2TOP2ABRCA2CXCR4FADDGPS2IRF4MLH3PARP3RAD21SLX4TP53BRIP1CYP17A1FAM46CGRIN2AIRS2MPLPBRM1RAD51SMAD3TP63BTG1CYP19A1FAM58AGRM3JAK1MRE11APCAPRAD51BSMAD4TRAF2BTG2CYP1B1FANCAGSX3BJAK2MSH2PDCD1LG2RAD51DSMARCA4TRAF7BTKCYP2C8FANCCGSTA1JAK3MSH3PDCD1LG2RAD51DSMARCB1TRAP		BCORL1	CSF3R	ESR1	GGH	IL8	MEF2B	P2RY8	PTPRD	SH2B3	TMEM127	
BIRC3CTLA4ETV1GL11INHBAMERTKPAK3PTPRSSHOC2TNFBIRC7CTNNA1ETV6GNA11INPP4AMETPAK7PTPRTSHQ1TNFAIP3BLMCTNNB1EWSR1GNA13INPP4BMGAPALB2QKISLCO1B1TNFRSF14BMPR1ACTTNEXT1GNAQINPP11MGMTPARK2RAB35SLCO1B3TNFSF11BRAFCUL3EZH1GNASINSRMITFPARP1RAC1SLIT1TOP1BRCA1CUL4AEZH2GPR124IRF2MKNK1PARP2RAC2SLIT2TOP2ABRCA2CXCR4FADDGPS2IRF4MLH1PARP3RAD21SLX4TP53BRD4CYLDFAM175AGREM1IRS1MLH3PAX5RAD50SMAD2TP53BP1BRIP1CYP17A1FAM46CGRIN2AIRS2MPLPBRM1RAD51SMAD3TP63BTG1CYP19A1FAM58AGRM3JAK1MRE11APCAPRAD51BSMAD4TRAF2BTG2CYP1B1FANCAGSX3BJAK2MSH3PDCD1LG2RAD51DSMARCB1TRAF7BTKCYP2C8FANCCGSTA1JAK3MSH3PDCD1LG2RAD51DSMARCB1TRAP		BCR	CTCF	ESR2	GID4	INHA	MEN1	PAK1	PTPRO	SH2D1A	TMPRSS2	
BIRC7CTNNA1ETV6GNA11INPP4AMETPAK7PTPRTSHQ1TNFAIP3BLMCTNNB1EWSR1GNA13INPP4BMGAPALB2QKISLCO1B1TNFRSF14BMPR1ACTTNEXT1GNAQINPP11MGMTPARK2RAB35SLCO1B3TNFSF11BRAFCUL3EZH1GNASINSRMITFPARP1RAC1SLIT1TOP1BRCA1CUL4AEZH2GPR124IRF2MKNK1PARP2RAC2SLIT2TOP2ABRCA2CXCR4FADDGPS2IRF4MLH1PARP3RAD21SLX4TP53BRD4CYLDFAM175AGREM1IRS1MLH3PAX5RAD50SMAD2TP53BP1BRIP1CYP17A1FAM58AGRM3JAK1MRE11APCAPRAD51BSMAD4TRAF2BTG2CYP1B1FANCAGSK3BJAK2MSH3PDCD1LG2RAD51DSMARCA1TRAPBTKCYP2C8FANCCGSTA1JAK3MSH3PDCD1LG2RAD51DSMARCB1TRAP		BIRC3	CTLA4	ETV1	GLI1	INHBA	MERTK	PAK3	PTPRS	SHOC2	TNF	
BLMCTNNB1EWSR1GNA13INPP4BMGAPALB2QKISLCO1B1TNFRSF14BMPR1ACTTNEXT1GNAQINPPL1MGMTPARK2RAB35SLCO1B3TNFSF11BRAFCUL3EZH1GNASINSRMITFPARP1RAC1SLIT1TOP1BRCA1CUL4AEZH2GPR124IRF2MKNK1PARP2RAC2SLIT2TOP2ABRCA2CXCR4FADDGPS2IRF4MLH1PARP3RAD21SLX4TP53BRD4CYLDFAM175AGREM1IRS1MLH3PAX5RAD50SMAD2TP53BP1BRG1CYP19A1FAM58AGRM3JAK1MRE11APCAPRAD51BSMAD4TRAF2BTG2CYP1B1FANCAGSK3BJAK2MSH3PDCD1LG2RAD51DSMARCB1TRAP		BIRC7	CTNNA1	ETV6	GNA11	INPP4A	MET	PAK7	PTPRT	SHQ1	TNFAIP3	
BMPR1ACTTNEXT1GNAQINPPL1MGMTPARK2RAB35SLC01B3TNFSF11BRAFCUL3EZH1GNASINSRMITFPARP1RAC1SLIT1TOP1BRCA1CUL4AEZH2GPR124IRF2MKNK1PARP2RAC2SLIT2TOP2ABRCA2CXCR4FADDGPS2IRF4MLH1PARP3RAD21SLX4TP53BRD4CYLDFAM175AGREM1IRS1MLH3PAX5RAD50SMAD2TP53BP1BRIP1CYP17A1FAM46CGRIN2AIRS2MPLPBRM1RAD51SMAD3TP63BTG1CYP19A1FAM58AGRM3JAK1MRE11APCAPRAD51BSMAD4TRAF2BTG2CYP1B1FANCAGSX3BJAK2MSH3PDCD1LG2RAD51DSMARCA4TRAF7BTKCYP2C8FANCCGSTA1JAK3MSH3PDCD1LG2RAD51DSMARCB1TRAP		BLM	CTNNB1	EWSR1	GNA13	INPP4B	MGA	PALB2	QKI	SLCO1B1	TNFRSF14	
