Whole-exome sequencing analysis identifies distinct mutational profile and novel prognostic biomarkers in primary gastrointestinal diffuse large B-cell lymphoma

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Abstract

Background: Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive non-Hodgkin lymphoma, and about 10% of DLBCL cases primarily occur in the gastrointestinal tract. Previous reports have revealed that primary gastrointestinal-DLBCL (pGI-DLBCL) harbors different genetic mutations from other nodal or extranodal DLBCL. However, the exonic mutation profile of pGI-DLBCL has not been fully addressed.

Methods: We performed whole-exome sequencing of matched tumor tissues and blood samples from 53 pGI-DLBCL patients. The exonic mutation profiles were screened, and the correlations between genetic mutations and clinicopathological characteristics were analyzed.

Results: A total of 6,588 protein-altering events were found and the five most frequent mutated genes in our pGI-DLBCL cohort were IGLL5 (47%), TP53 (42%), BTG2 (28%), P2RY8 (26%) and PCL2 (23%). Compared to the common DLBCL, significantly less or absence of MYD88 (0%), EZH2 (0%), BCL2 (2%) or CD79B (8%) mutations were identified in pGI-DLBCL. The recurrent potential driver genes were mainly enriched in pathways related to signal transduction, infectious disease and immune regulation. In addition, HBV infection had an impact on the mutational signature in pGI-DLBCL, as positive HBsAg was significantly associated with the TP53 and LRP1B mutations, two established tumor suppressor genes in many human cancers. Moreover, IGLL5 and LRP1B mutations were significantly correlated with patient overall survival and could serve as two novel prognostic biomarkers in pGI-DLBCL.
Conclusions: Our study provides a comprehensive view of the exonic mutation profile of the largest pGI-DLBCL cohort to date. The results could facilitate the clinical development of novel therapeutic and prognostic biomarkers for pGI-DLBCL.

Keywords: Whole-exome sequencing/WES, Diffuse large B-cell lymphoma/DLBCL, Gastrointestinal tract/GI tract, Mutation profile, IGLL5, LRP1B

Introduction

The incident rate of non-Hodgkin lymphomas (NHLs) in most countries has considerably increased in recent years [1]. Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of NHLs, accounting for nearly one-third of all lymphoid neoplasm in China annually [2, 3]. Though at least two DLBCL subtypes have been identified by RNA expression profiles, the germinal center B-cell-like (GCB) subtype and the activated B-cell-like (ABC) subtype, DLBCL still represents a clinical heterogeneous disease due to its complex and diverse histological characteristics [4, 5]. DLBCL patients often present with an aggressive clinical behavior, but most of them can be cured by the standard regimen based on rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) [6]. The application of next-generation sequencing has helped reveal a deep degree of molecular and genetic heterogeneity in hematological diseases, and confirmed that genetic aberrations contribute to occurrence and progression of DLBCL [7, 8].

DLBCL arises from extranodal organs in about 30% of total cases, and one third of extranodal DLBCL cases occur in the gastrointestinal tract, making it the most common primary extranodal site [9, 10]. Patient prognosis and recurrence risk of extranodal DLBCL vary according to the primary site of origin, which may harbor different genetic mutations clarified by high throughput sequencing studies [11, 12]. Primary gastrointestinal DLBCL (pGI-DLBCL) has a significantly decreased level of MYD88 and CD79B mutations compared to nodal DLBCL and other extranodal DLBCL in immune-privileged sites, such as central nervous system and testis [13, 14]. Meanwhile, genetic mutations of MYC or BCL2 rearrangements could be related to the survival and prognosis of pGI-DLBCL patients [15, 16]. The genetic mutation profiles discovered by more in-depth analysis revealed that pGI-DLBCL may have different modes of pathogenesis and progression from non-gastrointestinal DLBCL. Recently, by analyzing a small group of patients using whole-exome sequencing (WES), a study by Li et al. has shed a light on the genetic mutations in pGI-DLBCL [17]. However, comprehensive research focusing on the mutational landscape of pGI-DLBCL, and the correlation between its genetic mutations and clinicopathological features are still rare.

In the present study, we aimed to derive the predictive mutational profile by performing capture-based targeted WES on 53 Chinese pGI-DLBCL patients. The association between clinical characteristics and genetic alterations was also explored. In addition, we tried to identify genetic mutations possibly affecting patient survival and their underlying mechanisms. Our study provided a deeper insight into the genetic features of pGI-DLBCL, which may be helpful to clarify the lymphomagenesis process and develop putative therapeutic and prognostic biomarkers for this disease.

Materials and methods

Patient Cohort

Fifty-three patients diagnosed with pGI-DLBCL according to the criteria defined by Lewin et al. [18] were recruited in this study. All patients underwent partial gastrectomy or enterectomy plus R-CHOP based therapy in our hospital spanning from January 1, 2011 to July 21, 2021. Forty-six surgical resection specimens, seven biopsy specimens and matched patient peripheral blood mononuclear cells (PBMCs) were used for sequencing study. All specimens were reviewed by two independent hematopathologists (Yan Huang and Hai-Ling Liu) according to the 2017 World Health Organization classification criteria [19]. The corresponding medical records of all patients were reviewed to obtain the clinicopathological information. The study was approved by the institutional review board at the Sixth Affiliated Hospital of Sun Yat-Sen University.

WES

Tumor DNA was isolated from five 5-μm-thick sections of formalin-fixed paraffin-embedded tumor tissues with a minimum of 70% neoplastic cells using QIAamp FFPE DNA Tissue Kit (Qiagen, USA), and the paired normal control DNA of PBMCs was extracted with DNaseasy Tissue and Blood Kit (Qiagen, USA) according to the manufacturer’s instructions. Degradation and contamination were monitored on a 1% agarose gel, and the concentration was measured by using a Qubit® DNA Assay Kit in a Qubit® 2.0 Fluorometer (Life Technologies, USA). Qualified genomic DNA from tumors and matched PBMCs from 53 pGI-DLBCL patients were fragmented by Covaris technology with resultant library fragments of
180–280 bp, and then adapters were ligated to both ends of the fragments. Extracted DNA was then amplified by ligation-mediated PCR (LM-PCR), purified, and hybridized to the Agilent SureSelect Human Exome V6 (Santa Clara, USA) for enrichment, and nonhybridized fragments were then washed out. Both uncaptured and captured LM-PCR products were subjected to real-time PCR to estimate the magnitude of enrichment. Each captured library was then loaded onto the Illumina HiSeq X platform (Hangzhou Jichenjunchuang Medical Laboratory Co., Ltd, Beijing, China). We performed high-throughput sequencing for each captured library independently. Tumor and normal DNA samples were sequenced to an average depth of >100 × and >40 × in targeted exonic regions, respectively.

Genomic analysis
After generating raw data through base calling, paired-end reads were trimmed to remove stretches of low-quality bases (<Q10) and adapters in the sequences. The clean reads were mapped to NCBI Build 37 (hg19) using BWA-0.7.12 mem with the default settings. SAMtools-1.2 was used to sort and index all the BAM files; PicardTools-1.119 was used to remove the duplicates; and GATK-3.3–0 was used for InDel realignment and base quality score recalibration. MuTect-1.1.4 and Strelka were used to call somatic SNVs and InDels in the paired normal and tumor samples. Variants identified in the 1,000 Genomes database (https://www.1000genomes.org/) with a frequency >1% (unless they were in the Catalog of Somatic Mutations in Cancer (COSMIC) database) or in the Exome Aggregation Consortium (http://exac.broadinstitute.org/) with a frequency >0.1% were discarded from the analysis. Variants with an alternate allele depth <2 and a frequency <5% were also excluded. In addition, SNVs and InDels were filtered to remove benign changes predicted by the following predictive software programs, including PolyPhen2, Mutation-Taster, Mutation Assessor, FATHMM, Radial SVM, LR, SIFT, and LRT. ANNOVAR was used to annotate all the somatic mutations after filtering.

