PRODUCT DATA SHEET

DFCI Tissue-based Lymphoma Panel (TLP)

Overview

The Tissue-based Lymphoma Panel (TLP) assay is a targeted sequencing panel developed to interrogate fresh or archival blood, bone marrow, or tissue specimens for recurrent, clinically significant genetic variants in lymphoid malignancies. It has a baited footprint of 2.2 Mb and includes probes for 319 candidate cancer genes (CCGs) (Table 1), 58 selected focal somatic copy number alterations (CNA) (Table 2), all chromosome arms for detection of arm-level CNA (Table 3), and structural variants (SVs). The coding portions of the CCGs recurrently altered in lymphoma are tiled in their entirety, in addition to 3'-UTRs of selected genes (*NOTCH1*, *NFKBIZ*, *PDL1*, *PDL2*).

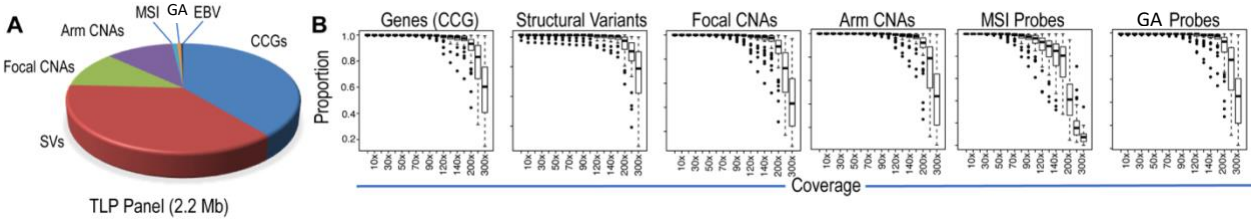

Figure 1. Targeted sequencing panel and coverage validation. (A) Tissue-based Lymphoma Panel (TLP) composition; (B) Proportion of candidate cancer genes (CCG), structural variants, focal CNAs, Arm-level CNAs, microsatellite instability (MSI) and genetic ancestry (GA) probes, with indicated coverage (*x*).

Baited SV regions encompass recurrent breakpoints identified in B-cell lymphomas (Burkitt lymphoma (*1*), diffuse large B-cell lymphoma (DLBCL) (*2-5*), chronic lymphocytic leukemia/small lymphocytic lymphoma(*6-8*), mantle cell lymphoma (*9-16*), Hodgkin lymphoma(*17-23*), or the closely related primary mediastinal B-cell lymphoma (*18, 24*)), or fusion genes identified in T-cell lymphomas (ALK-positive anaplastic large cell lymphoma (*25-28*), ALK-negative anaplastic large cell lymphoma (*29-32*), peripheral T-cell lymphomas (*33-41*), and cutaneous T-cell lymphomas (*42, 43*)). These baited regions allow detection of common fusions in B-cell lymphomas between immunoglobulin loci (*IGH, IGK, IGLL5*) and recurrent partners (*MYC, BCL2, BCL6, CCND1, CCND3*) with diagnostic and prognostic significance. Baits also target fusions between *TP63* and *TBL1XR1* and other structural variants of emerging importance in T cell lymphomas.

Epstein-Barr virus (EBV), has biological importance in B-cell lymphomas including Hodgkin lymphoma and DLBCL, is accounted for by probes covering two major genes (*LMP1* and *EBNA1*) in six strains of the virus. Additionally, the assay is designed to determine clinically integrated and biologically relevant features, such as, microsatellite instability (MSI), genetic ancestry (GA) and DLBCL molecular classification.

Methodology

TLP uses Illumina next-generation sequencing platforms to perform DNA sequencing. Bait design was optimized using the TWIST DNA chemistry which produces high-fidelity double-stranded DNA probes with increased specificity and uniform target enrichment. TWIST-designed probes are associated with increased sequencing depth due to the low frequency of dropout regions.

All chromosome arms are tiled with 120 bp SNP probes at a density of 1 probe every 0.6-1.0 megabases (MB). Focal CNA regions identified in B- & T-cell lymphomas by *GISTIC2.0* or cytogenetics are tiled with 120 bp SNP probes at a density of 1 probe every 200 kb (but no less than 10 probes per CNA). The use of SNP probes (population frequency > 10% and an alignment score > 0.5) permits detection of allelic shifts in addition to copy number determined by read pile-up. To optimize assay performance, the TLP preferentially tiles SNPs residing in exonic regions with alignment scores of 1 (per ENCODE Mappability metric), so that the probe sequences align to the genome only once. See Table 4 for more details.