BRAFCUL3EZH1GNASINSRMITFPARP1RAC1SLIT1TOP1BRCA1CUL4AEZH2GPR124IRF2MKNK1PARP2RAC2SLIT2TOP2ABRCA2CXCR4FADDGPS2IRF4MLH1PARP3RAD21SLX4TP53BRD4CYLDFAM175AGREM1IRS1MLH3PAX5RAD50SMAD2TP53BP1BRIP1CYP17A1FAM46CGRIN2AIRS2MPLPBRM1RAD51SMAD3TP63BTG1CYP19A1FAM58AGRM3JAK1MRE11APCAPRAD51BSMAD4TRAF2BTG2CYP1B1FANCAGSK3BJAK2MSH2PDCD1LG2RAD51DSMARCA1TRAPBTKCYP2C8FANCCGSTA1JAK3MSH3PDCD1LG2RAD51DSMARCB1TRAP		BMPR1A	CTTN	EXT1	GNAQ	INPPL1	MGMT	PARK2	RAB35	SLCO1B3	TNFSF11	
BRCA1CUL4AEZH2GPR124IRF2MKNK1PARP2RAC2SLIT2TOP2ABRCA2CXCR4FADDGPS2IRF4MLH1PARP3RAD21SLX4TP53BRD4CYLDFAM175AGREM1IRS1MLH3PAX5RAD50SMAD2TP53BP1BRIP1CYP17A1FAM46CGRIN2AIRS2MPLPBRM1RAD51SMAD3TP63BTG1CYP19A1FAM58AGRM3JAK1MRE11APCAPRAD51BSMAD4TRAF2BTG2CYP1B1FANCAGSK3BJAK2MSH2PDCD1RAD51CSMARCA4TRAF7BTKCYP2C8FANCCGSTA1JAK3MSH3PDCD1LG2RAD51DSMARCB1TRAP		BRAF	CUL3	EZH1	GNAS	INSR	MITF	PARP1	RAC1	SLIT1	TOP1	
BRCA2CXCR4FADDGPS2IRF4MLH1PARP3RAD21SLX4TP53BRD4CYLDFAM175AGREM1IRS1MLH3PAX5RAD50SMAD2TP53BP1BRIP1CYP17A1FAM46CGRIN2AIRS2MPLPBRM1RAD51SMAD3TP63BTG1CYP19A1FAM58AGRM3JAK1MRE11APCAPRAD51BSMAD4TRAF2BTG2CYP1B1FANCAGSK3BJAK2MSH2PDCD1RAD51CSMARCA4TRAF7BTKCYP2C8FANCCGSTA1JAK3MSH3PDCD1LG2RAD51DSMARCB1TRRAP		BRCA1	CUL4A	EZH2	GPR124	IRF2	MKNK1	PARP2	RAC2	SLIT2	TOP2A	
BRD4CYLDFAM175AGREM1IRS1MLH3PAX5RAD50SMAD2TP53BP1BRIP1CYP17A1FAM46CGRIN2AIRS2MPLPBRM1RAD51SMAD3TP63BTG1CYP19A1FAM58AGRM3JAK1MRE11APCAPRAD51BSMAD4TRAF2BTG2CYP1B1FANCAGSK3BJAK2MSH2PDCD1RAD51CSMARCA4TRAF7BTKCYP2C8FANCCGSTA1JAK3MSH3PDCD1LG2RAD51DSMARCB1TRAP		BRCA2	CXCR4	FADD	GPS2	IRF4	MLH1	PARP3	RAD21	SLX4	TP53	
BRIP1CYP17A1FAM46CGRIN2AIRS2MPLPBRM1RAD51SMAD3TP63BTG1CYP19A1FAM58AGRM3JAK1MRE11APCAPRAD51BSMAD4TRAF2BTG2CYP1B1FANCAGSK3BJAK2MSH2PDCD1RAD51CSMARCA4TRAF7BTKCYP2C8FANCCGSTA1JAK3MSH3PDCD1LG2RAD51DSMARCB1TRAP		BRD4	CYLD	FAM175A	GREM1	IRS1	MLH3	PAX5	RAD50	SMAD2	TP53BP1	
BTG1CYP19A1FAM58AGRM3JAK1MRE11APCAPRAD51BSMAD4TRAF2BTG2CYP1B1FANCAGSK3BJAK2MSH2PDCD1RAD51CSMARCA4TRAF7BTKCYP2C8FANCCGSTA1JAK3MSH3PDCD1LG2RAD51DSMARCB1TRAP		BRIP1	CYP17A1	FAM46C	GRIN2A	IRS2	MPL	PBRM1	RAD51	SMAD3	TP63	
BTG2CYP1B1FANCAGSK3BJAK2MSH2PDCD1RAD51CSMARCA4TRAF7BTKCYP2C8FANCCGSTA1JAK3MSH3PDCD1LG2RAD51DSMARCB1TRRAP		BTG1	CYP19A1	FAM58A	GRM3	JAK1	MRE11A	PCAP	RAD51B	SMAD4	TRAF2	
BTK CYP2C8 FANCC GSTA1 JAK3 MSH3 PDCD1LG2 RAD51D SMARCB1 TRRAP		BTG2	CYP1B1	FANCA	GSK3B	JAK2	MSH2	PDCD1	RAD51C	SMARCA4	TRAF7	
	-	BTK	CYP2C8	FANCC	GSTA1	JAK3	MSH3	PDCD1LG2	RAD51D	SMARCB1	TRRAP	

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**Figure S1** The distribution of mutation information in the JCH and TCGA samples. The mutations of *GP645* genes were distributed on 21 chromosomes in TCGA (A) and JCH datasets (B).