Pathway enrichment analysis
Gene clustering analysis of the driver mutations was performed by Database for Annotation, Visualization and Integrated Discovery (DAVID) online tool (https://david.ncifcrf.gov/) as previously described [20]. Only the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis which evaluates the modules at the functional level of the selected genes was executed. Bonferroni $P$ value <0.05 was set as the cut-off criterion and regarded as statistically significant.

Statistical analysis
Statistical analysis was performed using R version 4.1.2 and GraphPad Prism version 7 (La Jolla, CA, USA). The Mann–Whitney U test and the Spearman rank correlation test were employed to analyze the relationship between the mutated genes and clinicopathological characteristics. Survival analysis was performed using Kaplan–Meier curves and compared using the log-rank test. Comparative test differences were considered significant if the 2-tailed $P$ value was <0.05 otherwise indicated.

Results
Clinicopathological characteristics of the pGI-DLBCL patient cohort
The clinicopathological characteristics of the pGI-DLBCL patient cohort were summarized in Table 1 and Additional file 1: Table S1. Of note, we included 53 patients diagnosed with pGI-DLBCL in this study, which consisted of 40 males and 13 females, respectively. Tumors were primarily originated from the stomach of 11 patients, small intestine of 29 patients, or large intestine of 13 patients. Helicobacter pylori (Hp) or hepatitis B virus (HBV) infection was positive in 21 (39.6%) or 11 cases (20.8%), respectively. According to the Hans algorithm, 33 and 20 patients were classified as GCB (62.3%) and non-GCB (37.7%) DLBCL subtypes based on the immunohistochemical features. The cohort included 35 patients in clinical stage I or II, and 18 patients in clinical stage III or IV. By the end of the current study, the follow-up duration of the patients was as long as 128.4 months with 11 dead records.

Exonic mutational profile of pGI-DLBCL
We performed WES of patient-derived tumor tissue and matched blood DNA. Collectively, 6,588 protein-altering mutational events spanning 3,229 genes were identified from our patient cohort. Of these, 5,489 were missense variants, 171 were in frame insertions or deletions, 394 were frameshift variants, 187 were splice site mutations, 23 were start lost mutations, 13 were stop lost mutations, and 311 were stop gain mutations. The spectrum of the top 40 frequently mutated genes was presented in Fig. 1 and the mutational profile of the entire cohort was summarized in Additional file 2: Table S2. The gene with the highest mutation rate was IGLL5 (mutated in 47% pGI-DLBCL patients), which is also the top 1 mutated gene reported in HBV-related DLBCL [21]. Other most frequently mutated genes (≥15%) included TP53, BTG2, P2RY8, PCLO, HIST1H1E, IGHM, KMT2D, CSMID3, MUC16, RYR2, CCND3, DISP2, FAT4, IGHJ6, CARD11, HIST1H1C, LRPIB, MYC, NBPFI, SI. The genome-wide
mutational signatures were also characterized according to the 96 possible mutation types [22]. Three highly confident mutational signatures were extracted from our patient cohort. Of these 3 mutation signatures, signatures 1 and 3 were fitted with COSMIC signature 1 and 26, which have been linked to age and defective DNA mismatch repair in cancer, respectively. Meanwhile signature 2, which was mainly characterized by T to G mutations, was not correlated with any COSMIC signature (Fig. 2).

Potential driver mutations in pGI-DLBCL
In order to identify potential driver mutations in pGI-DLBCL, we compared the mutation profile of our patient cohort with those pathogenic genes associated with human tumors, which have been published and indexed in the COSMIC, MDG125 [23], SMG127 [24], CDG291 datasets [25]. A total of 417 potential driver genes were identified (Table 2). Among these genes, 30 commonly mutated driver genes were found in at least 5 pGI-DLBCL patients, including TP53, P2RY8, KMT2D, MUC16, CSMD3, FAT4, CCND3, HIST1H1C, CARD11, MYC, LRP1B, B2M, TET2, FOXO1, EBF1, BTG1, SETD1B, BCR, COL3A1, DDX3X, AHNAK2, PIM1, ID3, DNM2, PTPN6, FAT1, ROBO2, NFKBIA, BCL7A, SGK1. Next, we used those potential driver genes shared by at least 2 pGI-DLBCL patients to perform gene clustering analysis with the aid of DAVID algorithm. The result revealed that these recurrent driver genes were mainly enriched in pathways related to human cancers, signal transduction, cell metabolism, infection disease and immune regulation. Important signal transduction pathways were substantially affected such as thyroid hormone signaling, central carbon metabolism, HBV infection, FoxO signaling and B cell receptor signaling (Fig. 3 and Additional file 3: Table S3). These results indicated that abnormal signal transduction cascades, altered cell metabolism and virus infection may jointly contribute to the pathogenesis of pGI-DLBCL.

Associations between clinicopathological characteristics and exonic mutations in pGI-DLBCL patients
We analyzed the correlations between the status of top 30 mutated genes and the clinicopathological characteristics, such as age, gender, Hp or HBV infection, LDH level, Eastern Cooperative Oncology Group (ECOG) score, B symptoms, International Prognostic Index (IPI), tumor stage, etc. The result was displayed in Fig. 4, and the correlations with statistical significance were summarized in Additional file 4: Table S4. Interestingly, younger patients