Table 1. Genes for which coding regions are baited by the TLP and their respective genetic alterations.

ABCA13	●	*CLGN*	●	*HIST1H3B*	●	*NFKBIA*	●	*SCG3*	●		
ABL1	●	*CNKSR2*	●	*HIST2H2BE*	●◆	*NFKBIE*	●	*SEL1L3*	●		
ACTB	●	*COL6A3*	●	*HLA-A*	●◆	*NFKBIZ*	●□	*SESN3*	●		
ADAMTS4	●	*CRBN*	●	*HLA-B*	●◆	*NLRP8*	●◆	*SETD1B*	●		
ADD2	●	*CREBBP*	●	*HLA-C*	●◆	*NOL9*	●	*SETD2*	●		
ADGRB2	●	*CRIP1*	●	*HLA-DMA*	●◆	*NOTCH1*	●□	*SETD5*	●		
ADGRG6	●◆	*CSF2RB*	●	*HLA-DMB*	●◆	*NOTCH2*	●◆	*SETDB1*	●◆		
ADGRV1	●	*CTCF*	●	*HLA-DRA*	●	*NRAS*	●◆	*SETDB2*	●◆		
AKAP6	●	*CTSS*	●◆	*HNRNPD*	●◆	*NSD2*	●	*SF3B1*	●		
ALK	●□	*CXCR4*	●	*HVCN1*	●	*NTRK1*	●◆	*SGK1*	●◆		
ANKRD50	●	*DAZAP1*	●	*ID3*	●	*NUP214*	●	*SIN3A*	●		
AOC2	●	*DDX3X*	●	*IDH1*	●	*NXF1*	●	*SLC9A6*	●		
ARHGEF1	●	*DGKB*	●	*IDH2*	●	*OR51B6*	●	*SMARCA4*	●		
ARID1A	●◆	*DIRAS3*	●	*IGLL5*	●	*OSBPL10*	●	*SMG7*	●		
ARID1B	●◆	*DLC1*	●	*IGLV3-21*	●	*P2RY8*	●	*SOCS1*	●		
ARID2	●	*DLEU2*	●◆	*IKBKB*	●	*PABPC1*	●	*SOCS6*	●◆		
ARID5B	●	*DNMT3A*	●	*IKZF3*	●	*PAX5*	●□	*SP140*	●		
ASXL1	●	*DTX1*	●	*IL10RA*	●◆	*PCBP1*	●	*SPEN*	●		
ATM	●◆	*DUSP2*	●	*IL4R*	●	*PCLO*	●	*SPIB*	●		
ATP2A2	●	*DUSP22*	●□	*IL6*	●	*PDCD1*	●	*SRSF1*	●		
ATR	●	*DYRK1A*	●	*IRF2BP2*	●◆	*PDCD1LG2*	●◆□	*STAT3*	●		
AUTS2	●	*EBF1*	●	*IRF4*	●	*PDE4DIP*	●◆	*STAT5B*	●		
B2M	●◆	*ECT2L*	●◆	*IRF8*	●	*PDGFRB*	●	*STAT6*	●		
BAZ2A	●	*EEF1A1*	●	*ITK*	●□	*PEX14*	●	*SYNE1*	●◆		
BAZ2B	●	*EGR2*	●	*ITPKB*	●◆	*PIK3CA*	●	*TAF1*	●		
BCL10	●◆	*ENPP3*	●	*ITPR3*	●	*PIK3CD*	●	*TBL1XR1*	●□		
BCL11A	●◆	*ENTPD4*	●	*JAK1*	●	*PIM1*	●	*TCL1A*	●		
BCL2	●◆□	*EP300*	●	*JAK2*	●◆	*PIM2*	●	*TCTN2*	●		
BCL6	●◆□	*ERBB4*	●	*JAK3*	●◆	*PLCG1*	●	*TET2*	●		
BCL7A	●	*ETS1*	●	*KDM6A*	●	*PLCG2*	●	*TLR2*	●◆		
BCOR	●	*ETV6*	●◆□	*KIAA1671*	●	*PLXNB3*	●	*TMEM30A*	●◆		
BIRC3	●◆	*EZH2*	●	*KIR2DL3*	●◆	*POT1*	●	*TMSB4X*	●		