| Table 1 Clinicopathological characteristics of 53 pGI-DLBCL patients |
|-----------------|-----------------|-----------------|
| Characteristics | Patients n | Percentage |
| Age, years      |                |               |
| ≤60             | 28            | 52.8%         |
| >60             | 25            | 47.2%         |
| Gender          |                |               |
| Male            | 40            | 75.5%         |
| Female          | 13            | 24.5%         |
| Origin          |                |               |
| Large Intestine | 13            | 24.5%         |
| Small Intestine | 29            | 54.7%         |
| Stomach         | 11            | 20.8%         |
| Han’s Algorithm |                |               |
| GCB             | 33            | 62.3%         |
| non-GCB         | 20            | 37.7%         |
| B Symptom       |                |               |
| Yes             | 14            | 26.4%         |
| No              | 39            | 73.6%         |
| Hp Infection    |                |               |
| Positive        | 21            | 39.6%         |
| Negative        | 32            | 60.4%         |
| LDH Level       |                |               |
| Elevated        | 31            | 58.5%         |
| Normal          | 22            | 41.5%         |
| Hypoproteinemia |                |               |
| Yes             | 45            | 84.9%         |
| No              | 8             | 15.1%         |
| Anemia          |                |               |
| Yes             | 52            | 98.1%         |
| No              | 1             | 1.9%          |
| HBsAg           |                |               |
| Positive        | 11            | 20.8%         |
| Negative        | 42            | 79.2%         |
| ECOG PS         |                |               |
| <2              | 43            | 81.1%         |
| ≥2              | 10            | 18.9%         |
| Lugano Stage    |                |               |
| I-II            | 35            | 66.0%         |
| III-IV          | 18            | 34.0%         |
| IPI             |                |               |
| 0–1             | 28            | 52.8%         |
| 2–5             | 25            | 47.2%         |
| Survival        |                |               |
| Alive           | 42            | 79.2%         |
| Dead            | 11            | 20.8%         |
tended to have FAT4 and FOXO1 mutations, and patients with non-GCB tumors were correlated with CARD11 mutations. Hp infection showed no association with any parameter, however, HBV infection seemed to be related to certain mutations in pGI-DLBCL, as positive HBsAg was significantly associated with the mutations of TP53.
| #Gene Symbol | Sample | COSMIC | MDG125 | SMG127 | CDG291  | Patient_  |
|--------------|--------|--------|--------|--------|---------|------------|
|              |        |        |        |        |         | Number_    |
|              |        |        |        |        |         | Count      |
| TP53         | P01, P02, P03, P04, P05, P17, P18, P19, P20, P21, P22, P23, P33, P34, P35, P36, P37, P41, P42, P43, P50, P51 | oncogene, TSG, fusion | TSG | pan_can_fre:42.00% | Yes | 22 |
| P2RY8        | P09, P12, P13, P17, P18, P19, P20, P25, P27, P29, P30, P38, P52, P53 | oncogene, fusion | No | No | No | 14 |
| KMT2D        | P02, P08, P10, P21, P31, P32, P34, P40, P43, P46, P53 | oncogene, TSG | No | No | No | 11 |
| MUC16        | P01, P03, P09, P10, P13, P24, P36, P45, P50, P51 | oncogene | No | No | No | 10 |
| CSM3D        | P03, P06, P09, P21, P24, P28, P38, P45, P50, P53 | TSG | No | No | No | 10 |
| FAT4         | P01, P06, P08, P09, P19, P20, P27, P50, P52 | TSG | No | No | No | 9 |
| CCND3        | P06, P07, P11, P18, P22, P28, P40, P45, P48 | oncogene, fusion | No | No | No | 9 |
| HIST1H1C     | P06, P14, P18, P26, P34, P38, P53 | No | No | No | 8 |
| CARD11       | P01, P20, P40, P43, P45, P46, P48, P52 | oncogene, TSG | No | No | No | 8 |
| MYC          | P04, P14, P22, P33, P34, P37, P50 | oncogene, fusion | No | No | No | 8 |
| LRP1B        | P04, P19, P20, P26, P36, P41, P52 | TSG | No | No | No | 8 |
| B2M          | P09, P11, P20, P27, P31, P38 | TSG | No | No | Yes | 7 |
| TET2         | P07, P11, P14, P16, P27, P28, P50 | TSG | TSG | pan_can_fre:1.60% | Yes | 7 |
| FOXO1        | P04, P11, P14, P15, P29, P34, P50 | oncogene, TSG, fusion | No | No | No | 7 |
| EBF1         | P01, P04, P17, P18, P26, P32, P53 | TSG, fusion | No | No | No | 7 |
| BTG1         | P06, P25, P27, P39, P40, P42 | TSG, fusion | No | No | No | 7 |
| SETD1B       | P08, P18, P31, P33, P46, P47, P52 | TSG | No | No | No | 7 |
| BCR          | P15, P18, P26, P35, P48, P53 | fusion | No | No | No | 6 |
| COL3A1       | P05, P10, P23, P24, P28, P38 | fusion | No | No | No | 6 |
| DDX3X        | P09, P10, P20, P29, P32, P50 | TSG | No | No | Yes | 6 |
| AHNAK2       | P04, P06, P20, P24, P26, P31 | No | No | No | Yes | 6 |
| PIM1         | P21, P26, P35, P37, P46, P52 | oncogene, fusion | No | No | No | 6 |
| ID3          | P14, P15, P22, P26, P29, P51 | TSG | No | No | No | 6 |
| DNM2         | P01, P13, P20, P28, P38, P40 | TSG | No | No | No | 6 |
| PTPN6        | P06, P11, P12, P25, P38 | TSG | No | No | No | 5 |
| FAT1         | P03, P07, P09, P13, P36 | TSG | No | No | No | 5 |
| ROBO2        | P03, P06, P19, P24, P33 | TSG | No | No | No | 5 |
| NFKBIA       | P12, P18, P43, P50, P53 | No | No | No | 5 |
| BCL7A        | P12, P26, P34, P40, P53 | fusion | No | No | No | 5 |
| SGK1         | P04, P06, P18, P25, P28 | oncogene | No | No | Yes | 5 |
| ZEB2         | P06, P13, P31, P48 | No | No | No | Yes | 4 |
| MEF2B        | P08, P34, P47, P52 | No | No | No | Yes | 4 |
| PRDM1        | P36, P37, P44, P45 | TSG | TSG | No | No | 4 |
| CD79B        | P02, P03, P08, P46 | oncogene | No | No | No | 4 |
| NFKBIE       | P17, P19, P38, P48 | TSG | No | No | No | 4 |
| SOCS1        | P26, P28, P38, P43 | TSG | TSG | No | No | 4 |
| FAT3         | P05, P20, P21, P40 | No | No | No | Yes | 4 |
| CHD4         | P07, P24, P35, P40 | oncogene | No | No | Yes | 4 |
| NCOR2        | P02, P20, P36, P42 | TSG | No | No | Yes | 4 |
| ZFP36L2      | P08, P20, P26, P39 | No | No | No | Yes | 4 |
| DST          | P04, P05, P45, P47 | No | No | No | Yes | 4 |
| KIAA1549     | P20, P37, P40, P43 | fusion | No | No | No | 4 |
| AHNAK        | P17, P45, P47, P51 | No | No | No | Yes | 4 |
Table 2 (continued)

| #Gene Symbol | Sample | COSMIC | MDG125 | SMG127 | CDG291 | Patient_ Number_Count |
|--------------|--------|--------|--------|--------|--------|-----------------------|
| GNAQ         | P06, P38, P46, P51 | oncogene | Oncogene | No | No | 4 |
| TBL1XR1      | P06, P18, P26, P51 | oncogene, TSG, fusion | No | pancan_fre:0.80% | Yes | 4 |
| HLA-B        | P13, P19, P24, P27 | No | No | No | Yes | 4 |
| BRAF         | P01, P04, P06, P53 | oncogene, fusion | Oncogene | pancan_fre:1.50% | Yes | 4 |
| ACTB         | P06, P17, P20, P35 | No | No | No | Yes | 4 |
| PLEC         | P06, P11, P28, P40 | No | No | No | Yes | 4 |
| SYNE1        | P04, P06, P33, P34 | No | No | No | Yes | 4 |
| DCC          | P03, P24, P36, P52 | No | No | No | Yes | 4 |
| ROS1         | P01, P20, P24, P45 | oncogene, fusion | No | No | No | 4 |
| ARID1A       | P04, P11, P18, P22 | TSG, fusion | TSG | pancan_fre:5.40% | Yes | 4 |
| TNFRSF14     | P06, P11, P14, P25 | TSG | No | No | No | 4 |
| STAT3        | P04, P18, P19, P48 | oncogene | No | No | Yes | 4 |
| PIK3CD       | P13, P16, P20 | No | No | No | No | 3 |
| FAM135B      | P06, P20, P38 | No | No | No | No | 3 |
| TRIO         | P04, P36, P40 | No | No | No | Yes | 3 |
| TRIM24       | P03, P20, P50 | oncogene, TSG, fusion | No | No | No | 3 |
| UBR5         | P04, P20, P43 | TSG | No | No | No | 3 |
| FAM47C       | P04, P17, P34 | No | No | No | No | 3 |
| LRRK2        | P09, P42, P52 | No | No | pancan_fre:2.80% | Yes | 3 |
| GRIN2A       | P01, P04, P20 | TSG | No | No | No | 3 |
| FBN2         | P01, P09, P20 | No | No | No | Yes | 3 |
| NEB          | P01, P36, P51 | No | No | No | Yes | 3 |
| IRS2         | P02, P50, P53 | No | No | No | Yes | 3 |
| PRKCD        | P06, P11, P24 | No | No | No | Yes | 3 |
| ACTG1        | P06, P14, P26 | No | No | No | Yes | 3 |
| KALRN        | P20, P31, P43 | No | No | No | Yes | 3 |
| BIRC6        | P06, P09, P20 | oncogene, fusion | No | No | No | 3 |
| CLTC         | P16, P20, P50 | TSG, fusion | No | No | Yes | 3 |
| APC          | P06, P18, P36 | TSG | TSG | pancan_fre:7.30% | Yes | 3 |
| PTEN         | P01, P09, P35 | TSG | TSG | pancan_fre:9.70% | Yes | 3 |
| CXCR4        | P01, P26, P50 | oncogene | No | No | No | 3 |
| JMD10C       | P03, P08, P12 | No | No | No | Yes | 3 |
| FAS          | P06, P09, P18 | TSG | No | No | No | 3 |
| BCL6         | P05, P43, P52 | oncogene, fusion | No | No | No | 3 |
| PCBP1        | P09, P44, P46 | No | No | pancan_fre:0.30% | Yes | 3 |
| BCL11B       | P07, P11, P12 | oncogene, TSG, fusion | No | No | No | 3 |
| FPR3         | P01, P36, P50 | TSG | No | No | No | 3 |
| CIITA        | P11, P25, P40 | TSG, fusion | No | No | Yes | 3 |
| HGF          | P09, P36, P48 | No | No | pancan_fre:1.70% | Yes | 3 |
| IRF4         | P08, P38, P42 | oncogene, TSG, fusion | No | No | Yes | 3 |
| NIN          | P17, P27, P36 | fusion | No | No | No | 3 |
| RARA         | P10, P33, P48 | oncogene, fusion | No | No | No | 3 |
| TRRAP        | P20, P36, P50 | oncogene | No | No | No | 3 |
| MAP2K1       | P12, P28, P50 | oncogene | Oncogene | No | No | 3 |
| KMT2C        | P05, P11, P15 | TSG | No | No | No | 3 |
Table 2 (continued)

| #Gene Symbol | Sample     | COSMIC       | MDG125 | SMG127 | CDG291 | Patient Number Count |
|--------------|------------|--------------|--------|--------|--------|----------------------|
| PABPC1       | P25, P26, P32 | oncogene, TSG | No     | No     | Yes    | 3                    |
| PIK3CB       | P32, P53    | oncogene     | No     | No     | Yes    | 2                    |
| CBLB         | P26, P52    | TSG          | No     | No     | No     | 2                    |
| MDN1         | P09, P53    | No           | No     | No     | Yes    | 2                    |
| RAB11FIP5    | P07, P20    | No           | No     | No     | Yes    | 2                    |
| FIP1L1       | P01, P15    | fusion       | No     | No     | No     | 2                    |
| CFH          | P09, P20    | No           | No     | No     | Yes    | 2                    |
| KDM6B        | P26, P53    | No           | No     | No     | Yes    | 2                    |
| MYCN         | P25, P27    | oncogene     | No     | No     | No     | 2                    |
| CAMTA1       | P37, P51    | TSG, fusion  | No     | No     | No     | 2                    |
| TCF7         | P41, P44    | No           | No     | No     | Yes    | 2                    |
| PDGFRB       | P20, P40    | oncogene, fusion | Oncogene | pancan_fre:1.90% | Yes | 2                    |
| TET1         | P09, P20    | oncogene, TSG, fusion | No | No | No | 2 |
| ARHGAP32     | P01, P04    | No           | No     | No     | Yes    | 2                    |
| SFRP4        | P09, P12    | TSG          | No     | No     | No     | 2                    |
| PRRC2A       | P20, P50    | No           | No     | No     | Yes    | 2                    |
| NTRK2        | P04, P25    | No           | No     | No     | No     | 2                    |
| HSP90A1B     | P11, P20    | fusion       | No     | No     | Yes    | 2                    |
| KRAS         | P25, P28    | oncogene     | Oncogene | pancan_fre:6.70% | Yes | 2                    |
| PCM1         | P06, P24    | fusion       | No     | No     | Yes    | 2                    |
| SMARCA4      | P15, P28    | TSG          | TSG    | No     | Yes    | 2                    |
| CHD8         | P38, P50    | No           | No     | No     | Yes    | 2                    |
| NCOR1        | P03, P32    | TSG          | TSG    | No     | Yes    | 2                    |
| ZFP36L1      | P26, P46    | No           | No     | No     | Yes    | 2                    |
| MKI67        | P17, P45    | No           | No     | No     | Yes    | 2                    |
| RQPD3        | P45, P48    | No           | No     | No     | No     | 2                    |
| FBXO11       | P07, P51    | TSG          | No     | No     | Yes    | 2                    |
| LRIG3        | P01, P20    | TSG, fusion  | No     | No     | No     | 2                    |
| NFATC2       | P08, P43    | oncogene, fusion | No | No | No | 2 |
| KIT          | P10, P23    | oncogene     | Oncogene | pancan_fre:1.40% | Yes | 2                    |
| CREBBP       | P09, P20    | oncogene, TSG, fusion | TSG | No | No | 2 |
| TCL1A        | P07, P25    | oncogene, fusion | No | No | No | 2 |
| MSH3         | P12, P42    | No           | No     | No     | No     | 2                    |
| SF3B1        | P01, P11    | oncogene     | Oncogene | pancan_fre:1.30% | Yes | 2                    |
| PRKCB        | P04, P13    | No           | No     | No     | No     | 2                    |
| ZNF91        | P24, P40    | No           | No     | No     | Yes    | 2                    |
| BCLAF1       | P09, P53    | No           | No     | No     | Yes    | 2                    |
| MAP3K4       | P11, P13    | No           | No     | No     | Yes    | 2                    |
| FGFR4        | P45, P50    | oncogene     | No     | No     | No     | 2                    |
| FGFR2        | P45, P52    | oncogene, fusion | Oncogene | pancan_fre:1.50% | Yes | 2                    |
| PRPF8        | P01, P09    | No           | No     | No     | Yes    | 2                    |
| SPEN         | P11, P38    | TSG          | No     | No     | Yes    | 2                    |
| SPEG         | P45, P53    | No           | No     | No     | Yes    | 2                    |
| PGDE4DIP     | P03, P38    | fusion       | No     | No     | No     | 2                    |
| AFF3         | P01, P17    | oncogene, fusion | No | No | No | 2 |
| SALL4        | P40, P50    | oncogene     | No     | No     | No     | 2                    |
| #Gene Symbol | Sample        | COSMIC | MDG125 | SMG127 | CDG291 | Patient Number Count |
|--------------|---------------|--------|--------|--------|--------|----------------------|
| ANKRD11      | P04, P35      | No     | No     | No     | Yes    | 2                    |
| TFDP1        | P26, P42      | No     | No     | No     | Yes    | 2                    |
| INPP4B       | P36, P50      | No     | No     | No     | No     | 2                    |
| MICAL1       | P09, P40      | No     | No     | No     | Yes    | 2                    |
| SIN3A        | P15, P34      | No     | No     | No     | Yes    | 2                    |
| HLA-A        | P12, P18      | fusion | No     | No     | Yes    | 2                    |
| TFEB         | P04, P28      | oncogene, fusion | No | No | Yes | 2 |
| KIAA1109     | P20, P40      | No     | No     | No     | Yes    | 2                    |
| TNFAIP3      | P11, P36      | TSG    | TSG    | No     | No     | 2                    |
| TP63         | P09, P11      | oncogene, TSG | No | No | No | 2 |
| PTPRD        | P40, P45      | TSG    | No     | No     | No     | 2                    |
| CLTCL1       | P20, P48      | TSG, fusion | No | No | Yes | 2 |
| ZMYM3        | P09, P20      | TSG    | No     | No     | No     | 2                    |
| MGA          | P01, P41      | No     | No     | No     | Yes    | 2                    |
| NSD1         | P48, P51      | fusion | No     | No     | Yes    | 2                    |
| CSF1R        | P20, P42      | oncogene, Oncogene | No | No | No | 2 |
| MEGF6        | P11, P45      | No     | No     | No     | Yes    | 2                    |
| HIST1H3B     | P01, P26      | oncogene | Oncogene | No | No | No | 2 |
| ADCY1        | P03, P20      | No     | No     | No     | Yes    | 2                    |
| RET          | P17, P27      | oncogene, fusion | Oncogene | No | No | No | 2 |
| EPHA7        | P26, P36      | No     | No     | No     | No     | 2                    |
| EPHA3        | P20, P51      | No     | No     | No     | Yes    | 2                    |
| RBM15        | P04, P09      | fusion | No     | No     | No     | 2                    |
| ZNFS21       | P08, P09      | oncogene, fusion | No | No | No | 2 |
| CNTNAP2      | P09, P35      | TSG    | No     | No     | No     | 2                    |
| RASA1        | P28, P51      | No     | No     | No     | Yes    | 2                    |
| PTPRC        | P26, P31      | TSG    | No     | No     | No     | 2                    |
| CAD          | P30, P37      | No     | No     | No     | Yes    | 2                    |
| EPS15        | P32, P50      | TSG, fusion | No | No | No | 2 |
| EXT2         | P05, P20      | TSG    | No     | No     | No     | 2                    |
| RAG1         | P24, P38      | No     | No     | No     | Yes    | 2                    |
| CDH10        | P03, P12      | TSG    | No     | No     | No     | 2                    |
| ZFHX3        | P01, P20      | TSG    | No     | No     | Yes    | 2                    |
| MOR          | P07, P51      | oncogene | No | No | Yes | 2 |
| EP300        | P06, P09      | TSG, fusion | TSG | pancan fre:2.50% | Yes | 2 |
| CNDND1       | P06, P12      | TSG, fusion | No | No | No | 2 |
| ABCB1        | P24, P42      | No     | No     | No     | Yes    | 2                    |
| CNTNNA2      | P09, P25      | oncogene | No | No | No | 2 |
| NOTCH1       | P33, P37      | oncogene, TSG, fusion | TSG | pancan fre:3.10% | Yes | 2 |
| IKBKB        | P09, P27      | oncogene | No | No | No | 2 |
| MYOSA        | P01, P38      | fusion | No     | No     | No     | 2                    |
| STRN         | P20, P50      | fusion | No     | No     | No     | 2                    |
| NRG1         | P20, P53      | TSG, fusion | No | No | No | 2 |
| MALT1        | P28, P48      | oncogene, fusion | No | No | No | 2 |
| PHF6         | P08, P20      | TSG    | TSG    | No     | No     | 2                    |
| NAV3         | P04, P45      | No     | No     | No     | Yes    | 2                    |
| MYCBP2       | P04, P43      | No     | No     | No     | Yes    | 2                    |
| #Gene Symbol | Sample | COSMIC | MDG125 | SMG127 | CDG291 | Patient_Number_Count |
|--------------|--------|--------|--------|--------|--------|---------------------|
| NBEA         | P48, P53 |        | No     | No     | Yes    | 2                   |
| HSP90AA1     | P04, P26 | fusion | No     | No     | No     | 2                   |
| CHD7         | P31, P37 | No     | No     | No     | Yes    | 2                   |
| PIK3CG       | P52     | No     | No     | panCan_fre:1.70% | Yes | 1               |
| HIST1H4I     | P14     | fusion | No     | No     | No     | 1                   |
| HSPA8        | P04     | No     | No     | No     | Yes    | 1                   |
| NUP98        | P20     | oncoGene, fusion | No | No | Yes | 1 | |
| XPA          | P46     | TSG    | No     | No     | No     | 1                   |
| CEP89        | P04     | fusion | No     | No     | No     | 1                   |
| XPO1         | P28     | oncoGene | No | No | No | 1 | |
| CSDE1        | P51     | No     | No     | No     | Yes    | 1                   |
| TTK          | P09     | No     | No     | No     | No     | 1                   |
| COL1A1       | P26     | fusion | No     | No     | No     | 1                   |
| ZEB1         | P52     | oncoGene | No | No | No | 1 | |
| ITGAV        | P13     | No     | No     | No     | No     | 1                   |
| ZNF703       | P14     | No     | No     | No     | Yes    | 1                   |
| ERBB2IP      | P14     | No     | No     | No     | Yes    | 1                   |
| ARHGEF12     | P20     | TSG, fusion | No | No | No | 1 | |
| MUC1         | P29     | fusion | No     | No     | No     | 1                   |
| EWSR1        | P20     | oncoGene, fusion | No | No | Yes | 1 | |
| AHCTF1       | P26     | No     | No     | No     | No     | 1                   |
| RPL22        | P09     | TSG, fusion | No | panCan_fre:1.00% | Yes | 1 | |
| SIX2         | P22     | oncogene | No | No | No | 1 | |
| PRX          | P20     | No     | No     | panCan_fre:0.90% | Yes | 1 | |
| ARID2        | P06     | TSG    | TSG    | No     | Yes    | 1                   |
| SET          | P20     | oncogene, fusion | No | No | No | 1 | |
| ELK4         | P36     | oncoGene, fusion | No | No | No | 1 | |
| TRIM7        | P46     | No     | No     | No     | Yes    | 1                   |
| FBXW7        | P05     | TSG    | TSG    | panCan_fre:3.00% | Yes | 1 | |
| TGFB2        | P11     | TSG    | No     | panCan_fre:1.10% | Yes | 1 | |
| SH3PXD2A     | P20     | No     | No     | No     | Yes    | 1                   |
| SVIL         | P20     | No     | No     | No     | Yes    | 1                   |
| PHILDA1      | P21     | No     | No     | No     | Yes    | 1                   |
| NBF10        | P28     | No     | No     | No     | Yes    | 1                   |
| PBX1         | P50     | oncoGene, fusion | No | No | No | 1 | |
| ARHGAP35     | P20     | No     | No     | panCan_fre:2.50% | Yes | 1 | |
| PTCH1        | P33     | TSG    | TSG    | No     | No     | 1                   |
| CUL1         | P23     | No     | No     | No     | Yes    | 1                   |
| CDX2         | P20     | TSG, fusion | No | No | No | 1 | |
| PTPN13       | P12     | TSG    | No     | No     | Yes    | 1                   |
| IRS4         | P09     | oncogene, TSG | No | No | No | 1 | |
| DMD          | P06     | No     | No     | No     | Yes    | 1                   |
| PPM1D        | P09     | oncogene | No | No | No | 1 | |
| SRSF2        | P14     | oncogene | Oncogene | No | No | 1 | |
| RALGAPA1     | P17     | No     | No     | No     | Yes    | 1                   |
| EIF1AX       | P04     | No     | No     | No     | No     | 1                   |
| MED12        | P11     | TSG    | Oncogene | No | Yes | 1 | |
| NTRK3        | P45     | oncogene, fusion | No | No | No | 1 | |
### Table 2 (continued)