BRAF	●	*FADD*	●	*KIT*	●	*POU2AF1*	●◆	*TNFAIP3*	●◆		
BRCA1	●	*FAM50A*	●	*KLF2*	●◆	*POU2F2*	●	*TNFRSF10A*	●		
BRCA2	●◆	*FANCE*	●	*KLHL14*	●	*PPM1D*	●	*TNFRSF10B*	●		
BRCC3	●	*FAS*	●◆	*KLHL6*	●	*PPP4R3A*	●	*TNFRSF14*	●◆		
BRWD3	●	*FAT1*	●◆	*KMT2C*	●	*PRDM1*	●◆	*TNFRSF8*	●		
BTG1	●	*FAT2*	●	*KMT2D*	●	*PRKCB*	●	*TNIP1*	●		
BTG2	●◆	*FAT4*	●	*KRAS*	●	*PRUNE2*	●◆	*TOX*	●◆		
BTK	●	*FBXO11*	●	*LRP1B*	●	*PTCH1*	●◆	*TP53*	●		
CALR	●	*FBXW7*	●◆	*LTB*	●◆	*PTEN*	●◆	*TP63*	●◆□		
CARD11	●	*FOXC1*	●	*LYN*	●	*PTPN11*	●	*TRAF2*	●		
CCAR1	●	*FOXO1*	●	*MAGT1*	●	*PTPN14*	●◆	*TRAF3*	●◆		
CCDC27	●	*FYN*	●	*MAP2K1*	●	*PTPN6*	●	*TRRAP*	●◆		
CCL4	●	*GNA13*	●	*MAP2K2*	●	*PTPRD*	●	*TSC2*	●		
CCND1	●□	*GNAI2*	●	*MAP3K14*	●	*PTPRK*	●	*TUBGCP5*	●		
CCND2	●	*GNB1*	●	*MAPK1*	●	*RAC2*	●	*TUT4*	●		
CCND3	●◆□	*GNB2*	●	*MATN2*	●	*RAF1*	●	*UBE2A*	●		
CCR4	●	*GNE*	●	*MCL1*	●◆	*RB1*	●◆	*UBR5*	●		
CD19	●	*GPS2*	●	*MEF2B*	●◆	*RBM38*	●	*VAV1*	●◆		
CD274	●◆□	*GRB2*	●◆	*MEF2C*	●	*RCOR1*	●◆	*VMP1*	●		
CD58	●◆	*GRHPR*	●	*MGA*	●◆	*REL*	●◆	*WDFY3*	●◆		
CD70	●◆	*GRM7*	●	*MGARP*	●	*RELN*	●◆	*XPO1*	●◆		
CD79A	●	*HAVCR2*	●	*MIR15A*	●	*RET*	●	*YY1*	●		
CD79B	●	*HIST1H1B*	●	*MIR16-1*	●	*RFX7*	●	*ZC3H12A*	●		
CD83	●	*HIST1H1C*	●	*MIR17HG*	●◆	*RHOA*	●◆	*ZC3H18*	●		
CDKN1A	●□	*HIST1H1D*	●	*MS4A1*	●	*RIMS2*	●	*ZEB2*	●◆		
CDKN1B	●◆	*HIST1H1E*	●	*MTOR*	●	*ROS1*	●□	*ZFP36L1*	●		
CDKN2A	●◆	*HIST1H2AC*	●	*MYC*	●□	*RP1L1*	●	*ZNF217*	●		
CDKN2B	●◆	*HIST1H2AG*	●	*MYCBP2*	●	*RPS15*	●	*ZNF292*	●		
CHD2	●	*HIST1H2AM*	●	*MYD88*	●	*RPS17*	●	*ZNF296*	●◆		
CHD8	●	*HIST1H2BC*	●	*NCOR1*	●	*RPS23*	●	*ZNF423*	●		
CHEK2	●	*HIST1H2BD*	●	*NCOR2*	●□	*RRAS*	●	*ZNF608*	●		
CIITA	●□	*HIST1H2BK*	●	*NFKB1*	●	*S1PR1*	●				

Note: Only focal CNAs are shown in this table. SNV=●, CNA=◆, SV=□.