| #Gene Symbol | Sample | COSMIC | MDG125 | SMG127 | CDG291 | Patient_Number_Count |
|--------------|--------|--------|--------|--------|--------|----------------------|
| MED13        | P20    | No     | No     | No     | Yes    | 1                    |
| ARHGAP26     | P21    | TSG, fusion | No     | No     | No     | 1                    |
| SRGAP3       | P01    | fusion | No     | No     | No     | 1                    |
| ACSL6        | P01    | fusion | No     | No     | No     | 1                    |
| FLI1         | P01    | oncogene, fusion | No     | No     | No     | 1                    |
| CHD2         | P28    | TSG    | No     | No     | No     | 1                    |
| POLG         | P20    | TSG    | No     | No     | No     | 1                    |
| DDX5         | P23    | oncogene, fusion | No     | No     | No     | 1                    |
| MN1          | P52    | oncogene, fusion | No     | No     | No     | 1                    |
| PRDM16       | P24    | oncogene, fusion | No     | No     | No     | 1                    |
| POT1         | P53    | TSG    | No     | No     | No     | 1                    |
| ARHGAP5      | P20    | oncogene | No     | No     | No     | 1                    |
| SOS1         | P51    | No     | No     | No     | Yes    | 1                    |
| KIF20B       | P20    | No     | No     | No     | Yes    | 1                    |
| TSHZ2        | P47    | No     | No     | pan-can_freq:1.80% | No | 1                    |
| EIF3E        | P45    | TSG, fusion | No     | No     | No     | 1                    |
| BCL2L12      | P39    | oncogene | No     | No     | No     | 1                    |
| KAT6A        | P41    | oncogene, fusion | No     | No     | No     | 1                    |
| CDH11        | P27    | TSG, fusion | No     | No     | No     | 1                    |
| BAP1         | P53    | TSG    | TSG    | pan-can_freq:2.00% | Yes | 1                    |
| UBE4A        | P20    | No     | No     | No     | Yes    | 1                    |
| JAK2         | P09    | oncogene, fusion | Oncogene | No     | Yes    | 1                    |
| N4BP2        | P26    | TSG    | No     | No     | No     | 1                    |
| GRM3         | P13    | oncogene | No     | No     | No     | 1                    |
| ZNF384       | P06    | fusion | No     | No     | No     | 1                    |
| AKAP9        | P01    | fusion | No     | No     | Yes    | 1                    |
| EEF1A1       | P08    | No     | No     | No     | Yes    | 1                    |
| PBRM1        | P20    | TSG    | TSG    | pan-can_freq:5.40% | Yes | 1                    |
| ERC1         | P48    | fusion | No     | No     | No     | 1                    |
| ERG          | P36    | oncogene, fusion | No     | No     | No     | 1                    |
| MYOD1        | P36    | oncogene | No     | No     | No     | 1                    |
| CDK12        | P25    | TSG    | No     | pan-can_freq:1.50% | Yes | 1                    |
| A1CF         | P45    | oncogene | No     | No     | No     | 1                    |
| WT1          | P23    | oncogene, TSG, fusion | TSG    | pan-can_freq:1.00% | Yes | 1                    |
| BARD1        | P31    | TSG    | No     | No     | Yes    | 1                    |
| BAZ1A        | P31    | TSG    | No     | No     | No     | 1                    |
| FNI          | P01    | No     | No     | No     | Yes    | 1                    |
| FUBP1        | P51    | oncogene | TSG    | No     | No     | 1                    |
| PRRX1        | P51    | fusion | No     | No     | No     | 1                    |
| ATR          | P25    | TSG    | No     | pan-can_freq:2.40% | Yes | 1                    |
| BRIP1        | P53    | TSG    | No     | No     | No     | 1                    |
| FLT1         | P01    | No     | No     | No     | No     | 1                    |
| FANCF        | P40    | TSG    | No     | No     | No     | 1                    |
| PTK6         | P12    | oncogene, TSG | No     | No     | No     | 1                    |
| MSH6         | P20    | TSG    | TSG    | No     | No     | 1                    |
| SPECC1       | P45    | fusion | No     | No     | No     | 1                    |
| PRKCI        | P01    | No     | No     | No     | No     | 1                    |
Table 2 (continued)

| #Gene Symbol | Sample | COSMIC | MDG125 | SMG127 | CDG291 | Patient_Number_Count |
|--------------|--------|--------|--------|--------|--------|----------------------|
| MATK         | P48    | No     | No     | No     | Yes    | 1                    |
| ACKR3        | P50    | oncogene, fusion | No     | No     | No     | 1                    |
| ERBB3        | P32    | oncogene | No     | No     | No     | 1                    |
| IDH2         | P42    | oncogene | Oncogene | pancan_fre:0.80% | Yes | 1                   |
| FGFR3        | P13    | oncogene, fusion | Oncogene | pancan_fre:1.00% | Yes | 1                   |
| FGFR1        | P51    | oncogene, fusion | No     | No     | No     | 1                    |
| AFF4         | P31    | oncogene, fusion | No     | No     | No     | 1                    |
| MAP1 B       | P08    | No     | No     | No     | Yes    | 1                    |
| EBP41L3      | P04    | No     | No     | No     | Yes    | 1                    |
| TPR          | P43    | fusion | No     | No     | Yes    | 1                    |
| GNAS         | P19    | oncogene | Oncogene | No     | Yes    | 1                    |
| RBMX         | P53    | No     | No     | No     | Yes    | 1                    |
| AFF1         | P06    | fusion | No     | No     | No     | 1                    |
| CDKN2C       | P26    | TSG    | No     | pancan_fre:0.20% | Yes | 1                   |
| WHSC1L1      | P04    | oncogene, fusion | No     | No     | Yes    | 1                    |
| GOT2         | P47    | No     | No     | No     | Yes    | 1                    |
| LYN          | P11    | No     | No     | No     | Yes    | 1                    |
| MGMT         | P06    | TSG    | No     | No     | No     | 1                    |
| PMS1         | P20    | No     | No     | No     | No     | 1                    |
| PMS2         | P20    | TSG    | No     | No     | No     | 1                    |
| LHFIP        | P14    | fusion | No     | No     | No     | 1                    |
| AMER1        | P52    | TSG    | No     | No     | No     | 1                    |
| NACA         | P09    | fusion | No     | No     | No     | 1                    |
| FGF4         | P13    | No     | No     | No     | No     | 1                    |
| FGF3         | P35    | No     | No     | No     | No     | 1                    |
| HOXD11       | P40    | oncogene, fusion | No     | No     | No     | 1                    |
| SMCHD1       | P03    | No     | No     | No     | Yes    | 1                    |
| JAZF1        | P19    | fusion | No     | No     | No     | 1                    |
| BCOR         | P40    | TSG, fusion | TSG    | No     | Yes    | 1                    |
| ADAM10       | P03    | No     | No     | No     | Yes    | 1                    |
| G3BP1        | P09    | No     | No     | No     | Yes    | 1                    |
| BCL10        | P05    | TSG, fusion | No     | No     | No     | 1                    |
| CDKN1B       | P40    | TSG    | No     | pancan_fre:0.70% | Yes | 1                   |
| SETBP1       | P12    | oncogene, fusion | Oncogene | pancan_fre:2.20% | No | 1                   |
| AKT1         | P14    | oncogene | Oncogene | No     | Yes    | 1                    |
| PSIP1        | P50    | oncogene, fusion | No     | No     | No     | 1                    |
| CCDC6        | P36    | TSG, fusion | TSG    | No     | No     | 1                    |
| ARHGEF10     | P25    | TSG    | No     | No     | No     | 1                    |
| REL          | P19    | oncogene | No     | No     | No     | 1                    |
| COL2A1       | P17    | fusion | No     | No     | No     | 1                    |
| TSC1         | P12    | TSG    | TSG    | No     | No     | 1                    |
| SMC3         | P26    | No     | No     | No     | No     | 1                    |
| ARID5B       | P37    | No     | No     | No     | No     | 1                    |
| IGF1R        | P15    | No     | No     | No     | No     | 1                    |
| HNF1A        | P20    | TSG    | TSG    | No     | No     | 1                    |
| ELF3         | P26    | No     | No     | No     | No     | 1                    |
| ARHGEF6      | P51    | No     | No     | No     | Yes    | 1                    |
| CDH1         | P48    | TSG    | TSG    | pancan_fre:2.50% | Yes | 1                   |
Table 2 (continued)