Table 2. Chromosomal regions of focal CNAs and lymphoma relevant CCGs present in these regions.

Region	Lymphoma CCGs	Region	Lymphoma CCGs
1q32.1	*BTG2, PTPN14*	9p24.1	*PDCD1LG2 (CD274), JAK2*
1p36.32	*TNFRSF14*	9p21.3	*CDKN2A, CDKN2B*
1p36.11	*ARID1A*	9q21.13	*PRUNE2, PTCH1*
1p31.1	--	10q23.31	*FAS, PTEN*
1p21-p22	*BCL10*	11q22-q23	*ATM, BIRC3, IL10RA, POU2AF1*
1p13.1	*CD58, NRAS*	11q23.3	*IL10RA*
1q23.3	*CTSS, MCL1, NBPF15, NOTCH2, NTRK1, PDE4DIP, SETDB1, HIST2H2BE*	12p13.2	*CDKN1B, ETV6*
1q42.12	*IRF2BP2, ITPKB, OR2M3*	13q12.3-q13.1	*BRCA2*
2p15	*BCL11A, REL, XPO1*	13q14.2	*DLEU2, RB1, SETDB2*
2q13	--	13q31.3	*MIR17HG*
2q22.2	*ZEB2*	13q34	--
3p21.31	*RHOA*	14q32.31	*RCOR1, TRAF3*
3q28	*BCL6, TP63*	15q25.2	--
4q21.22	*HNRNPD, WDFY3*	15q15.3	*B2M, MGA*
4q35.1	*FAT1, FBXW7, TLR2*	16q22.1	--
5p15.33	--	16q12.1	--
5q32	--	17p13.3	--
6p21.33	*CCND3*	17q24.3	--
6q25.3	*ARID1B, SYNE1*	17q25.1	*GRB2*
6p21	*HLA-A, HLA-B, HLA-C, HLA-DMA, HLA-DMB, LTB*	18q11.2	--
6q12	--	18q21.2	--
6q14.1	*TMEM30A*	18q21.32	--
6q21	*PRDM1*	18q22.2	*BCL2, SOCS6*
6q23.3	*ADGRG6, ECT2L, SGK1, TNFAIP3*	19q13.32	*ZNF296*
7q36.1	--	19p13.3	*CD70, VAV1*
7q22.1	*RELN, TRRAP*	19p13.2	--
8p11.23	--	19p13.1	*JAK3, KLF2, MEF2B*
8q12.1	*TOX*	19q13.42	*KIR2DL3, NLRP8*
8q24.22	--	21q11.2	--

Note: Chromosomal regions were baited with a resolution of at least 200kb to identify focal CNAs. Genes labeled in grey are not baited by TLP, genes in bold text are also present in Table 1.

Table 3. Arm-level chromosomal regions for CNA detection and lymphoma relevant CCGs present in these regions.

Chromosome arm	Lymphoma CCGs
1Q	*BTG2, CTSS, IRF2BP2, ITPKB, MCL1, NTRK1, OR2M3, PDE4DIP, SETDB1*
3P	*GNAI2, GRM7, MYD88, RHOA, SETD2, SETD5*
3Q	*ATR, BCL6, KLHL6, NFKBIZ, PIK3CA, TBL1XR1, TP63*
5Q	*ADGRV1, EBF1, FAT2, HAVCR2, ITK, PDGFRB, TNIP1, ZNF608*
6P	*CCND3, CD83, DUSP22, FANCE, FOXC1, HLA-A, HLA-B, HLA-C, HLA-DMA, HLA-DMB, IRF4, ITPR3, LTB, NFKBIE, PIM1*
6Q	*ADGRG6, ARID1B, ECT2, EEF1A1, ENPP3, FYN, PRDM1, PTPRK, ROS1, SGK1, SYNE1, TMEM30A, TNFAIP3, ZNF292*
7Q	*ABCA13, ACTB, CARD11, DGKB, IL6*
7Q	*AUTS2, BRAF, EZH2, KMT2C, PCLO, POT1, RELN, TRRAP*
9Q	*ABL1, NOTCH1, NUP214, PRUNE2, PTCH1*
11Q	*ATM, BIRC3, CCND1, ETS1, IL10RA, MS4A1, POU2AF1*
12P	*CDKN1B, ETV6, KRAS, PTPN6*
13q	*BRCA2, DLEU2, FOXO1, MIR17HG, MYCBP2, PABPC3, RB1, SETDB2*
17p	*GPS2, NCOR1, TP53, USP6*
18Q	*BCL2, KLHL14, SOCS6*
19Q	*ARHGEF1, CD79A, KIR2DL3, NLRP8, POU2F2, SPIB, ZNF296*