| #Gene Symbol | Sample | COSMIC | MDG125 | SMG127 | CDG291 | Patient_Number_Count |
|--------------|--------|--------|--------|--------|--------|---------------------|
| KIFC3        | P01    | No     | No     | No     | Yes    | 1                   |
| ARHGEF10L    | P21    | TSG    | No     | No     | No     | 1                   |
| NEK8         | P17    | No     | No     | No     | Yes    | 1                   |
| FAM129B      | P20    | No     | No     | No     | Yes    | 1                   |
| IL7R         | P36    | oncogene | No   | No     | No     | 1                   |
| MYH9         | P10    | TSG, fusion | No | No     | Yes    | 1                   |
| CYLD         | P20    | TSG    | TSG    | No     | Yes    | 1                   |
| CASC5        | P09    | TSG, fusion | No | No     | No     | 1                   |
| NUTM1        | P48    | oncogene, fusion | No | No     | Yes    | 1                   |
| SOX17        | P11    | No     | No     | pan can_fre:0.30% | Yes | 1                   |
| BRCA1        | P11    | TSG    | TSG    | pan can_fre:1.90% | Yes | 1                   |
| BRCA2        | P20    | TSG    | TSG    | pan can_fre:2.70% | Yes | 1                   |
| WNK2         | P53    | TSG    | No     | No     | No     | 1                   |
| P4HB         | P26    | No     | No     | No     | Yes    | 1                   |
| ARNT         | P53    | oncogene, TSG, fusion | No | No     | No     | 1                   |
| BCL3         | P07    | oncogene, fusion | No | No     | No     | 1                   |
| RNF213       | P20    | fusion | No     | No     | Yes    | 1                   |
| DOCK2        | P32    | No     | No     | No     | Yes    | 1                   |
| 09-Sep       | P31    | fusion | No     | No     | No     | 1                   |
| 05-Sep       | P12    | fusion | No     | No     | No     | 1                   |
| DCAF12L2     | P23    | No     | No     | No     | No     | 1                   |
| NEDD4L       | P20    | No     | No     | No     | Yes    | 1                   |
| RAP1GD51     | P38    | oncogene, fusion | No | No     | No     | 1                   |
| RPP38        | P20    | No     | No     | No     | Yes    | 1                   |
| CTNND2       | P43    | oncogene | No | No     | No     | 1                   |
| ATRX         | P19    | TSG    | TSG    | pan can_fre:2.80% | Yes | 1                   |
| RAD51B       | P44    | TSG, fusion | No | No     | No     | 1                   |
| TPS38P1      | P20    | No     | No     | No     | Yes    | 1                   |
| PICALM       | P20    | fusion | No     | No     | No     | 1                   |
| BCL2         | P26    | oncogene, fusion | Oncogene | No | No     | 1                   |
| ASXL2        | P40    | TSG    | No     | No     | No     | 1                   |
| SMC1A        | P35    | TSG    | No     | pan can_fre:1.50% | Yes | 1                   |
| TLR4         | P43    | No     | No     | pan can_fre:1.90% | Yes | 1                   |
| KDM6A        | P50    | oncogene, TSG | TSG | pan can_fre:2.00% | Yes | 1                   |
| MET          | P06    | oncogene | Oncogene | No | No     | 1                   |
| DNM3         | P36    | No     | No     | No     | Yes    | 1                   |
| BCL11A       | P20    | oncogene, fusion | No | No     | No     | 1                   |
| GATA3        | P20    | oncogene, TSG | TSG | pan can_fre:3.20% | Yes | 1                   |
| RPN1         | P45    | fusion | No     | No     | No     | 1                   |
| EPPK1        | P11    | No     | No     | pan can_fre:1.40% | Yes | 1                   |
| AXL          | P20    | No     | No     | No     | No     | 1                   |
| CBL          | P26    | oncogene, TSG, fusion | Oncogene | No | No     | 1                   |
| PRDM2        | P46    | TSG    | No     | No     | Yes    | 1                   |
| GIGYF2       | P03    | No     | No     | No     | Yes    | 1                   |
| NR4A2        | P12    | No     | No     | No     | Yes    | 1                   |
| MTF          | P38    | oncogene | No | No     | No     | 1                   |
| #Gene Symbol | Sample | COSMIC | MDG125 | SMG127 | CDG291 | Patient_Number_Count |
|--------------|--------|--------|--------|--------|--------|----------------------|
| RPTOR        | P08    | No     | No     | No     | No     | 1                    |
| CNOT3        | P46    | TSG    | No     | No     | No     | 1                    |
| BRD3         | P20    | oncogene, fusion | No     | No     | No     | 1                    |
| SPTAN1       | P43    | No     | No     | No     | Yes    | 1                    |
| PPF1BP1      | P20    | fusion | No     | No     | No     | 1                    |
| MKL1         | P50    | oncogene, TSG, fusion | No     | No     | No     | 1                    |
| FANCD2       | P50    | TSG    | No     | No     | No     | 1                    |
| ZBTB16       | P06    | TSG, fusion | No     | No     | No     | 1                    |
| DOCK4        | P47    | No     | No     | No     | Yes    | 1                    |
| SND1         | P50    | oncogene, fusion | No     | No     | No     | 1                    |
| ERCC3        | P45    | TSG    | No     | No     | No     | 1                    |
| USP6         | P07    | oncogene, fusion | No     | No     | No     | 1                    |
| HIP1         | P52    | oncogene, fusion | No     | No     | No     | 1                    |
| INTS1        | P32    | No     | No     | No     | Yes    | 1                    |
| TGOLN2       | P38    | No     | No     | No     | Yes    | 1                    |
| IDH1         | P14    | oncogene | Oncogene | pancan_fre:1.50% | Yes    | 1                    |
| PTPRK        | P39    | TSG, fusion | No     | No     | No     | 1                    |
| GMPS         | P40    | fusion | No     | No     | No     | 1                    |
| ATIC         | P03    | fusion | No     | No     | No     | 1                    |
| FOXA2        | P20    | No     | No     | No     | Yes    | 1                    |
| CDKN2A       | P22    | TSG    | TSG    | pancan_fre:0.50% | Yes    | 1                    |
| SKI          | P45    | oncogene | No     | No     | No     | 1                    |
| CCR7         | P11    | oncogene | No     | No     | No     | 1                    |
| FOSL2        | P06    | No     | No     | No     | Yes    | 1                    |
| PWWP2A       | P51    | fusion | No     | No     | No     | 1                    |
| DDR2         | P09    | oncogene | No     | No     | No     | 1                    |
| CD274        | P07    | TSG, fusion | No     | No     | No     | 1                    |
| CDH17        | P32    | oncogene | No     | No     | No     | 1                    |
| FANCA        | P26    | TSG    | No     | No     | Yes    | 1                    |
| ARID1B       | P38    | TSG    | TSG    | No     | No     | 1                    |
| NIPBL        | P09    | No     | No     | No     | Yes    | 1                    |
| KMT2A        | P19    | oncogene, fusion | No     | No     | No     | 1                    |
| ANKRND6      | P01    | No     | No     | No     | Yes    | 1                    |
| CTNNBD1      | P03    | No     | No     | No     | Yes    | 1                    |
| MACF1        | P11    | No     | No     | No     | Yes    | 1                    |
| PABPC4       | P27    | No     | No     | No     | Yes    | 1                    |
| PREX2        | P26    | oncogene | No     | No     | No     | 1                    |
| ZNRF3        | P04    | TSG    | No     | No     | No     | 1                    |
| ETV1         | P20    | oncogene, fusion | No     | No     | No     | 1                    |
| ETV5         | P09    | oncogene, fusion | No     | No     | No     | 1                    |
| TAF1         | P06    | No     | No     | No     | pancan_fre:2.30% | Yes    | 1                    |
| HOXA11       | P14    | oncogene, TSG, fusion | No     | No     | No     | 1                    |
| ABL2         | P01    | oncogene, fusion | No     | No     | No     | 1                    |
| POLD1        | P20    | TSG    | No     | No     | No     | 1                    |
| HMGA2        | P13    | oncogene, fusion | No     | No     | No     | 1                    |
| MSN          | P04    | fusion | No     | No     | Yes    | 1                    |
| ZRSR2        | P22    | TSG    | No     | No     | No     | 1                    |
and LRP1B, two important tumor suppressor genes (TSGs) reported in many human cancers (Fig. 5A, B). Moreover, HBsAg positive pGI-DLBCL patients have a significant shorter overall survival (OS), when compared to those without HBV infection (Fig. 5C). These results indicated that genetic mutations in pGI-DLBCL patients were associated with certain clinicopathological parameters, and HBV infection could possibly cause worse prognosis due to mutation in TSGs.

**Mutations correlated with patient survival in pGI-DLBCL**

In order to find potential genetic mutations with predictive value for patient OS, we performed survival analysis with the top 30 mutated genes in our pGI-DLBCL patient cohort. Most of the mutated genes were not significantly associated with patient OS. However, we did observe that patients with IGLL5 mutations presented with a better OS, and LRP1B mutations led to a shorter OS (Fig. 6A). A large proportion of the mutations in IGLL5 were missense variants located at its N-terminus uncharacterized domains, and the LRP1B mutations were all missense variants evenly distributed across the entire protein structure (Fig. 6B and Additional file 5: Table S5). How these mutations affect individual gene function and the patient survival needs further exploration.

**Discussion**

In the current study, we performed WES of the largest cohort of pGI-DLBCL to date and identified putative cancer driver mutations and their enriched signaling pathways. We also revealed that HBV infection had an impact on the exonic mutation profile pGI-DLBCL, and mutations of IGLL5 and LRP1B genes could predict patient survival, which to our knowledge, was previously unreported by others.

In accordance with the previous reports [17], our analysis of the pGI-DLBCL exome confirmed the high prevalence of mutations in the cell cycle and apoptosis regulatory pathway, with potential tumor driver mutations in TP53 (22/53), CCND3 (9/53) and MYC (8/53) in over 60% patients. TP53 mutations displayed a significantly increased frequency and MYD88 (0/53), NFKBIE (4/53) or CD79B (4/53) mutations were less or not found in our pGI-DLBCL cohort, suggesting that the pathogenesis of pGI-DLBCL were different from the nodal or other extranodal DLBCL, which relies on an activated NF-κB signaling pathway due to the common mutations in the above mentioned MYD88, NFKBIE, or CD79B genes [26]. Furthermore, mutation frequencies of MUC16 (10/53), CSMD3 (10/53), RYR2 (10/53), FAT4 (9/53), TET2 (7/53), EBF1 (7/53) and
SETD1B (7/53), which functions at the transcriptional regulation, epigenetic modification or either cellular attachment, were also increased compared to those in common DLBCL according to COSMIC database. Third, we also identified a relatively large proportion of gene mutations, like P2RY8 (14/53), LRP1B (8/53), B2M (7/53), BCR (6/53), that seldom mentioned by other DLBCL sequencing studies but may probably become the oncogenic events by modulating the B cell migratory behavior and signaling activation [27, 28].
Therefore, we hypothesized that the mutation signature of pGI-DLBCL was different from other DLBCL subtypes, and the potential oncogenic driver mutations should be validated by further research.

Another important finding of our study was that HBV infection may affect the mutation spectrum of pGI-DLBCL. We showed that the oncogenic driver mutations were significantly enriched in the HBV regulatory pathway, and patients with positive HBsAg status had a relatively shorter OS and were more likely to carry TP53 and LRP1B mutations, both of which are supposed to function as TSGs during lymphomagenesis process. Previous studies have shown that HBV infection could cause an enhanced rate of mutagenesis and a distinct set of mutation targets in common DLBCL genome [21]. It is worth mentioning that the three genes, namely IGLL5,
TP53 and BTG2, are among the top 5 most mutated genes among their and our WES data. Interestingly, LRP1B have been described as a common target gene for HBV integration in liver cancer [29]. In addition, meta-analysis also revealed that patients infected with HBV had a higher risk of developing DLBCL, and those HBsAg-positive DLBCL patients tended to be diagnosed at a younger age with a more advanced clinical stage and worse outcome [30, 31]. Our study presents the first genmic analysis reinforcing the relationship between HBV infection and the mutation signature of pGI-DLBCL. However, further investigations are needed to verify the interactive mechanism between HBV integration and pGI-DLBCL genome, and how the HBV-related mutations affect the pathogenesis and development processes of pGI-DLBCL disease.

Highlighting the clinical significance of our finding, we identified that two recurrent mutations, IGLL5 and LRP1B, could serve as prognostic biomarkers for pGI-DLBCL patients. Although the function of IGLL5 has not been clarified, previous reports have shown that it was commonly mutated in DLBCL [32, 33] and is homologous to IGLL1, a gene which is critical for B-cell development [34]. In chronic lymphocytic leukemia (CLL), IGLL5 mutations were associated with a trend towards decreased overall gene expression, and patients bearing IGLL5 mutations were suggestive for the low-risk of CLL [35], which to some extent, was consistent to our result showing that IGLL5 mutated pGI-DLBCL patients had a better OS. On the other hand, LRP1B is giant membrane molecule that is among the most altered genes in human malignancies [36]. Functional studies have confirmed that LRP1B expression in cancer cells could reduce in vitro cell proliferation and migration abilities, and also suppress in vivo tumorigenicity in mouse models [37–40]. Genetic alteration events, such as deletions, point mutations or frameshift mutations commonly led to the inactivation of this TSG [41–43]. Therefore, it is speculated that LRP1B mutations found in our pGI-DLBCL cohort was associated with the impairment of its gene function, which could cause inferior result on disease progression. Despite we first propose that mutations of IGLL5 and LRP1B were significantly related to the survival of pGI-DLBCL patients, there is still a lack of detailed information on how the mutations affect their expression and/or functional role. Some research suggested that Tumor mutation burden estimated by cancer gene panels (CGPs) could be a potential predictor for prognostic stratification of Chinese DLBCL patients [44]. However, IGLL5 and LRP1B discovered in our study as potential biomarkers for the therapeutics or prognosis of pGI-DLBCL remain to be fully elucidated.

In summary, we performed a comprehensive analysis of the exonic mutation profile of the largest pGI-DLBCL cohort to date, which was characterized by an increased mutation frequency in TP53 and MYC, and a decrease rate or absence of MYD88 or CD79B alteration. We also revealed that HBV infection was related to the mutational signature and patient prognosis of pGI-DLBCL. IGLL5 and LRP1B could serve as predictive biomarkers for patient survival. Our study provides a deeper understanding of the genomic information of pGI-DLBCL and could facilitate the clinical development of novel therapeutic and prognostic biomarkers for pGI-DLBCL.

**Abbreviations**

ABC: Activated B-cell-like; CLL: Chronic lymphocytic leukemia; COSMIC: Catalog of somatic mutations in cancer; DAVID: Database for annotation, visualization and integrated discovery; DLBCL: Diffuse large B-cell lymphoma; ECOG: Eastern cooperative oncology group; GCB: Germinal center B-cell-like; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; InDel: Insertion or deletion; IPI: International prognostic index; KEGG: Kyoto encyclopedia of genes and genomes; LM-PCR: Ligation-mediated PCR; NHL: Non-Hodgkin lymphoma; OS: Overall survival; PMBCs: Peripheral blood mononuclear cells; pGI-DLBCL: Primary gastrointestinal diffuse large B-cell lymphoma; R-CHOP: Rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; SNV: Single nucleotide variant; TSG: Tumor suppressor gene; WES: Whole-exome sequencing.

**Supplementary Information**

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**Additional file 1:** Table S1. Clinicopathological information of 53 pGI-DLBCL patients.

**Additional file 2:** Table S2. Exonic mutation profile of 53 pGI-DLBCL patients.

**Additional file 3:** Table S3. KEGG enrichment results of recurrent driver genes in pGI-DLBCL.

**Additional file 4:** Table S4. Summary of the statistically significant correlations in the matrix.

**Additional file 5:** Table S5. Summary of IGLL5 and LRP1B mutations in pGI-DLBCL.

**Author contributions**

LSS, LYF and XJ conceived and designed the study. LSS, ZHX, LTZ, CTY, CDM, XLX, GXQ, CX and HWJ collected samples and patient information. LSS, ZHX and LHL performed the experiment. LHL and HY reviewed and confirmed the specimens. LSS, HY, LYF and XJ analyzed the data. LSS and LYF wrote the manuscript. LYF and XJ supervised the project and provided funding. All authors contributed to the article and approved the submitted version. All authors read and approved the final manuscript.

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Availablilty of data and materials
The data that support the findings of this study are available from the corresponding authors upon reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the Institute Research Ethics Committee at the Sixth Affiliated Hospital of Sun Yat-sen University. Written informed consent was obtained from each patient.

Competing interests
The authors declare that they have no competing interests.

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