Note: All chromosome arms were baited with a resolution of at least 600kb to identify arm-level CNAs. The table only depicts those chromosomal arms which carry Lymphoma CCG's. Genes labeled in grey are not baited by TLP, genes in bold text are also present in Table 1.

Table 4. Technical specifications of the TLP assay.

Targeted Coverage	*2.2 Mb*
Coverage Deliverable	*≥400 MTC*
Sample Format	*Tumor only*
Input Materials	*200 ng gDNA for FFPE; 100 ng gDNA for fresh frozen samples*
Compatible Tissue	*FFPE tissue, fresh-frozen tissue, whole blood, dissociated cells, buffy coat*
Library preparation	*Enzymatic fragmentation; TWIST chemistry*
Adapters	*UMI-UDI*
Library cleanup	*TWIST Library Prep Kit 2 DNA Purification Beads*
Quantification and pooling	*Qubit*
Sequencing platform	*NextSeq 550Dx high-output; PE150*
Bcl2fastq	*v.2.19.1*
Raw data processing	*BWA-Mem v 0.7.15-r1140*
UMI correction	*Fgbio (v0.4.0)*
Variant caller	*GATK (v4.1.6.0)/MuTect2 & Strelka2 (v2.9.10)*
CNA caller	*GATK CNV (v4.1.6.0), CNVkit; compare to FACETS (v0.5.6)*
Structural variant caller	*Consensus calls of LUMPY, SVaBA, Manta-SV*
DLBCL molecular classifier	*Custom code*
dMMR/MSI caller	*Compare MSIDetect, MSI-SEQ, MSISensor, and MANTIS*
EBV detection	*Disambiguate v1.0.0 and custom code*
TMB estimation	*Custom code*
Fingerprinting	*NSGCheckMate*
Ancestry	*Custom code*
Data file formats	*FASTQ, BAM, VCF, MAF, BED*
Genome version	*hg19 (plan to transition to hg38 in the near future)*
Metrics	*GATK (v4.1.6.0) and Fgbio (v0.4.0)*
Variant annotation	*Integrate Ensembl Variant Effect Predictor (VEP), Oncotator, OncoPanelKB, VICC, and ASH Somatic Working Group systems*
Pipeline cutoff	*5 alternate reads and 1% VAF (NB: reporting cut-off will be higher)*

TLP Cost

Library prep and sequencing will be performed at the DFCI Center for Cancer Genomics, a part of the Precision Cancer Medicine effort at DFCI, Brigham and Women's Hospital, and Boston Children's Hospital. There is a cost of $60 per sample for DNA extraction and $52.67 per sample for data analysis. In addition, the per sample cost for targeted sequencing with the TLP is determined by the number of samples used per run as indicated below *.

- Sample count = 23; Sample QC, library construction and library QC, 3 custom captures, and sequencing using one SP-200 flow cell
  Total cost $15,047.60; $654.20 per sample
- Sample count = 47; Sample QC, library construction and library QC, 6 custom captures, and sequencing using one S1-200 flow cell
  Total cost $22,961.60; $488.50 per sample
- Sample count = 85; Sample QC, library construction and library QC, 11 custom captures, and sequencing using one S2-200 flow cell
  Total cost $39,341.83 ; $462.85 per sample

** Pricing estimates are valid only uptil September 2023.*

Data delivery, access, and retention

Users will receive annotated MAF files, segmentation files for CNAs, and annotated SV calls, as well as intermediary files (such as vcf files and analysis ready BAM files) through DNAnexus, a cloud-based data management and analysis platform. Details for creating a DNAnexus account are available here.

Data will remain freely available on DNAnexus for 120 days, during which users are encouraged to download or transfer data to their chosen platform. After 120 days, data will be transferred to archival storage. Archived data retrieval will require a small egress fee. As an additional paid service, users may request data transfer to another cloud storage platform (Amazon, Google or Wasabi).

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